Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 06-96986

54. **TÍTULO** COMPUESTOS, COMPOSICIONES FARMACEUTICAS Y METODICOSPARA EL USO EN EL TRATAMIENTO DE DESORDENES

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** AMGEN. INC.

DOMICILIO CALIFORNIA 91320-1799, ESTADOS UNIDOS DE AMERICA

74. **APODERADO** EMILIO FERRERO

C.C. 438.019 de Usaquén

22. **BOGOTÁ, D. C.,**

(FORMA P-10)

SS

90971 -Imprenta nacional de Colombia- 2004

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-096986- -00000-0000
Fec: 2006-09-26 17:23:47 Dep: 2020 NUEGREACIONES
Tra: 11 PATENTEIYE
Eve: 870 FASENACIONALI
Act 411 PRESENTACION Folios: 362

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 27-09-06

1 SOLICITUD DE:

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

2 SOLICITANTE (71)

Nombre: **AMGEN INC.**
sociedad constituida y existente bajo las leyes del Estado de Delaware, Estados Unidos de América.

Dirección: One Amgen Center Drive
Thousand Oaks
California 91320-1799
Estados Unidos de América

Domicilio: Thousand Oaks
California 91320-1799
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@camyp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

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

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California 94403
Estados Unidos de América

(5) **PCT (86)**
Solicitud Internacional No. PCT/US2005/005815 Fecha: 24 de febrero de 2005
Publicación Internacional No. WO 2005/086661 A2 Fecha: 22 de septiembre de 2005

(6) **Título (54)**
COMPUESTOS, COMPOSICIONES FARMACEUTICAS Y METODOS PARA EL USO EN EL TRATAMIENTO DE DESORDENES

(7) **Clasificación Internacional (51)** A61K 31/19 A61P 3/10 A61K 31/192

(8) **Prioridad** SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	27 de febrero de 2004	60/548,741
US	12 de agosto de 2004	60/601,579

(9) **Comprobante de pago No.:** 06-71,889 **Fecha:** 18 de septiembre de 2006

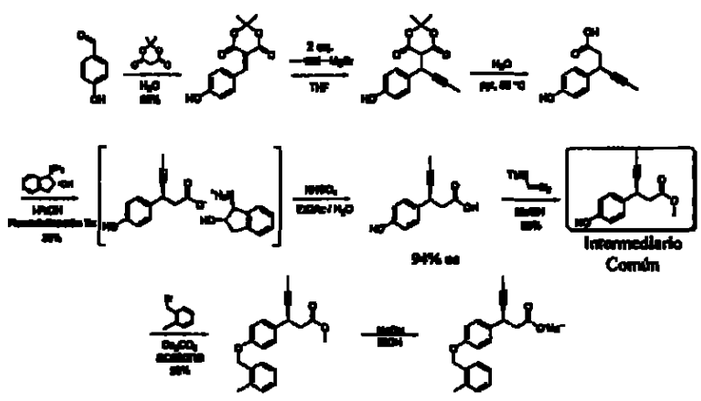
(10) **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 463.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA

Figure 1



12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA :

C.C. 438.019 de Usaquén T.P. 31.929

JDF

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2005/086661 A2
   Descripción:
2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.
3. ☒ Extracto de publicación.
4. ☒ Forma PCT/IB/306: Adición de los inventores **Michael J. SCHMITT, Yingcai WANG, Jinqian LIU y Zhihua Ma**

NO SE REALIZARON MODIFICACIONES EN FASE INTERNACIONAL

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

193

Representación, Ratificación 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, ratification 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, RATIFICACION Y PODER

REPRESENTATION, RATIFICATION AND POWER-OF-ATTORNEY

15143
15203

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

AMGEN INC.

domiciliado (s) en/of

One Amgen Center Drive
Thousand Oaks, California 91320
United States of América

por el presente ratificamos las solicitudes de patente Nos. 06.014.624 y 06.047.666 presentadas por Emilio Ferrero

como agente oficioso ante Superintendencia de Industria y Comercio

en Bogotá

el 14 de febrero de 2006 y el 18 de mayo de 2006 respectivamente

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y DANIEL PEÑA, tpa. 65620 domiciliados en la Carrera 4ª N° 72..35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare 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 u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos

Hereby ratify the Patent Applications Nos. 06.014.624 and 06.047.666

filed without a Power of Attorney by Emilio Ferrero

before Patent Office

in Bogotá

on February 14, 2006 and May 18, 2006 respectively

and do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and DANIEL PEÑA, tpa. 65620, domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, in due compliance with the terms of Paragraph 1st. of Article 543 of the Commercial Code, 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 [illegible] 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 alternate may 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

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 o judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la 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.

(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 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.

RE: Patent Applicaction
PCTUS2004/022876

Dado y firmado hoy/Given and signed this 24 February 2006

Stuart L. Watt

en/in _____

por/by Stuart L. Watt, Vice President, Law

Signed in Thousand Oaks, Ventura County, CA, US

Firma Signature

COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
20 SET 2006
PABLO MENDEZ BARAJAS
NOTARIO (E)

A-860 (CO)

7

State of California

SECRETARY OF STATE

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by L. Holtke*
3. *acting in the capacity of Notary Public, State of California*
4. *bears the seal/stamp of L. Holtke, Notary Public, State of California*

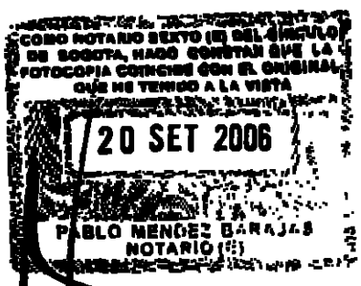
CERTIFIED

5. *At Sacramento, California*
6. *the 8th day of April 2006*
7. *by Deputy Secretary of State, State of California*
8. *No. 281687*
9. *Seal/Stamp:*

OFFICE OF SECRETARY OF



10. Signature



Secretary of State

NP-24 A (REV. 4-05)

BY C Cacha

OSP 05 80772

ALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of VENTURA } ss.

On 21 FEBRUARY 2006 (Date), before me, L. HOLTKE (Name and Title of Officer (e.g., "Jane Doe, Notary Public")),

personally appeared STUART L. WATT (Name(s) of Signer(s))

☒ personally known to me
☐ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

L. HOLTKE
Comm. # 1399086
NOTARY PUBLIC - CALIFORNIA
Los Angeles County
My Comm. Expires Feb. 8, 2007

WITNESS my hand and official seal.

Place Notary Seal Above — Signature of Notary Public

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

Description of Attached Document
Title or Type of Document: REPRESENTATION, RATIFICATION, POWER OF ATTORNEY

Document Date: _____ Number of Pages: _____

Signer(s) Other Than Named Above: _____

Capacity(ies) Claimed by Signer
Signer's Name: STUART L. WATT

- ☐ Individual
- ☒ Corporate Officer — Title(s): VICE PRESIDENT, LEGAL
- ☐ Partner — ☐ Limited ☐ General
- ☐ Attorney In Fact
- ☐ Trustee
- ☐ Guardian or Conservator
- ☐ Other: _____

Signer Is Representing: AMGEN INC.

Top of thumb here

CONSUL GENERAL DE ESPAÑA
COTEJO NOTARIAL DE LA COPIA QUE PRECEDE
FOTOCOPIA CONFORME CON EL ORIGINAL
28 SET 2006
PEDRO MENDEZ BARAJAS
NOTARIO (E)

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A-860C (CO)

7
9

CORPORATE CERTIFICATE

State of California)
) SS:
County of Ventura)

I, Stuart L. Watt, am the person who signed the foregoing instrument as Vice President, Law, of Amgen Inc., and I hereby certify the following:

1. That Amgen is a corporation duly organized and legally existing under the laws of the State of Delaware and is domiciled at One Amgen Center Drive, Thousand Oaks, California 91320-1799 USA.

2. That I am its legitimate Vice President in accordance with the appointment issued in the City of Los Angeles, California on June 27, 2000, by the Board of Directors of said corporation, which was duly elected by the General Meeting of Stockholders held in Los Angeles, California on May 11, 2000, as evidenced by the minutes, which I have seen, and I have the competence of representing same, including faculties to grant powers.

3. That I am duly authorized to sign the foregoing instrument in the name of said corporation in accordance with my above-mentioned position and/or with a resolution of the Board of Directors of said corporation, which I have seen, taken on June 27, 2000, in the City of Los Angeles, California.

4. That the purposes for which said instrument is granted are within the scope of the objects or activities of said corporation, in accordance with the Act of Incorporation issued in the City of Dover, Delaware and dated October 31, 1986, and/or the Amended and Restated By-Laws issued in the City of Thousand Oaks, California and dated April 11, 1996, both of which I have seen.

Witness (Karen Podgorny)

Stuart L. Watt
Vice President, Law

Witness (Debbie Merrill)

CONSUL NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
20 SET 2006
PABLO MENDEZ BARAJAS
NOTARIO (E)

State of California)
) SS:
County of Ventura)

On this 22 day of February, 2006, before me, L. Holtke, Notary Public, personally appeared Stuart L. Watt, Vice President, Law, and Associate General Counsel, personally known to me to be the person, whose name is subscribed to the within instrument and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

Witness my hand and seal.

Notary Public

L. HOLTKE
Comm. # 1399086
NOTARY PUBLIC - CALIFORNIA
Los Angeles County
My Comm. Expires Feb. 8, 2007

A-860 (CO)

TRADUCCIÓN OFICIAL 161/2006 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL DE ACUERDO CON EL CUAL **AMGEN INC.**, EMPRESA DOMICILIADA EN ONE AMGEN CENTER DRIVE THOUSAND OAKS, CALIFORNIA 91320 ESTADOS UNIDOS DE AMÉRICA RATIFICAN LAS SOLICITUDES DE PATENTE NOS. 06.014.624 Y 06.047.666 PRESENTADAS POR EMILIO FERRERO EL 14 DE FEBRERO DE 2006 Y EL 18 DE MAYO DE 2006 RESPECTIVAMENTE, COMO AGENTE OFICIOSO ANTE LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO EN BOGOTÁ Y OTORGA PODER A EMILIO FERRERO, TPA 31929, GONZALO PERDOMO, TPA 831; LUZ CLEMENCIA DE PAEZ, TPA 23555 Y A DANIEL PEÑA, TPA 65620.

EXPEDIDO Y FIRMADO HOY 24 DE FEBRERO DE 2006 POR STUART L. WATT, VICEPRESIDENTE ASUNTOS JURÍDICOS. FIRMADO EN THOUSAND OAKS, VENTURA COUNTY, CA, US.

RE: SOLICITUD DE PATENTE PCTUS2004/022876

RECONOCIMIENTO MULTIPROPÓSITO DE CALIFORNIA

ESTADO DE CALIFORNIA

CONDADO DE VENTURA

DECLARACIÓN JURADA

El 24 de febrero de 2006, ante mi L. HOLTKE, compareció personalmente STUART WATT, conocido personalmente por mí o demostrado por medio de [illegible] persona cuyo nombre aparece firmado en el documento adjunto y reconoció ante mi haber firmado el mismo en su calidad autorizada y que mediante su firma en el documento la persona o entidad en nombre de la cual la persona actuaba, firmó el documento.

COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL DOCUMENTO ORIGINAL QUE HE TENIDO A LA VISTA
20 FEB 2006
PABLO MENDEZ BARAJAS
NOTARIO (E)

Atestiguo mediante mi firma y sello oficial

Firma ilegible

DESCRIPCIÓN DEL DOCUMENTO ADJUNTO:

Tipo de documento o título: REPRESENTACIÓN, RATIFICACIÓN Y PODER.

CALIDAD RECLAMADA POR EL FIRMANTE:

NOMBRE DEL FIRMANTE:

STUART L. WATT, VICEPRESIDENTE ASUNTOS JURÍDICOS

EL FIRMANTE REPRESENTA A AMGEN, INC.

CERTIFICADO SOCIETARIO

ESTADO DE CALIFORNIA, CONDADO DE VENTURA

DECLARACIÓN JURAMENTADA

Yo, Stuart L. Watt, soy la persona que firmó el documento precedente en mi calidad de vicepresidente de asuntos jurídicos de Amgen Inc. y por la presente verifico lo siguiente:

1. Que Amgen es una sociedad debidamente constituida y legalmente existente de acuerdo con las leyes del estado de Delaware y se encuentra domiciliada en ONE AMGEN CENTER DRIVE, THOUSAND OAKS, CALIFORNIA 91320-1799, USA (Estados Unidos de América).

2. Que soy su vicepresidente legítimo de acuerdo con el nombramiento realizado en la ciudad de Los Angeles, California el 27 de junio de 2000 por la junta directiva de dicha empresa, que fue debidamente elegida por la reunión general de accionistas realizada en Los Angeles, California el 11 de mayo de 2000, tal como se evidencia por las actas que he visto y que tengo competencia para representarla, incluyendo con facultades para otorgar poderes.

3. Que estoy debidamente autorizado para firmar el documento precedente a nombre de dicha sociedad en concordancia con mi cargo arriba mencionado y/con una resolución de la junta directiva de dicha sociedad, que he visto, tomada el 27 de junio de 2000 en la ciudad de Los Angeles, California.

4. Que los objetos por los cuales se otorga dicho instrumento están bajo el alcance del objeto social de dicha empresa, en concordancia con el acta de constitución expedida en la ciudad de

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
28 SET 2000
PABLO MENDEZ BARAJAS
NOTARIO (E)

Dover, Delaware y de fecha 31 de octubre de 1986 y con los estatutos reformados y reestructurados emitidos en la ciudad de Thousand Oaks, California y de fecha 11 de abril de 1986, los cuales ambos he visto.

FIRMADO: STUART L. WATT, vicepresidente asuntos jurídicos.

Firmado: dos testigos, Karen Podgorny y Debbie Merrill

ESTADO DE CALIFORNIA

CONDADO DE VENTURA

DECLARACION JURADA

Hoy 22 de febrero de 2006, ante mí, L HOCTKE, notario público, compareció personalmente STUART L. WATT, vicepresidente asuntos jurídicos, y abogado general asociado, de quien me consta es la persona cuyo nombre aparece escrito en el documento adjunto y reconoció ante mí haber firmado el mismo en su calidad autorizada, y que mediante su firma en el documento la persona o la entidad a nombre de la cual actuaba la persona, firmó el documento.

Atestiguo mediante mi firma y sello.

Firmado: (ilegible) notario público

SELLO: L HOLTKE, Nombramiento #139086, notario público, California. Condado de Los Angeles. Mi cargo [illegible] febrero de 2007.



ESTADO DE CALIFORNIA

SECRETARÍA DE ESTADO

APOSTILLA

(CONVENCIÓN DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAIS: ESTADOS UNIDOS DE AMÉRICA

Este documento público

2. ha sido firmado por L. HOLTKE

3. quien actúa en su calidad de NOTARIO PÚBLICO, ESTADO DE CALIFORNIA

4. y lleva el sello/estampilla de L. HOLTKE, notario público, estado de California.

CERTIFICADO

5. en Sacramento, California 6. el 8 de abril de 2006

7. por el Secretario de estado suplente del estado de California

8. Certificado número 281687

9. Sello: EL GRAN SELLO DEL ESTADO DE CALIFORNIA

10. Firma: (ILEGIBLE)

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COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTÁ, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
20 SET 2006
PABLO MENDEZ R.
NOTARIO

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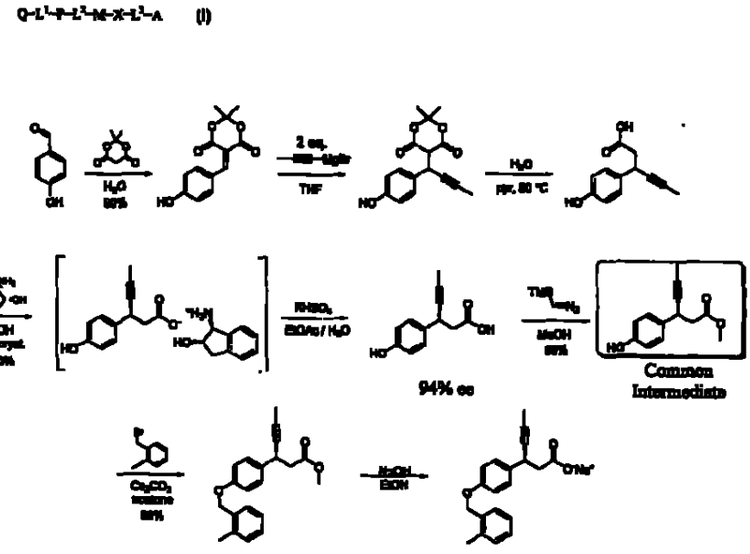
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(54) Title: COMPOUNDS, PHARMACEUTICAL COMPOSITIONS AND METHODS FOR USE IN TREATING METABOLIC DISORDERS



(57) Abstract: The present invention provides compounds useful, for example, for modulating insulin levels in a subject and that have the general formula Q-L¹-P-L²-M-X-L³-A wherein the definitions of the variables Q, L¹, P, L², M, X, L³ and A are provided herein. The present invention also provides compositions and methods for use of the compounds, for instance, for treatment of type II diabetes.

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COMPOUNDS, PHARMACEUTICAL COMPOSITIONS AND METHODS FOR USE IN TREATING METABOLIC DISORDERS

RELATED APPLICATIONS

[001] This application claims the benefit of United States provisional application no. 60/548,741, filed February 27, 2004, and United State provisional application no. 60/601,579, filed August 12, 2004, which are incorporated herein by reference in their entireties.

1. FIELD OF THE INVENTION

[002] The present invention relates to compounds capable of modulating the G-protein-coupled receptor GPR40, compositions comprising the compounds, and methods for their use for controlling insulin levels *in vivo* and for the treatment of conditions such as type II diabetes, hypertension, ketoacidosis, obesity, glucose intolerance, and hypercholesterolemia and related disorders associated with abnormally high or low plasma lipoprotein, triglyceride or glucose levels.

2. BACKGROUND OF THE INVENTION

[003] The production of insulin is central to the regulation of carbohydrate and lipid metabolism. Insulin imbalances lead to conditions such as type II diabetes mellitus, a serious metabolic disease that afflicts around 5% of the population in Western Societies and over 150 million people worldwide. Insulin is secreted from pancreatic β cells in response to elevated plasma glucose which is augmented by the presence of fatty acids. The recent recognition of the function of the G-protein coupled receptor GPR40 in modulating insulin secretion has provided insight into regulation of carbohydrate and lipid metabolism in vertebrates, and further provided targets for the development of therapeutic agents for disorders such as obesity, diabetes, cardiovascular disease and dyslipidemia.

[004] GPR40 is a member of the gene superfamily of G-protein coupled receptors ("GPCRs"). GPCRs are membrane proteins characterized as having seven putative transmembrane domains that respond to a variety of molecules by activating intra-cellular signaling pathways critical to a diversity of physiological functions. GPR40 was first identified as an orphan receptor (*i.e.*, a receptor without a known ligand) from a human genomic DNA fragment. Sawzdargo *et al.* (1997) *Biochem. Biophys. Res. Commun.* 239: 543-547. GPR40 is highly expressed in pancreatic β cells and insulin-secreting cell lines.

GPR40 activation is linked to modulation of the G_q family of intra-cellular signaling proteins and concomitant induction of elevated calcium levels. It has been recognized that fatty acids serve as ligands for GPR40, and that fatty acids regulate insulin secretion through GPR40. Itoh *et al.* (2003) *Nature* 422:173-176; Briscoe *et al.* (2003) *J. Biol. Chem.* 278: 11303-11311; Kotarsky *et al.* (2003) *Biochem. Biophys. Res. Commun.* 301: 406-410.

[005] The prevalence of type II diabetes, obesity, hypertension, cardiovascular disease and dyslipidemia underscores the need for new therapies to effectively treat or prevent these conditions.

3. SUMMARY OF THE INVENTION

[006] Provided herein are compounds, pharmaceutical compositions and methods useful for treating or preventing a condition or disorder such as type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer or edema.

[007] In one aspect, the compounds of the invention have the general formula (I):

$$Q\text{–}L^1\text{–}P\text{–}L^2\text{–}M\text{–}X\text{–}L^3\text{–}A$$

I

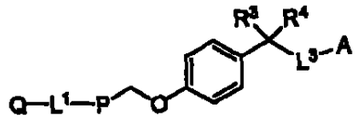
wherein Q is hydrogen, aryl, heteroaryl, $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$heteroalkyl; L^1 is a bond, $(C_1\text{-}C_4)$alkylene, $(C_2\text{-}C_4)$heteroalkylene, O, $S(O)_m$, $N(R^1)$, $C(O)$-$(C_3\text{-}C_7)$heterocycloalkylene, $(C_1\text{-}C_4)$alkylene-$SO_2N(R^2)$, $(C_1\text{-}C_4)$alkylene-$N(R^2)SO_2$ or $C(O)N(R^2)$; P is an aromatic ring, a heteroaromatic ring, $(C_3\text{-}C_8)$heterocycloalkylene or $(C_3\text{-}C_8)$cycloalkylene; L^2 is a bond, $(C_1\text{-}C_6)$alkylene, $(C_2\text{-}C_6)$heteroalkylene, O, $S(O)_m$, $N(R^1)$, $C(O)N(R^2)$, $SO_2N(R^2)$, $(C_1\text{-}C_4)$alkylene-$C(O)N(R^2)$, $(C_1\text{-}C_4)$alkylene-$N(R^2)C(O)$, $(C_2\text{-}C_4)$alkenylene-$C(O)N(R^2)$, $(C_2\text{-}C_4)$alkenylene-$N(R^2)C(O)$, $(C_1\text{-}C_4)$alkylene-$SO_2N(R^2)$, $(C_1\text{-}C_4)$alkylene-$N(R^2)SO_2$, $(C_2\text{-}C_4)$alkenylene-$SO_2N(R^2)$ or $(C_2\text{-}C_4)$alkenylene-$N(R^2)SO_2$; M is an aromatic ring, a heteroaromatic ring, $(C_5\text{-}C_8)$cycloalkylene, aryl$(C_1\text{-}C_4)$alkylene or heteroaryl$(C_1\text{-}C_4)$alkylene; X is CR^3R^4, $N(R^5)$, O or $S(O)_n$; L^3 is a bond, $(C_1\text{-}C_5)$alkylene or $(C_2\text{-}C_5)$heteroalkylene, provided that L^3 is not a bond when L^2 is a bond; A is $-CO_2H$, tetrazol-5-yl, $-SO_3H$, $-PO_3H_2$, $-SO_2NH_2$, $-C(O)NHSO_2CH_3$, $-CHO$, $-C(O)R^6$, $-C(O)NHR^6$, $-C(O)NHOR^7$, thiazolidinedion-yl, hydroxyphenyl or pyridyl; R^1 is $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$heteroalkyl; R^2 is hydrogen, $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$heteroalkyl; R^3

is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$, $-NR^{12}C(O)R^{13}$ or $-NR^{12}S(O)_pR^{13}$; R^4 is hydrogen, cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl or (C_2-C_8)alkynyl, optionally R^3 and R^4 are combined to form a 3-, 4-, 5-, 6- or 7-membered ring containing from zero to three heteroatoms selected from N, O and S; R^5 hydrogen, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or (C_3-C_8)cycloalkyl; R^6 is heteroaryl; R^7 is hydrogen or (C_1-C_5)alkyl; R^8 and R^9 are independently hydrogen, (C_1-C_5)alkyl, oxy(C_1-C_5)alkyl or carboxy(C_1-C_5)alkyl, optionally, R^8 and R^9 are combined to form a 4-, 5-, 6- or 7-membered ring containing the nitrogen atom to which they are attached and from 0 to 2 additional heteroatoms selected from N, O and S; R^{10}, R^{11} and R^{12} are independently selected from hydrogen, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_3-C_8)cycloalkyl and (C_3-C_8)heterocycloalkyl, optionally, R^{10} and R^{11} are combined to form a 4-, 5-, 6- or 7-membered ring containing the nitrogen atom to which they are attached and from 0 to 2 additional heteroatoms selected from N, O and S; R^{13} is aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_3-C_8)cycloalkyl or (C_3-C_8)heterocycloalkyl; the subscripts m and n are independently 0, 1 or 2; and the subscript p is 1 or 2; and wherein the compound is other than 3-(4-(4-methoxybenzyloxy)phenyl)pent-4-ynoic acid; β-ethenyl-4-phenylmethoxy-benzenepropanoic acid; 4-(2-quinolinylmethoxy)-β-[4-(2-quinolinylmethoxy)phenyl]-benzenepropanoic acid; N-[4-(benzoylamino)phenyl]-N-phenyl-glycine; 3-(4-(isopentyloxy)benzamido)-3-phenylpropanoate; 3-(4-isobutoxybenzamido)-3-phenylpropanoate; (*R*)-2-((*1R,4R*)-4-isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid; (*R*)-3-(4-(benzyloxy)phenyl)-2-(tert-butoxycarbonyl)propanoic acid; 3-(4-chlorophenyl)-3-(furan-2-carboxamido)propanoic acid; 3-(3,4-dimethoxyphenyl)-3-(furan-2-carboxamido)propanoic acid; 3-(4-chlorobenzamido)-3-(4-(dimethylamino)phenyl)propanoic acid; 3-(2-(2-(3,4-dimethylphenoxy)ethylthio)-1*H*-benzo[d]imidazol-1-yl)propanoic acid; {2-Bromo-4-[(3,4-dichloro-phenyl)-hydrazonomethyl]-6-ethoxy-phenoxy}-acetic acid; 2-(4-(2-(2-(4-chlorophenyl)furan-5-carboxamido)ethyl)phenoxy)-2-methylpropanoic acid; 5-(3-(3,4-dimethoxyphenyl)-5-(2-fluorophenyl)-4,5-dihydropyrazol-1-yl)-5-oxopentanoic acid; 2-(2-(3-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-2-methyl-4-oxo-4*H*-chromen-7-yloxy)acetamido)acetic acid; 3-(4'-Bromo-biphenyl-4-yl)-4-phenyl-butyric acid; 3-(4'-Bromo-biphenyl-4-yl)-3-phenylsulfanyl-propionic acid; 3-(5-(2-chloro-6-fluoro-4-(trifluoromethyl)phenoxy)-2,4-dinitrophenyl)propanoic acid; 3-(3-(2-chloro-4-(trifluoromethyl)phenoxy)phenyl)propanoic acid; 3-(4-(4-methoxybenzyloxy)phenyl)pent-4-ynoic acid; 3-(4-(4-methoxybenzyloxy)phenyl)-5-(trimethylsilyl)pent-4-ynoic acid; β,β-dimethyl-4-[[[4-

methyl-2-[4-(trifluoromethyl)phenyl]-5-thiazolyl]methyl]thio]-benzenepropanoic acid; β-amino-4-[(4-bromo-2,5-dihydro-2-methyl-5-oxo-1-phenyl-1H-pyrazol-3-yl)methoxy]-3-methoxy-benzenepropanoic acid; or salt thereof.

[008] The compounds of the invention include pharmaceutically acceptable salts, solvates or prodrugs thereof.

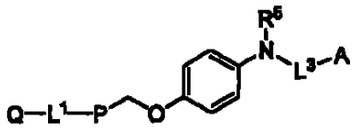
[009] In certain embodiments, the present invention provides a compound having the formula (Ia):



Ia

where Q, L^1, P, L^3, A, R^3 and R^4 are as defined with regard to formula I above.

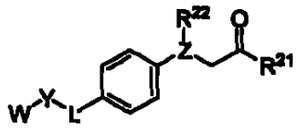
[010] In certain embodiments, the present invention provides a compound having the formula (Ib):



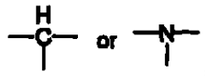
Ib

where Q, L^1, P, L^3, A and R^5 are as defined with regard to formula I above.

[011] In another aspect, the compounds of the inventions have the general formula (II):



II

wherein Z is  ; R^{21} is -H, -OH, $-NHS(O_2)CH_3$, heteroaryl, or -NH-heteroaryl; R^{22} is $-(C_2-C_8)$alkyl, $-(C_3-C_8)$alkenyl, $-NR^{23}R^{24}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C\equiv N$, or $-C\equiv C-R^{25}$, or optionally where Z is a nitrogen atom, R^{22} is -H; R^{23} and R^{24} are independently -H, $-(C_1-C_5)$alkyl, or $-(C_1-C_5)$oxyalkyl; R^{25} is -H, $-(C_1-C_5)$alkyl, -hetero(C_1-C_5)alkyl, $-(C_1-C_5)$oxyalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; L is -O-, -S-, or $-N(R^{26})-$; R^{26} is -H, $-(C_1-C_5)$alkyl, substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; Y is absent or is $-CH_2-$, $-CH_2CH_2-$, -CH=CH-, $-C(O)CH_2-$, $-C(O)CH_2CH_2-$, -C(O)CH=CH-, $-S(O_2)-$, $-S(O_2)CH_2-$,

-S(O$_2$)CH$_2$CH$_2$-, -S(O$_2$)CH=CH-, or -C(O)-; W is a substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[012] In another aspect, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier, diluent or excipient and a compound of formula I, Ia, Ib or II.

[013] In another aspect, the invention provides methods for treating or preventing a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease atherosclerosis, kidney disease, ketoacidosis, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, thrombotic disorders, dermatopathy, dyspepsia, hypoglycemia, hypertension, cancer and edema comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, Ia, Ib or II.

[014] In another aspect, the invention provides methods for treating or preventing a disease or condition responsive to the modulation of GPR40 comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, Ia, Ib or II.

[015] In another aspect, the invention provides methods for treating or preventing a disease or condition mediated, regulated or influenced by pancreatic β cells comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, Ia, Ib or II.

[016] In another aspect, the invention provides methods for modulating GPR40 function in a cell, comprising contacting a cell with a compound of formula I, Ia, Ib or II.

[017] In another aspect, the invention provides methods for modulating GPR40 function comprising contacting GPR40 with a compound of formula I, Ia, Ib or II.

[018] In another aspect, the invention provides methods for modulating circulating insulin concentration in a subject, comprising administering a compound of formula I, Ia, Ib or II to the subject.

[019] Other objects, features and advantages of the invention will become apparent to those skilled in the art from the following description and claims.

4. BRIEF DESCRIPTION OF THE FIGURES

[020] FIG. 1 provides a scheme for synthesis of exemplary compounds of the invention.

5. DETAILED DESCRIPTION OF THE INVENTION

5.1 Abbreviations and Definitions

[021] The terms "treat", "treating" and "treatment", as used herein, are meant to include alleviating or abrogating a condition or disease and/or its attendant symptoms and alleviating. The terms "prevent", "preventing" and "prevention", as used herein, refer to a method of delaying or precluding the onset of a condition or disease and/or its attendant symptoms, barring a subject from acquiring a condition or disease or reducing a subject's risk of acquiring a condition or disease.

[022] The term "therapeutically effective amount" refers to that amount of the compound that will elicit the biological or medical response of a tissue, system, or subject that is being sought. The term "therapeutically effective amount" includes that amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated in a subject. The therapeutically effective amount in a subject will vary depending on the compound, the disease and its severity and the age, weight, *etc.*, of the subject to be treated.

[023] The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[024] The terms "modulate", "modulation" and the like refer to the ability of a compound to increase or decrease the function or activity of GPR40 either directly or indirectly. Inhibitors are compounds that, for example, bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate signal transduction, such as, for instance, antagonists. Activators are compounds that, for example, bind to, stimulate, increase, activate, facilitate, enhance activation, sensitize or up regulate signal transduction, such as agonists for instance. Modulation may occur *in vitro* or *in vivo*.

[025] As used herein, the term "GPR40-mediated condition or disorder" and the like refer to a condition or disorder characterized by inappropriate, for example, less than or greater than normal, GPR40 activity. A GPR40-mediated condition or disorder may be completely or partially mediated by inappropriate GPR40 activity. However, a GPR40-mediated condition or disorder is one in which modulation of GPR40 results in some effect on the underlying condition or disease (*e.g.*, a GPR40 modulator results in some improvement in patient well-being in at least some patients). Exemplary GPR40-mediated

conditions and disorders include cancer and metabolic disorders, *e.g.*, diabetes, type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, ketoacidosis, hypoglycemia, thrombotic disorders, metabolic syndrome, syndrome X and related disorders, *e.g.*, cardiovascular disease, atherosclerosis, kidney disease, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia and edema.

[026] The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which is fully saturated, having the number of carbon atoms designated (*e.g.*, C_1-C_{10} means one to ten carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl and the like.

[027] The term "alkenyl", by itself or as part of another substituent, means a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (*i.e.*, C_2-C_8 means two to eight carbons) and one or more double bonds. Examples of alkenyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl) and higher homologs and isomers thereof.

[028] The term "alkynyl", by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (*i.e.*, C_2-C_8 means two to eight carbons) and one or more triple bonds. Examples of alkynyl groups include ethynyl, 1- and 3-propynyl, 3-butynyl and higher homologs and isomers thereof.

[029] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from alkyl, as exemplified by $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 12 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[030] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule *via* an oxygen atom, an amino group, or a sulfur atom, respectively. Similarly, the

term "dialkylamine" refers to an amino group having two attached alkyl groups that can be the same or different.

[031] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any position of the heteroalkyl group. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, and $-CH_2-CH=N-OCH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$. When a prefix such as (C_2-C_8) is used to refer to a heteroalkyl group, the number of carbons (2 to 8, in this example) is meant to include the heteroatoms as well. For example, a C_2-heteroalkyl group is meant to include, for example, $-CH_2OH$ (one carbon atom and one heteroatom replacing a carbon atom) and $-CH_2SH$.

[032] To further illustrate the definition of a heteroalkyl group, where the heteroatom is oxygen, a heteroalkyl group is a oxyalkyl group. For instance, $(C_2.C_5)$oxyalkyl is meant to include, for example $-CH_2-O-CH_3$ (a C_3-oxyalkyl group with two carbon atoms and one oxygen replacing a carbon atom), $-CH_2CH_2CH_2CH_2OH$, and the like.

[033] The term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-CH_2-CH_2-S-CH_2CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

[034] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Thus, the terms "cycloalkyl" and "heterocycloalkyl" are meant to be included in the terms "alkyl" and "heteroalkyl," respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl,

4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[035] The term "cycloalkylene" and "heterocycloalkylene," by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkylene" and "heteroalkylene," respectively. Thus, the terms "cycloalkylene" and "heterocycloalkylene" are meant to be included in the terms "alkylene" and "heteroalkylene," respectively. Additionally, for heterocycloalkylene, one or more heteroatoms can occupy positions at which the heterocycle is attached to the remainder of the molecule. Typically, a cycloalkylene or heterocycloalkylene will have from 3 to 9 atoms forming the ring, more typically, 4 to 7 atoms forming the ring, and even more typically, 5 or 6 atoms will form the cycloalkylene or hetercycloalkylene ring.

[036] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl", are meant to include alkyl substituted with halogen atoms which can be the same or different, in a number ranging from one to $(2m' + 1)$, where m' is the total number of carbon atoms in the alkyl group. For example, the term "halo(C_1-C_4)alkyl" is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. Thus, the term "haloalkyl" includes monohaloalkyl (alkyl substituted with one halogen atom) and polyhaloalkyl (alkyl substituted with halogen atoms in a number ranging from two to $(2m' + 1)$ halogen atoms). The term "perhaloalkyl" means, unless otherwise stated, alkyl substituted with $(2m' + 1)$ halogen atoms, where m' is the total number of carbon atoms in the alkyl group. For example, the term "perhalo(C_1-C_4)alkyl", is meant to include trifluoromethyl, pentachloroethyl, 1,1,1-trifluoro-2-bromo-2-chloroethyl, and the like.

[037] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms selected from the group consisting of N, O and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 5-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl,

dibenzofuryl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4- pyridazinyl, 5-benzothiazolyl, 2-benzoxazolyl, 5-benzoxazolyl, benzo[c][1,2,5]oxadiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1H-indazolyl, carbazolyl, α–carbolinyl, β-carbolinyl, γ-carbolinyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl and 8-quinolyl.

[038] Preferably, the term "aryl" refers to a phenyl or naphthyl group which is unsubstituted or substituted. Preferably, the term "heteroaryl" refers to a pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, purinyl, benzimidazolyl, indolyl, isoquinolyl, quinoxalinyl or quinolyl group which is unsubstituted or substituted.

[039] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[040] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") is meant to include both substituted and unsubstituted forms of the indicated radical, unless otherwise indicated. Preferred substituents for each type of radical are provided below.

[041] Substituents for the alkyl and heteroalkyl radicals (as well as those groups referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl and heterocycloalkenyl) can be a variety of groups selected from: -OR′, =O, =NR′, =N-OR′, -NR′R″, -SR′, halogen, -OC(O)R′, -C(O)R′, -CO_2R′, -CONR′R″, -OC(O)NR′R″, -NR″C(O)R′, -NR′-C(O)NR″R‴, -NR′-SO_2NR″R‴, -NR″CO_2R′, -NH-C(NH_2)=NH, -NR′C(NH_2)=NH, -NH-C(NH_2)=NR′, -SiR′R″R‴, -S(O)R′, -SO_2R′, -SO_2NR′R″, -NR″SO_2R, -CN and -NO_2, in a number ranging from zero to three, with those groups having zero, one or two substituents being particularly preferred. R′, R″ and R‴ each independently refer to hydrogen, unsubstituted (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with one to three halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, halo(C_1-C_4)alkyl, or aryl-(C_1-C_4)alkyl groups. When R′ and R″ are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a

5-, 6- or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl.

[042] Typically, an alkyl or heteroalkyl group will have from zero to three substituents, with those groups having two or fewer substituents being preferred in the present invention. More preferably, an alkyl or heteroalkyl radical will be unsubstituted or monosubstituted. Most preferably, an alkyl or heteroalkyl radical will be unsubstituted. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as trihaloalkyl (*e.g.*, $-CF_3$ and $-CH_2CF_3$).

[043] Preferred substituents for the alkyl and heteroalkyl radicals are selected from: -OR', =O, -NR'R", -SR', halogen, -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', $-NR"CO_2R'$, -NR'-SO_2NR"R"', -S(O)R', $-SO_2R'$, $-SO_2$NR'R", $-NR"SO_2R$, -CN and $-NO_2$, where R' and R" are as defined above. Further preferred substituents are selected from: -OR', =O, -NR'R", halogen, -OC(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', $-NR"CO_2R'$, -NR'-SO_2NR"R"', $-SO_2R'$, $-SO_2$NR'R", $-NR"SO_2R$, -CN and $-NO_2$.

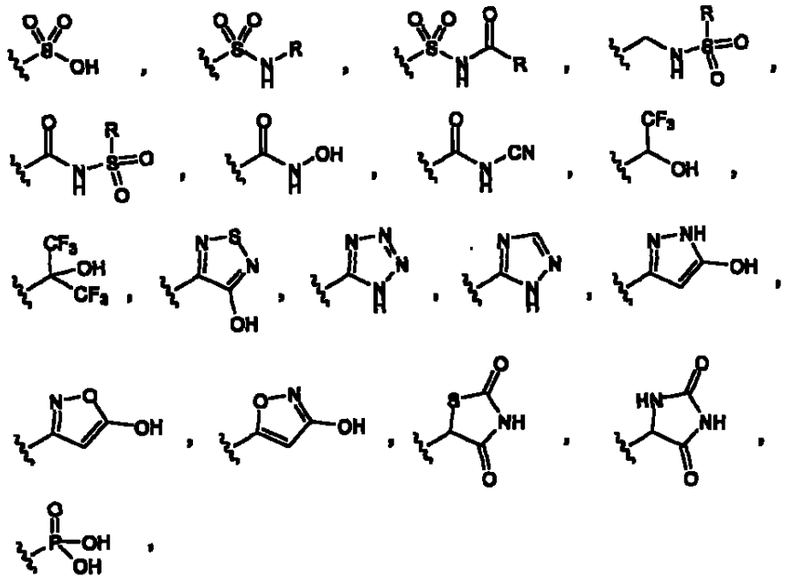
[044] Similarly, substituents for the aryl and heteroaryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, $-NO_2$, $-CO_2R'$, -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', $-NR"C(O)_2R'$, -NR'-C(O)NR"R"', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', $-S(O)_2R'$, $-S(O)_2$NR'R", $-N_3$, $-CH(Ph)_2$, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R"' are independently selected from hydrogen, (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-(C_1-C_4)alkyl, and (unsubstituted aryl)oxy-(C_1-C_4)alkyl.

[045] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-$(CH_2)_q$-U-, wherein T and U are independently -NH-, -O-, $-CH_2-$ or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently $-CH_2-$, -O-, -NH-, -S-, -S(O)-, $-S(O)_2-$, $-S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CH_2)_s$-X-$(CH_2)_t$-, where s and t are independently integers of from 0 to 3, and X is -O-,

-NR'-, -S-, -S(O)-, -S(O)$_2$-, or -S(O)$_2$NR'-. The substituent R' in -NR'- and -S(O)$_2$NR'- is selected from hydrogen or unsubstituted (C_1-C_6)alkyl. Otherwise, R' is as defined above.

[046] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), and sulfur (S).

[047] As used herein, the phrase "bioisostere of -CO_2H" is meant that the the substituent -CO_2H may be optionally replaced with bioisosteric replacements such as:



and the like. *See, e.g., The Practice of Medicinal Chemistry*, Wermuth, C.G., Ed., Academic Press: New York, 1996, p. 203.

[048] The term "pharmaceutically acceptable salt" is meant to include a salt of the active compound which is prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compound described herein. When a compound of the invention contains relatively acidic functionalities, a base addition salt can be obtained by contacting the neutral form of such compound with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When a compound of the invention contains relatively basic functionalities, an acid addition salt can be obtained by contacting the neutral form of such compound with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the

salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginine and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, for example, Berge *et al.* (1977) *J. Pharm. Sci.* 66:1-19). Certain specific compounds of the invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[049] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the invention.

[050] In addition to salt forms, the invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the invention. Additionally, prodrugs can be converted to the compounds of the invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound of the invention which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[051] As used herein, "solvate" refers to a compound of the present invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

[052] Certain compounds of the invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the invention and are intended to be within the scope of the invention.

[053] Certain compounds of the invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, enantiomers, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the invention.

[054] As used herein and unless otherwise indicated, the term "stereoisomer" or "stereomerically pure" means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. It should be noted that if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

[055] Various compounds of the invention contain one or more chiral centers, and can exist as racemic mixtures of enantiomers, mixtures of diastereomers or enantiomerically or optically pure compounds. This invention encompasses the use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular compound of the invention may be used in methods and compositions of the invention. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.*, Jacques, J., *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al.* (1997) *Tetrahedron* 33:2725; Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill,

NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[056] The compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). Radiolabled compounds are useful as therapeutic or prophylactic agents, research reagents, *e.g.*, GPR40 assay reagents, and diagnostic agents, *e.g.*, *in vivo* imaging agents. All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention.

5.2 Embodiments of the Invention

[057] In one aspect, a class of compounds that modulate GPR40 is described herein. Depending on the biological environment (*e.g.*, cell type, pathological condition of the subject, *etc.*), these compounds can modulate, *e.g.*, activate or inhibit, the actions of GPR40. By modulating GPR40, the compounds find use as therapeutic agents capable of regulating insulin levels in a subject. The compounds find use as therapeutic agents for modulating diseases and conditions responsive to modulation of GPR40 and/or mediated by GPR40 and/or mediated by pancreatic β cells. As noted above, examples of such diseases and conditions include diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, cancer, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, ketoacidosis, hypoglycemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, nephropathy, thrombotic disorders, diabetic neuropathy, diabetic retinopathy, dermatopathy, dyspepsia and edema. Additionally, the compounds are useful for the treatment and/or prevention of complications of these diseases and disorders (*e.g.*, type II diabetes, sexual dysfunction, dyspepsia and so forth).

[058] While the compounds of the invention are believed to exert their effects by interacting with GPR40, the mechanism of action by which the compounds act is not a limiting embodiment of the invention.

[059] Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein.

5.2.1 Compounds

[060] In one aspect, the present invention provides a compound having the formula (I):

$$Q\text{–}L^1\text{–}P\text{–}L^2\text{–}M\text{–}X\text{–}L^3\text{–}A$$

I

where Q, L^1, P, L^2, M, X, L^3 and A are defined below.

[061] Q is hydrogen, aryl, heteroaryl, $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$heteroalkyl.

[062] In preferred embodiments, Q is aryl.

[063] In further preferred embodiments, Q is 4-(trifluoromethyl)phenyl or *p*-tolyl.

[064] L^1 is a bond, $(C_1\text{-}C_4)$alkylene, $(C_2\text{-}C_4)$heteroalkylene, O, $S(O)_m$, $N(R^1)$, $C(O)$-$(C_5\text{-}C_7)$heterocycloalkylene, $(C_1\text{-}C_4)$alkylene-$SO_2N(R^2)$, $(C_1\text{-}C_4)$alkylene-$N(R^2)SO_2$ or $C(O)N(R^2)$.

[065] In certain embodiments, L^1 is a bond, $(C_1\text{-}C_4)$alkylene, $(C_2\text{-}C_4)$heteroalkylene, O, $S(O)_m$, $N(R^1)$ or $C(O)N(R^2)$.

[066] In certain embodiments, L^1 is a bond, O or $N(R^1)$.

[067] In preferred embodiments, L^1 is a bond.

[068] P is an aromatic ring, a heteroaromatic ring, $(C_3\text{-}C_8)$heterocycloalkylene or $(C_3\text{-}C_8)$cycloalkylene. In certain embodiments where P is an aromatic ring, the term aromatic includes aryl. In other embodiments where P is a heteroaromatic ring, the term heteroaromatic includes heteroaryl.

[069] In some embodiments, P is an aromatic ring or a heteroaromatic ring.

[070] In certain embodiments, P is a monocyclic aromatic ring or a moncyclic heteroaromatic ring.

[071] In some embodiments, P is a selected from the group consisting of benzene, naphthalene, pyrrole, pyrazole, imidazole, pyrazine, oxazole, isoxazole, thiazole, furan, thiophene, pyridine, pyrimidine, pyridazine, benzothiazole, purine, benzimidazole, benzoxazole, triazole, oxadiazole, thiadiazole, benzooxadiazole, dibenzofuran, indole, indazole, carbazole, carboline, isoquinoline, quinoxaline and quinoline. For example, P can be benzene, naphthalene, pyrrole, pyrazine, pyridine, pyrimidine, pyridazine, purine, indole, carboline, isoquinoline, quinoxaline or quinoline. In some embodiments, P is a benzene, thiazole, or oxazole ring.

[072] In preferred embodiments, L^1 is a bond, O or $N(R^1)$ and P is an aromatic ring or a heteroaromatic ring.

[073] L^2 is a bond, $(C_1\text{-}C_6)$alkylene, $(C_2\text{-}C_6)$heteroalkylene, oxymethylene, O, $S(O)_m$, $N(R^1)$, $C(O)N(R^2)$, $SO_2N(R^2)$, $(C_1\text{-}C_4)$alkylene-$C(O)N(R^2)$,

(C_1-C_4)alkylene-$N(R^2)C(O)$, (C_2-C_4)alkenylene-$C(O)N(R^2)$, (C_2-C_4)alkenylene-$N(R^2)C(O)$, (C_1-C_4)alkylene-$SO_2N(R^2)$, (C_1-C_4)alkylene-$N(R^2)SO_2$, (C_2-C_4)alkenylene-$SO_2N(R^2)$ or (C_2-C_4)alkenylene-$N(R^2)SO_2$.

[074] In certain embodiments, L^2 is a bond, (C_1-C_6)alkylene, (C_2-C_6)heteroalkylene, oxymethylene, O, $S(O)_m$, $N(R^1)$, $C(O)N(R^2)$, $SO_2N(R^2)$, (C_1-C_4)alkylene-$C(O)N(R^2)$, (C_2-C_4)alkenylene-$C(O)N(R^2)$, (C_1-C_4)alkylene-$SO_2N(R^2)$ or (C_2-C_4)alkenylene-$SO_2N(R^2)$.

[075] In certain embodiments, L^2 is (C_2-C_6)heteroalkylene.

[076] In some embodiments, L^2 is (C_2-C_4)heteroalkylene.

[077] In some embodiments, L^1 is a bond, O or $N(R^1)$ and L^2 is (C_2-C_6)heteroalkylene.

[078] In certain embodiments, L^2 is oxymethylene or thiomethylene.

[079] In preferred embodiments, L^1 is a bond and L^2 is oxymethylene or thiomethylene.

[080] M is an aromatic ring, a heteroaromatic ring, (C_3-C_8)cycloalkylene, aryl(C_1-C_4)alkylene or heteroaryl(C_1-C_4)alkylene. In certain embodiments where M is an aromatic ring, the term aromatic includes aryl. In other embodiments where M is a heteroaromatic ring, the term heteroaromatic includes heteroaryl.

[081] In some embodiments, M is an aromatic ring or a heteroaromatic ring.

[082] In some embodiments, M is a (C_5-C_8)cycloalkylene.

[083] In certain embodiments, M is a monocyclic aromatic, a monocyclic heteroaromatic ring or (C_5-C_8)cycloalkylene.

[084] In some embodiments, M is an unsubstituted monocyclic aromatic ring or an unsubstituted monocyclic heteroaromatic ring.

[085] In certain embodiments, M is a benzene ring or a heteroaromatic ring.

[086] In preferred embodiments, M is a benzene ring.

[087] In preferred embodiments, P is an aromatic ring or a heteroaromatic ring and M is an aromatic ring, a heteroaromatic ring or (C_5-C_8)cycloalkylene.

[088] X is CR^3R^4, $N(R^5)$, O or $S(O)_n$.

[089] In preferred embodiments, X is CR^3R^4 or $N(R^5)$.

[090] In further preferred embodiments, X is CHR^3.

[091] In certain embodiments, M is a substituted or unsubstituted benzene ring and X is *para* to L^2.

[092] In certain preferred embodiments, M is an aromatic ring, a heteroaromatic ring or (C_5-C_8)cycloalkylene and X is CR^3R^4 or $N(R^5)$.

[093] In preferred embodiments, P is an aromatic ring or a heteroaromatic ring and X is CR^3R^4 or $N(R^5)$.

[094] L^3 is a bond, (C_1-C_5)alkylene or (C_2-C_5)heteroalkylene, provided that L^3 is not a bond when L^2 is a bond.

[095] In some embodiments, L^3 is (C_1-C_5)alkylene or (C_2-C_5)heteroalkylene.

[096] In certain embodiments, L^3 is (C_1-C_3)alkylene.

[097] In some embodiments, L^3 is methylene.

[098] In certain embodiments, L^3 is a methylene substituted with a monocyclic aryl or monocyclic heteroaryl.

[099] In certain embodiments, X is CR^3R^4 or $N(R^5)$, and L^3 is substituted or unsubstituted methylene.

[0100] In preferred embodiments, L^2 is (C_2-C_4)heteroalkylene and L^3 is (C_1-C_3)alkylene.

[0101] In certain preferred embodiments, L^1 is a bond, O or $N(R^1)$, L^2 is (C_2-C_4)heteroalkylene and L^3 is (C_1-C_3)alkylene.

[0102] A is $-CO_2H$, tetrazol-5-yl, $-SO_3H$, $-PO_3H_2$, $-SO_2NH_2$, $-C(O)NHSO_2CH_3$, $-CHO$, $-C(O)R^6$, $-C(O)NHR^6$, $-C(O)NHOR^7$, thiazolidinedion-yl, hydroxyphenyl or pyridyl.

[0103] In certain embodiments, A is a bioisostere of $-CO_2H$.

[0104] In certain embodiments, A is $-CO_2H$ or tetrazol-5-yl, $-C(O)NHSO_2CH_3$ or $-C(O)NHR^6$.

[0105] In some embodiments, A is $-CO_2H$ or tetrazol-5-yl.

[0106] In preferred embodiments, A is $-CO_2H$ or a salt thereof.

[0107] In some embodiments, P is an aromatic ring or a heteroaromatic ring and A is $-CO_2H$.

[0108] In certain embodiments, X is CR^3R^4 or $N(R^5)$ and A is $-CO_2H$.

[0109] In preferred embodiments, M is an aromatic ring, a heteroaromatic ring or (C_5-C_8)cycloalkylene and A is $-CO_2H$ or tetrazol-5-yl.

[0110] In certain preferred embodiments, M is an aromatic ring, a heteroaromatic ring or (C_5-C_8)cycloalkylene, X is CR^3R^4 or $N(R^5)$, L^3 is (C_1-C_5)alkylene or (C_2-C_5)heteroalkylene and A is $-CO_2H$.

[0111] R^1 is (C_1-C_6)alkyl, aryl(C_1-C_3) alkyl or (C_2-C_6)heteroalkyl.

[0112] In certain embodiments, R^1 is (C_1-C_6)alkyl or (C_2-C_6)heteroalkyl.

[0113] R^2 is hydrogen, (C_1-C_6)alkyl or (C_2-C_6)heteroalkyl.

[0114] R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)alkynyl, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$, $-NR^{12}C(O)R^{13}$ or $-NR^{12}S(O)_pR^{13}$.

[0115] In certain embodiments, R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$, $-NR^{12}C(O)R^{13}$ or $-NR^{12}S(O)_pR^{13}$.

[0116] In some embodiments, R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl or $-NR^8R^9$.

[0117] In certain embodiments, R^3 is cyano, heteroaryl, (C_2-C_6) alkenyl or (C_2-C_6)alkynyl.

[0118] In certain embodiments, R^3 is (C_2-C_8)alkyl, (C_3-C_8)alkenyl or (C_3-C_8)alkynyl.

[0119] In some embodiments, R^3 is aryl or heteroaryl.

[0120] In certain preferred embodiments, R^3 is tetrazolyl, thiazolyl, pyrazolyl, isoxazolyl, oxazolyl, pyrrolyl, thienyl or prop-1-ynyl.

[0121] In certain embodiments, R^3 is tetrazolyl, thiazolyl, or prop-1-ynyl.

[0122] R^4 is hydrogen, cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl or (C_2-C_8)alkynyl.

[0123] Optionally, R^3 and R^4 are combined to form a 3-, 4-, 5-, 6- or 7-membered ring containing from zero to three heteroatoms selected from N, O and S. The ring formed by combining R^3 and R^4 may be a saturated or unsaturated ring.

[0124] In some embodiments, R^4 is hydrogen or methyl.

[0125] In preferred embodiments, R^4 is hydrogen.

[0126] In further preferred embodiments, R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)alkynyl or $-NR^8R^9$ and R^4 is hydrogen.

[0127] R^5 is hydrogen, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or (C_3-C_8)cycloalkyl.

[0128] R^6 is heteroaryl.

[0129] R^7 is hydrogen or (C_1-C_5)alkyl.

[0130] R^8 and R^9 are independently hydrogen, (C_1-C_5)alkyl, oxy(C_1-C_5)alkyl or carboxy(C_1-C_5)alkyl.

[0131] Optionally, R^8 and R^9 are combined to form a 4-, 5-, 6- or 7-membered ring containing the nitrogen atom to which they are attached and from 0 to 2 additional heteroatoms selected from N, O and S. The ring formed by combining R^8 and R^9 may be a saturated, unsaturated or aromatic ring.

[0132] R^{10}, R^{11} and R^{12} are independently selected from hydrogen, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_3-C_8)cycloalkyl and (C_3-C_8)heterocycloalkyl.

[0133] Optionally, R^{10} and R^{11} are combined to form a 4-, 5-, 6- or 7-membered ring containing the nitrogen atom to which they are attached and from 0 to 2 additional heteroatoms selected from N, O and S. The ring formed by combining R^{10} and R^{11} may be a saturated, unsaturated or aromatic ring.

[0134] R^{13} is aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_3-C_8)cycloalkyl or (C_3-C_8)heterocycloalkyl.

[0135] The subscripts m and n are independently 0, 1 or 2.

[0136] The subscript p is 1 or 2.

[0137] In some embodiments, P is an aromatic ring or a heteroaromatic ring, X is CR^3R^4 and R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or $-NR^8R^9$.

[0138] In some embodiments, A is $-CO_2H$, X is CR^3R^4 and R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or $-NR^8R^9$.

[0139] In certain embodiments, when P and M are benzene, at least two of L^2, X and L^3 are other than CH_2.

[0140] In certain embodiments, the compounds of formula I do not include 3-(4-(4-methoxybenzyloxy)phenyl)pent-4-ynoic acid; β-ethenyl-4-phenylmethoxy-benzenepropanoic acid; 4-(2-quinolinylmethoxy)-β-[4-(2-quinolinylmethoxy)phenyl]-benzenepropanoic acid; N-[4-(benzoylamino)phenyl]-N-phenyl-glycine; 3-(4-(isopentyloxy)benzamido)-3-phenylpropanoate; 3-(4-isobutoxybenzamido)-3-phenylpropanoate; (*R*)-2-((*1R,4R*)-4-isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid; (*R*)-3-(4-(benzyloxy)phenyl)-2-(tert-butoxycarbonyl)propanoic acid; 3-(4-chlorophenyl)-3-(furan-2-carboxamido)propanoic acid; 3-(3,4-dimethoxyphenyl)-3-(furan-2-carboxamido)propanoic acid; 3-(4-chlorobenzamido)-3-(4-(dimethylamino)phenyl)propanoic acid; 3-(2-(2-(3,4-dimethylphenoxy)ethylthio)-1*H*-benzo[d]imidazol-1-yl)propanoic acid; {2-Bromo-4-[(3,4-dichloro-phenyl)-hydrazonomethyl]-6-ethoxy-phenoxy}-acetic acid; 2-(4-(2-(2-(4-chlorophenyl)furan-5-carboxamido)ethyl)phenoxy)-2-methylpropanoic acid; 5-(3-(3,4-dimethoxyphenyl)-5-(2-fluorophenyl)-4,5-dihydropyrazol-1-yl)-5-oxopentanoic acid; 2-(2-(3-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-2-methyl-4-oxo-4*H*-chromen-7-yloxy)acetamido)acetic acid; 3-(4'-Bromo-biphenyl-4-yl)-4-phenyl-butyric acid; 3-(4'-Bromo-biphenyl-4-yl)-3-phenylsulfanyl-propionic acid; 3-(5-(2-chloro-6-fluoro-4-(trifluoromethyl)phenoxy)-2,4-dinitrophenyl)propanoic acid; 3-(3-(2-chloro-4-(trifluoromethyl)phenoxy)phenyl)propanoic

acid; 3-(4-(4-methoxybenzyloxy)phenyl)pent-4-ynoic acid; or 3-(4-(4-methoxybenzyloxy)phenyl)-5-(trimethylsilyl)pent-4-ynoic acid, salts thereof, or esters thereof.

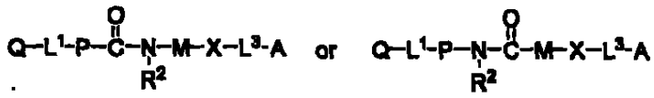
[0141] In certain embodiments, it is to be understood that compounds of formula I do not include compounds wherein P is a 1,2-azole ring when Q is aryl or heteroaryl, L^1 is a bond, M is a monocyclic aromatic ring, X is $N(R^5)$, O or $S(O)_m$, and A contains a carbonyl group.

[0142] In certain embodiments, it is to be understood that compounds of formula I do not include compounds wherein P is furan or thiophene when Q is aryl, L^1 is a bond, M is an aromatic ring, X is CR^3R^4, O or $S(O)_m$ and A contains a carbonyl group.

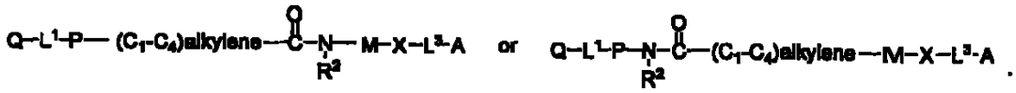
[0143] The compounds of the invention include pharmaceutically acceptable salts, solvates or prodrugs thereof.

[0144] In certain embodiments, ester prodrugs are preferred.

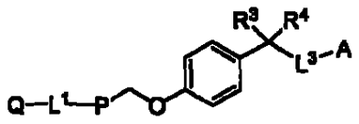
[0145] Those of skill in art will understand that, unless otherwise indicated, divalent groups such as $C(O)N(R^2)$, $SO_2N(R^2)$,$(C_1\text{-}C_4)$alkylene-$C(O)N(R^2)$ and the like, both possible orientations of the groups are permitted. For example, in formula I where L^2 is $C(O)N(R^2)$, the carbon atom may be attached to P or to M, as shown:



As another example, in formula I where L^2 is $(C_1\text{-}C_4)$alkylene-$C(O)N(R^2)$ in formula Ia, the alkylene group may be attached to P or to M, as shown:



[0146] In certain embodiments, the present invention provides a compound having the formula (Ia):



Ia

where Q, L^1, P, L^3, A R^3 and R^4 are as defined with regard to formula I above.

[0147] In some embodiments of formula Ia, Q is substituted or unsubstituted benzene, and L^1 is a bond, $(C_1\text{-}C_4)$alkylene, O or $S(O)_m$.

[0148] In some embodiments, P is selected from the group consisting of benzene, naphthalene, pyrrole, imidazole, pyrazine, oxazole, thiazole, pyridine, pyrimidine,

pyridazine, benzothiazole, purine, benzimidazole, indole, indazole, carbazole, carboline, isoquinoline, quinoxaline and quinoline.

[0149] In certain embodiments where P is benzene, Q is hydrogen, aryl, heteroaryl or $(C_1\text{-}C_6)$alkyl, and L^1 is a bond, $(C_1\text{-}C_4)$alkylene, O or $S(O)_m$.

[0150] In some embodiments, L^3 is $(C_1\text{-}C_5)$alkylene. In certain embodiments, L^3 is methylene.

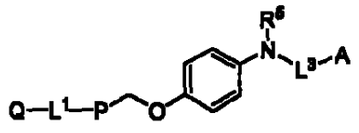
[0151] In certain embodiments, R^3 is cyano, aryl, heteroaryl, $(C_2\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$alkenyl, $(C_3\text{-}C_8)$alkynyl, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$, $-NR^{12}C(O)R^{13}$ or $-NR^{12}S(O)_pR^{13}$ and R^4 is hydrogen, cyano, aryl, heteroaryl, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl or $(C_2\text{-}C_8)$alkynyl.

[0152] In certain embodiments, R^3 is cyano, an unsubstituted aryl or heteroaryl monocyclic ring, $(C_2\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$alkenyl, $(C_3\text{-}C_8)$alkynyl, or $-C(O)NR^{10}R^{11}$, R^4 is hydrogen, and P is selected from the group consisting of benzene, naphthalene, pyrrole, imidazole, pyrazine, oxazole, thiazole, pyridine, pyrimidine, pyridazine, benzothiazole, purine, benzimidazole, indole, indazole, carbazole, carboline, isoquinoline, quinoxaline and quinoline.

[0153] In some embodiments, R^3 is cyano, an unsubstituted aryl or heteroaryl monocyclic ring, $(C_3\text{-}C_8)$alkenyl, $(C_3\text{-}C_8)$alkynyl, $-C(O)NR^{10}R^{11}$, R^4 is hydrogen, and L^3 is methylene.

[0154] In certain embodiments, Q is aryl, heteroaryl, $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$heteroalkyl, L^1 is a bond, $(C_1\text{-}C_4)$alkylene, $(C_2\text{-}C_4)$heteroalkylene, $S(O)_m$, $N(R^1)$, $(C_1\text{-}C_4)$alkylene-$SO_2N(R^2)$, $(C_1\text{-}C_4)$alkylene-$N(R^2)SO_2$ or $C(O)N(R^2)$, P is selected from the group consisting of benzene, naphthalene, pyrrole, imidazole, pyrazine, oxazole, thiazole, pyridine, pyrimidine, pyridazine, benzothiazole, purine, benzimidazole, indole, indazole, carbazole, carboline, isoquinoline, quinoxaline and quinoline, R^3 is cyano, an unsubstituted aromatic or heteroaromatic monocyclic ring, $(C_2\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$alkenyl, $(C_3\text{-}C_8)$alkynyl, or $-C(O)NR^{10}R^{11}$, R^4 is hydrogen, and L^3 is methylene.

[0155] In certain embodiments, the present invention provides a compound having the formula (Ib):



Ib

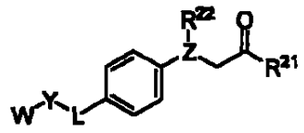
where Q, L^1, P, L^3, A and R^3 are as defined with regard to formula I above.

[0156] In some embodiments of formula Ib, P is selected from the group consisting of benzene, naphthalene, pyrrole, imidazole, pyrazine, oxazole, thiazole, furan, thiophene,

pyridine, pyrimidine, pyridazine, benzothiazole, purine, benzimidazole, indole, indazole, carbazole, carboline, isoquinoline, quinoxaline and quinoline.

[0157] In certain embodiments, R^5 is an unsubstituted or substituted benzene.

[0158] In another aspect, the present invention provides a compound having the formula (II):



II

where R^{21}, R^{22}, Z, L, Y and W are defined below.

[0159] R^{21} is -H, -OH, $-NHS(O_2)CH_3$, heteroaryl, or -NH-heteroaryl.

[0160] In certain embodiments, R^{21} is -OH, $-NHS(O_2)CH_3$, -NH-tetrazolyl, or tetrazolyl.

[0161] In certain embodiments, R^{21} is tetrazolyl, pyrimidinyl, or pyridinyl.

[0162] In preferred embodiments, R^{21} is -OH, or a salt thereof.

[0163] R^{22} is -H, $-(C_2-C_8)$alkyl, $-(C_3-C_8)$alkenyl, $-NR^{23}R^{24}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C\equiv N$, or $-C\equiv C-R^{25}$.

[0164] In some embodiments, R^{22} is $-(C_2-C_8)$alkyl, $-(C_3-C_8)$alkenyl, $-NR^{23}R^{24}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C\equiv N$, or $-C\equiv C-R^{25}$.

[0165] In certain embodiments, R^{22} is $-(C_2-C_3)$alkyl, $-NR^{23}R^{24}$, substituted or unsubstituted phenyl, $-CH=C(CH_3)_2$, $-CH_2CH=CH_2$, or $-C\equiv C-R^{25}$.

[0166] In other embodiments, R^{22} is unsubstituted aryl or unsubstituted heteroaryl. In other embodiments, R^{22} is substituted aryl and the substitution onto the aryl is unsubstituted $-(C_1-C_5)$alkyl, $-(C_1-C_5)$oxyalkyl, or -halo(C_1-C_5)alkyl.

[0167] In certain embodiments, R^{22} is $-C\equiv C-R^{25}$ and R^{25} is $-(C_1-C_5)$alkyl having 0 or 1 heteroatoms.

[0168] In preferred embodiments, R^{22} is $-C\equiv CCH_3$.

[0169] In some embodiments, R^{22} is $-CH=C(CH_3)_2$, or $-CH_2CH=CH_2$.

[0170] R^{23} and R^{24} are independently -H, $-(C_1-C_5)$alkyl, or $-(C_1-C_5)$oxyalkyl.

[0171] R^{25} is -H, $-(C_1-C_5)$alkyl, -hetero(C_1-C_5)alkyl, $-(C_1-C_5)$oxyalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

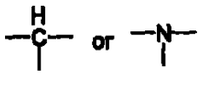
[0172] In some embodiments, R^{25} is $-(C_1-C_5)$alkyl,$-(C_1-C_5)$oxyalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0173] In some embodiments, R^{25} is -hetero(C_1-C_5)alkyl that does not contain Si.

[0174] In some embodiments, R^{25} is unsubstituted phenyl.

[0175] In other embodiments, R^{25} is a substituted phenyl.

[0176] In preferred embodiments, R^{25} is methyl.

[0177] Z is  . In some embodiments, Z is nitrogen. In other embodiments, Z is carbon.

[0178] L is -O-, -S-, or -N(R^{26})-. In some embodiments, L is -O-. In other embodiments, L is -S-. In other embodiments, L is -N(R^{26})-.

[0179] In certain embodiments, Z is nitrogen and L is -N(R^{26})-.

[0180] R^{26} is -H , -(C_1-C_5)alkyl, substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0181] In certain embodiments, R^{26} is -H , substituted or unsubstituted aryl(C_1-C_{10})alkyl or substituted or unsubstituted aryl.

[0182] In some embodiments, R^{26} is -H.

[0183] In other embodiments, R^{26} is substituted or unsubstituted phenyl.

[0184] Y is absent or is -CH_2- , -CH_2CH_2- , -CH=CH- , -C(O)CH_2- , -C(O)CH_2CH_2- , -C(O)CH=CH- , -S(O_2)-, -S(O_2)CH_2- , -S(O_2)CH_2CH_2- , -S(O_2)CH=CH-, or -C(O)-.

[0185] In certain embodiments, Y is -CH_2- , -CH_2CH_2- , -CH=CH- , -C(O)CH_2- , -C(O)CH_2CH_2- , -C(O)CH=CH- , -S(O_2)-, -S(O_2)CH_2- , -S(O_2)CH_2CH_2- , -S(O_2)CH=CH-.

[0186] In some embodiments Y is -CH_2-.

[0187] In some embodiments L is -O- or -S-, and Y is -CH_2-, -CH_2CH_2-.

[0188] W is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0189] For example and without limitation, W can be a ring such as a benzene, naphthalene, pyrrole, pyrazole, imidazole, pyrazine, oxazole, isoxazole, thiazole, furan, thiophene, pyridine, pyrimidine, pyridazine, benzothiazole, purine, benzimidazole, benzoxazole, triazole, oxadiazole, thiadiazole, benzooxadiazole, dibenzofuran, indole, indazole, carbazole, carboline, isoquinoline, quinoxaline or quinoline., and so forth.

[0190] In some embodiments, W is a substituted or unsubstituted monocyclic aryl ring or a substituted or unsubstituted monocyclic heteroaryl ring.

[0191] In some embodiments, W is substituted or unsubstituted fused aryl bicyclic ring or substituted or unsubstituted fused heteroaryl bicyclic ring. In certain embodiments,

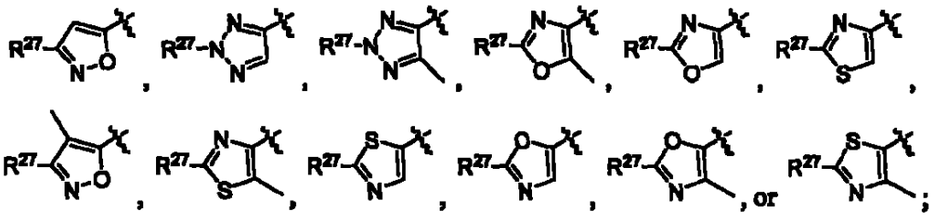
W is an 8- to 11-membered fused aryl bicyclic ring or an 8- to 11-membered fused heteroaryl bicyclic ring.

[0192] In other embodiments, W is a substituted or unsubstituted 5- or 6-membered aryl ring or substituted or unsubstituted 5- or 6-membered heteroaryl ring.

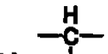
[0193] In certain embodiments where W is a substituted aryl or heteroaryl ring, the substituting group can be a halogen, substituted or unsubstituted (C_1-C_{10})alkyl, substituted or unsubstituted hetero(C_1-C_{10})alkyl, substituted or unsubstituted halo(C_1-C_{10})alkyl, substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0194] In some embodiments, W is a 5-membered ring having two or more heteroatoms.

[0195] In certain embodiments, W is a 5-membered ring selected from the group consisting of



and R^{27} is substituted or unsubstituted (C_1-C_{10})alkyl, substituted or unsubstituted hetero(C_1-C_{10})alkyl, substituted or unsubstituted halo(C_1-C_{10})alkyl, substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0196] In some embodiments where Z is  , R^{21} is -OH, L is -O-, -S-, or -N(R^{26})-, and Y is -CH_2- , -CH_2CH_2- , -CH=CH- , -C(O)CH_2- , -C(O)CH_2CH_2- , -C(O)CH=CH- , or -C(O)-, then W is not furan or thiophene.

[0197] In certain embodiments, W is a substituted or unsubstituted phenyl.

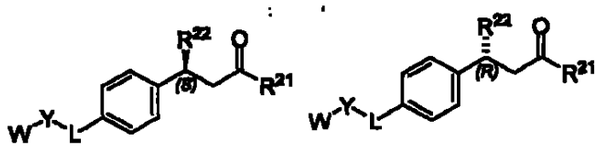
[0198] In some embodiments, Z is carbon and R^{22} is -(C_2-C_8)alkyl, -(C_3-C_8)alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or —C≡C-R^{25} .

[0199] In some embodiments where Z is carbon, W is a benzene ring, R^{22} is —C≡C-R^{25} , R^{25} is -hetero(C_1-C_5)alkyl, L is -O- or -S-, then any heteroatom in R^{25} is not Si.

[0200] In some embodiments, where R^{21} is -OH, L is -O-, Y is -CH_2-, and W is *para*-methoxyphenyl, R^{22} is —C≡C-R^{25} , then R^{25} is not -H.

[0201] In certain embodiments, where L is -N(R^{26})-, Z is nitrogen, R^{22} is a phenyl, R^{26} is hydrogen or a phenyl and W is a phenyl, then Y is not -C(O)-.

[0202] It will be apparent that in embodiments of formula II where Z is  and R^{22} is -(C_2-C_8)alkyl, -(C_3-C_8)alkenyl, -$NR^{23}R^{24}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C\equiv N$, or $-C\equiv C-R^{25}$, then the carbon at Z is a chiral carbon as shown:



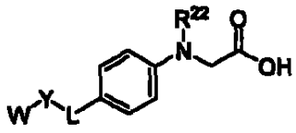
Thus, a compound of the invention can be an *S*-enantiomer, an *R*-enantiomer, or a mixture of both an *S*-enantiomer and an *R*-enantiomer.

[0203] In preferred embodiments, a compound is an *S*-enantiomer.

[0204] In certain embodiments, R^{21} is -OH; L is -O-, or -S-; and Y is $-CH_2-$, or $-CH_2CH_2-$.

[0205] In some embodiments where Z is nitrogen, then W is not a 1,2-azole ring.

[0206] In certain other embodiments, the present invention provides a compound having the formula (III):



III

or a pharmaceutically acceptable salt, hydrate or prodrug thereof, where R^{22}, L, Y, and W are as defined with regard to formula II above.

[0207] In some embodiments, R^{22} is -H, -(C_2-C_3)alkyl, -$NR^{23}R^{24}$, or substituted or unsubstituted phenyl.

[0208] In certain embodiments, L is -O-, -S-, or -$N(R^{26})$-.

[0209] In some embodiments, R^{26} is -H, substituted or unsubstituted aryl(C_1-C_{10})alkyl or substituted or unsubstituted aryl.

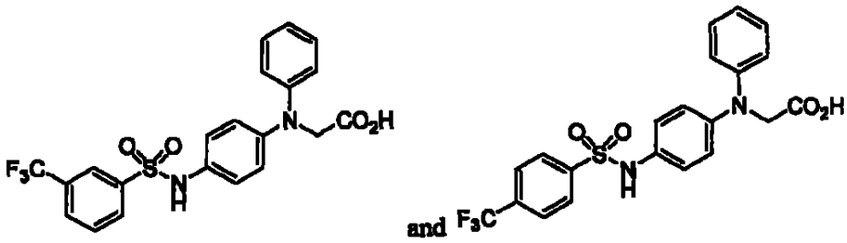
[0210] In some embodiments, Y is $-CH_2-$, $-CH_2CH_2-$, -CH=CH-, $-C(O)CH_2-$, $-C(O)CH_2CH_2-$, -C(O)CH=CH-, $-S(O_2)CH_2-$, $-S(O_2)CH_2CH_2-$, -C(O)-, or $-S(O_2)CH=CH-$.

[0211] In some embodiments, W is a substituted or unsubstituted 5- or 6-membered aryl ring or substituted or unsubstituted 5- or 6-membered heteroaryl ring with the proviso if R^{22} is phenyl, L is -O-, -S-, or -$N(R^{26})$-, and W is a benzene ring then Y may not be -C(O)-.

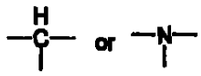
[0212] In some embodiments, L is -$N(R^{26})$-, and R^{26} is hydrogen.

[0213] In certain embodiments, W is not a 1,2-azole ring.

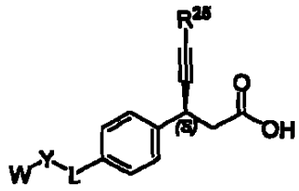
[0214] In other embodiments, the compound of formula III is selected from the group consisting of



or a salt thereof.

[0215] In further embodiments, the present invention provides a compound of formula II or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{21} is -OH, $-NHS(O_2)CH_3$, -NH-tetazolyl, or tetrazolyl; R^{22} is $-(C_2-C_8)$alkyl, $-NR^{23}R^{24}$, substituted or unsubstituted phenyl, $-CH=C(CH_3)_2$, $-CH_2CH=CH_2$, or $-C\equiv C-R^{25}$; R^{23} and R^{24} are independently -H, $-(C_1-C_5)$alkyl, or $-(C_1-C_5)$oxyalkyl; R^{25} is -H, $-(C_1-C_5)$alkyl, $-(C_1-C_5)$oxyalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; Z is  ; L is -O-, -S-, or $-N(R^{26})-$; R^{26} is -H , $-(C_1-C_5)$alkyl , substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; Y is $-CH_2-$, $-CH_2CH_2-$, -CH=CH- , $-C(O)CH_2-$, $-C(O)CH_2CH_2-$, -C(O)CH=CH- , $-S(O_2)CH_2-$, $-S(O_2)CH_2CH_2-$, or $-S(O_2)CH=CH-$; and W is a substituted or unsubstituted 5- or 6- membered aryl ring or substituted or unsubstituted 5- or 6- membered heteroaryl ring.

[0216] In certain embodiments, the present invention provides compounds according to formula (IV):



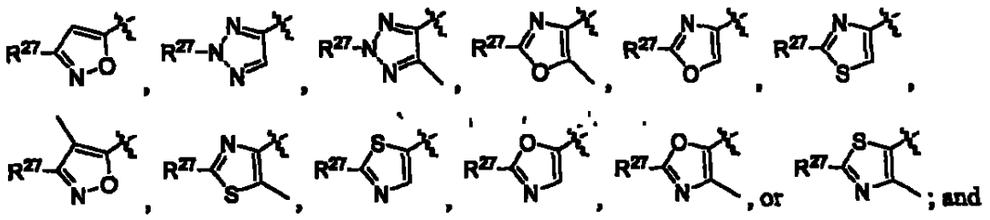
IV

or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein R^{25}, W, Y, and L are defined as above in paragraph [0215].

[0217] In some embodiments, R^{25} is methyl.

[0218] In some embodiments, L is -O- or -S- and Y is $-CH_2-$ or $-CH_2CH_2-$.

[0219] In some embodiments, W is a 5-membered ring selected from the group consisting of



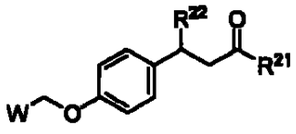
; and

R^{27} is substituted or unsubstituted (C_1-C_{10})alkyl, substituted or unsubstituted hetero(C_1-C_{10})alkyl, substituted or unsubstituted halo(C_1-C_{10})alkyl, substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0220] In certain embodiments, R^{27} is substituted phenyl.

[0221] In other embodiments, R^{27} is unsubstituted phenyl.

[0222] In some embodiments, the present invention provides compounds according to formula (V):



V

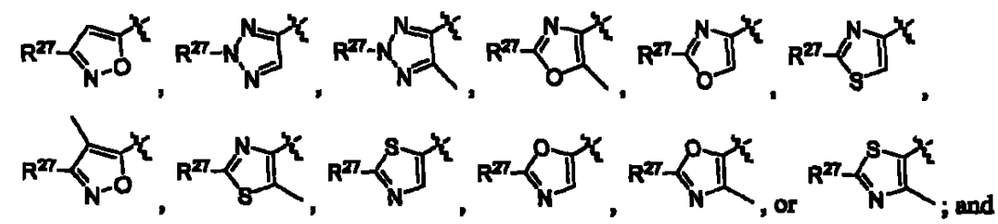
or a pharmaceutically acceptable salt, hydrate or prodrug thereof, where R^{21}, R^{22} and W are defined as above, paragraph [0215].

[0223] In some embodiments, R^{21} is -OH, or a salt thereof.

[0224] In some embodiments, W is substituted phenyl.

[0225] In certain embodiments, W is substituted with substituted or unsubstituted (C_1-C_{10})alkyl, substituted or unsubstituted hetero(C_1-C_{10})alkyl, substituted or unsubstituted halo(C_1-C_{10})alkyl, substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0226] In other embodiments, W is a 5-membered ring selected from the group consisting of



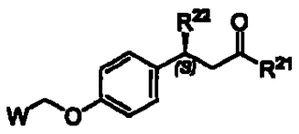
; and

R^{27} is hydrogen, substituted or unsubstituted (C_1-C_{10})alkyl, substituted or unsubstituted

heteroaryl(C_1-C_{10})alkyl, substituted or unsubstituted halo(C_1-C_{10})alkyl, substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0227] In certain embodiments, a compound of formula V is a racemate. In certain embodiments, the compound of formula V comprises a mixture of (*S*) and (*R*) enantiomers.

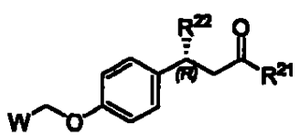
[0228] In certain embodiments, the present invention provides compounds having the formula (Va):



Va

where R^{21}, R^{22} and W are defined above in formula V.

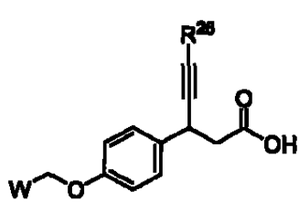
[0229] In other embodiments, the compound has the formula (Vb):



Vb

where R^{21}, R^{22} and W are defined above in formula V.

[0230] In certain embodiments, the present invention provides compounds according to formula (VI):

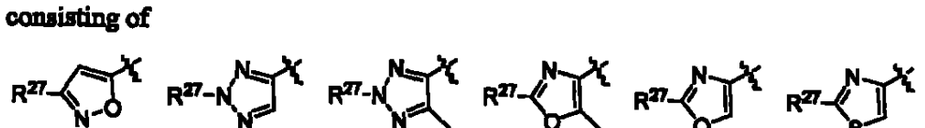


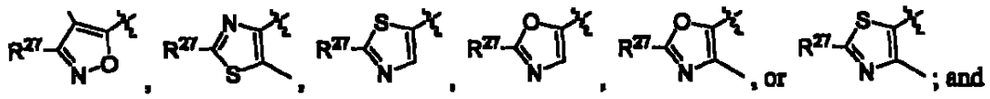
VI

or a pharmaceutically acceptable salt, solvate or prodrug thereof, where R^{25} and W are defined in paragraph **[0215]** above.

[0231] In some embodiments, R^{25} is methyl.

[0232] In some embodiments, W is a 5-membered ring selected from the group consisting of

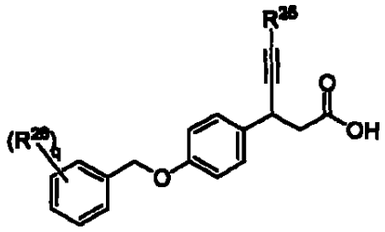




R^{27} is hydrogen, substituted or unsubstituted (C_1-C_{10})alkyl, substituted or unsubstituted hetero(C_1-C_{10})alkyl, substituted or unsubstituted halo(C_1-C_{10})alkyl, substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0233] In certain embodiments, the compound of formula VI comprises a stereomerically pure *S*-enantiomer. In other embodiments, the compound of formula VI comprises a stereomerically pure *R*-enantiomer. In yet other embodiments, the compound of formula VI comprises a mixture of *S*- and *R*-enantiomers.

[0234] In certain embodiments, the present invention provides compounds according to formula (VII):



VII

or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein each R^{28} is independently selected from the group consisting of substituted or unsubstituted (C_1-C_{10})alkyl, substituted or unsubstituted hetero(C_1-C_{10})alkyl, substituted or unsubstituted halo(C_1-C_{10})alkyl, substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, the subscript q is an integer from 0 to 5, and R^{25} is as defined above in paragraph [0215].

[0235] In some embodiments, the subscript q is 0, 1, or 2.

[0236] In other embodiments, R^{28} is a methoxy, ethoxy, trihalomethyl, methyl, halo, or cyano group and the subscript q is 1 or 2.

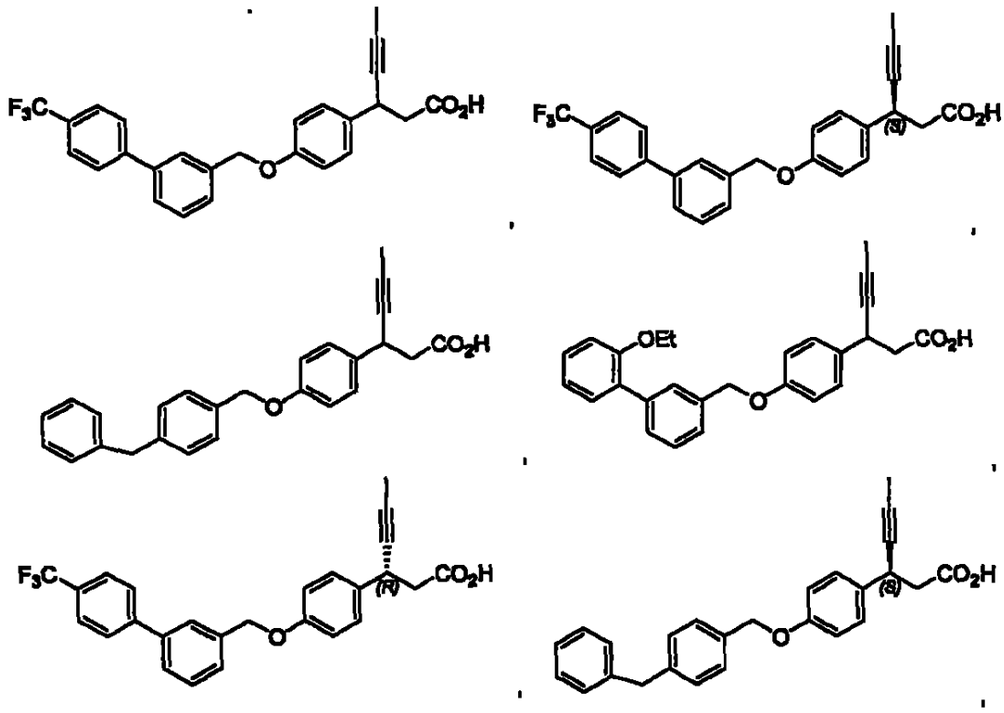
[0237] In other embodiments, R^{28} is a phenyl, methoxyphenyl, methylphenyl, trihalomethylphenyl, benzyl, phenoxy, ethoxyphenyl, cyanophenyl, halophenyl, halobenzyl, pyridyl, methoxybenyl, or pyryl group and the subscript q is 1 or 2.

[0238] In other embodiments, R^{25} is methyl.

[0239] In certain embodiments, the compound of formula VII comprises a stereomerically pure *S*-enantiomer. In other embodiments, the compound of formula VII

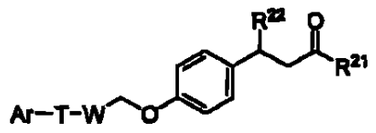
comprises a stereomerically pure *R*-enantiomer. In yet other embodiments, the compound of formula VII comprises a mixture of *S*- and *R*-enantiomers.

[0240] In other embodiments, the formula is selected from the group consisting of



and salts thereof.

[0241] In certain embodiments, the present invention provides compounds according to formula (VIII):



VIII

or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{21}, R^{22} and W are defined in paragraph [0215] above and Ar and T are defined below.

[0242] T is a direct bond, $(C_1$-$C_5)$alkylene, hetero$(C_1$-$C_5)$alkylene, O, C(O)-$(C_3$-$C_7)$heterocycloalkylene, $(C_1$-$C_4)$alkylene-SO_2NH, or $(C_1$-$C_4)$alkylene-$NHSO_2$.

[0243] In some embodiments, T is a direct bond, substituted or unsubstituted $(C_1$-$C_5)$alkyl or substituted or unsubstituted hetero$(C_1$-$C_5)$alkyl.

[0244] Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0245] In certain embodiments, Ar is a benzene, naphthalene, pyrrole, pyrazole, imidazole, pyrazine, oxazole, isoxazole, thiazole, furan, thiophene, pyridine, pyrimidine, pyridazine, benzothiazole, purine, benzimidazole, benzoxazole, triazole, oxadiazole, thiadiazole, benzooxadiazole, dibenzofuran, indole, indazole, carbazole, carboline, isoquinoline, quinoxaline or quinoline.

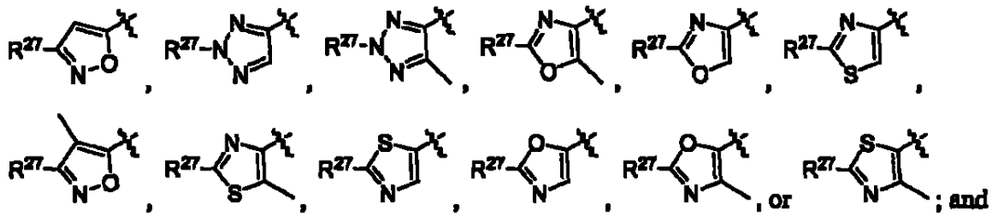
[0246] In some embodiments, R^{22} is $-C\equiv C-CH_3$.

[0247] In some embodiments, R^{21} is -OH.

[0248] In certain embodiments, T is a direct bond and Ar is a substituted or unsubstituted benzene ring.

[0249] In some embodiments, W is phenyl.

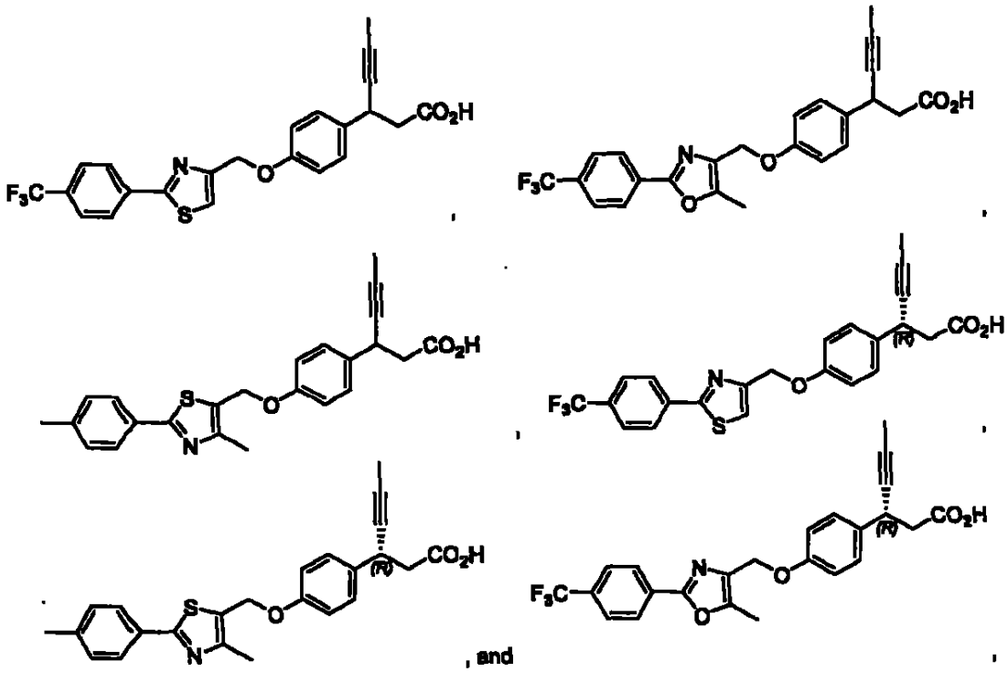
[0250] In other embodiments, W is a 5-membered ring selected from the group consisting of



; and R^{27} is Ar-T-.

[0251] In certain embodiments, the compound of formula VIII comprises a stereomerically pure *S*-enantiomer. In other embodiments, the compound of formula VIII comprises a stereomerically pure *R*-enantiomer. In yet other embodiments, the compound of formula VIII comprises a mixture of *S*- and *R*-enantiomers.

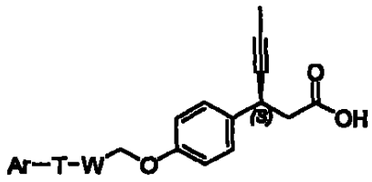
[0252] In certain embodiments, the compound is selected from the group consisting of:



, and

or a salt thereof.

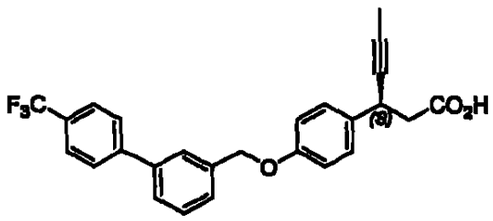
[0253] In certain embodiments, the present invention provides compounds according to formula (IX)



IX

or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein W, T and Ar are as defined above in formula VIII.

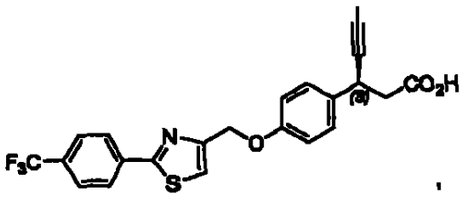
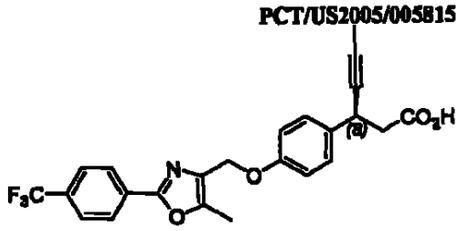
[0254] In some embodiments, the compound has the formula:

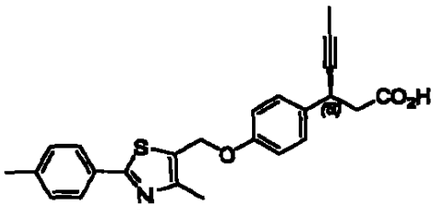


, or a salt thereof.

[0255] In an embodiment, the compound is selected from the group consisting of:

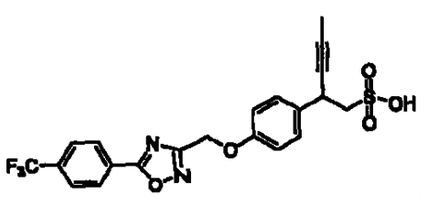
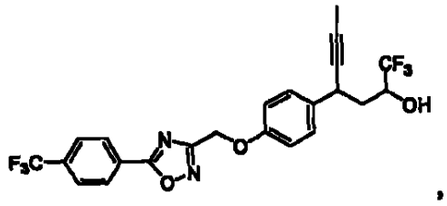
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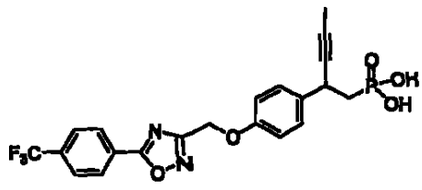
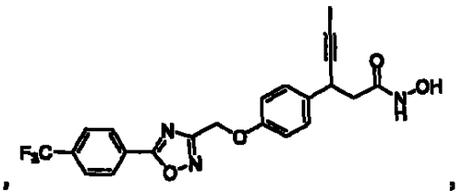


, and



or a salt thereof.

[0256] In certain embodiments, the present invention provides compounds, for example, of formula III, IV, VI, VII, or IX, that include a bioisostere of $-CO_2H$ in place of $-CO_2H$. For illustration, compounds that include a bioisostere of $-CO_2H$ in place of the $-CO_2H$ on examplary compound 27.1, described in the examples below, can include the following:


,

,


,

, and the

like, without limitation, as recognized by those of skill in the art. *See, e.g., The Practice of Medicinal Chemistry*, Wermuth, C.G., Ed., Academic Press: New York, 1996, incorporated herein by reference in its entirety.

[0257] In certain embodiments, the invention provides compounds according to the above formulas so long as the compound is not one of the following acids, or salt thereof, including:

3-(4-(4-methoxybenzyloxy)phenyl)pent-4-ynoic acid;

β-ethenyl-4-phenylmethoxy-benzenepropanoic acid;

4-(2-quinolinylmethoxy)-β-[4-(2-quinolinylmethoxy)phenyl]-benzenepropanoic acid;

N-[4-(benzoylamino)phenyl]-N-phenyl-glycine;

3-(4-(isopentyloxy)benzamido)-3-phenylpropanoate;

3-(4-isobutoxybenzamido)-3-phenylpropanoate;

(*R*)-2-((*1R,4R*)-4-isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid;

(*R*)-3-(4-(benzyloxy)phenyl)-2-(tert-butoxycarbonyl)propanoic acid;

3-(4-chlorophenyl)-3-(furan-2-carboxamido)propanoic acid;

3-(3,4-dimethoxyphenyl)-3-(furan-2-carboxamido)propanoic acid;

3-(4-chlorobenzamido)-3-(4-(dimethylamino)phenyl)propanoic acid;

3-(2-(2-(3,4-dimethylphenoxy)ethylthio)-1*H*-benzo[d]imidazol-1-yl)propanoic acid;

{2-Bromo-4-[(3,4-dichloro-phenyl)-hydrazonomethyl]-6-ethoxy-phenoxy}-acetic acid;

2-(4-(2-(2-(4-chlorophenyl)furan-5-carboxamido)ethyl)phenoxy)-2-methylpropanoic acid;

5-(3-(3,4-dimethoxyphenyl)-5-(2-fluorophenyl)-4,5-dihydropyrazol-1-yl)-5-oxopentanoic acid;

2-(2-(3-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-2-methyl-4-oxo-4*H*-chromen-7-yloxy)acetamido)acetic acid;

3-(4'-Bromo-biphenyl-4-yl)-4-phenyl-butyric acid;

3-(4'-Bromo-biphenyl-4-yl)-3-phenylsulfanyl-propionic acid;

3-(5-(2-chloro-6-fluoro-4-(trifluoromethyl)phenoxy)-2,4-dinitrophenyl)propanoic acid;

3-(3-(2-chloro-4-(trifluoromethyl)phenoxy)phenyl)propanoic acid;

3-(4-(4-methoxybenzyloxy)phenyl)pent-4-ynoic acid;

3-(4-(4-methoxybenzyloxy)phenyl)-5-(trimethylsilyl)pent-4-ynoic acid;

β,β-dimethyl-4-[[[4-methyl-2-[4-(trifluoromethyl)phenyl]-5-thiazolyl]methyl]thio]-benzenepropanoic acid; or

β-amino-4-[(4-bromo-2,5-dihydro-2-methyl-5-oxo-1-phenyl-1H-pyrazol-3-yl)methoxy]-3-methoxy-benzenepropanoic acid.

5.2.2 Preparation of the Compounds

[0258] The compounds of the invention can be prepared by a variety of synthetic or semisynthetic techniques. FIG. 1 and the Examples in Section 6 below provide a variety of synthesis routes to the compounds provided herein. Appropriate starting materials can be prepared by techniques known or apparent to those of skill in the art or the starting materials may be commercially available. One of skill in the art will understand that the synthetic routes can be modified to use different starting materials or alternative reagents and that suitable adjustments in conditions (*e.g.*, temperatures, solvents, etc.) can be made to accomplish the desired transformations. Additionally, one of skill in the art will recognize that protecting groups may be necessary for the preparation of certain compounds and will

be aware of these conditions compatible with a selected protecting group. Accordingly, the exemplary methods and the examples described herein are illustrative of the present invention and are not to be construed as limiting the scope thereof.

5.2.3 Compositions

[0259] In another aspect, the invention provides pharmaceutical compositions suitable for pharmaceutical use comprising one or more compounds of the invention and a pharmaceutically acceptable carrier, excipient or diluent.

[0260] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients (and in the specified amounts, if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant that the carrier or excipient is compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0261] In certain embodiments, the present invention provides a pharmaceutical composition comprising a compound of formula II, wherein R^{22} comprises an alkynyl containing Si, and where R^{21}, L, Y, and W are as defined above in formula II.

[0262] In some embodiments, the Si atom is substituted with up to three alkyl groups.

[0263] In some embodiments, R^{22} is $-C\equiv C-Si(CH_3)_3$.

[0264] Composition formulation may improve one or more pharmacokinetic properties (*e.g.*, oral bioavailability, membrane permeability) of a compound of the invention (herein referred to as the active ingredient).

[0265] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

[0266] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or

elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,256,108; 4,166,452 and 4,265,874 to form osmotic therapeutic tablets for control release.

[0267] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0268] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous 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.

[0269] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, 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, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0270] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, 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 sweetening, flavoring and coloring agents, may also be present.

[0271] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0272] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[0273] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0274] The pharmaceutical compositions may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating 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 materials are cocoa butter and polyethylene glycols.

[0275] For topical use, creams, ointments, jellies, solutions or suspensions, *etc.*, containing the compounds of the invention are employed. As used herein, topical application is also meant to include the use of mouthwashes and gargles.

[0276] The pharmaceutical compositions and methods of the invention may further comprise other therapeutically active compounds, as noted herein, useful in the treatment of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

5.2.4 Methods of Use

[0277] In another aspect, the invention provides methods of treating or preventing a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema, comprising administering to a subject in need thereof a therapeutically effective amount of a compound or composition of the invention.

[0278] In one embodiment, the disease or condition is type II diabetes.

[0279] In another aspect, the present invention provides a method for treating a disease or condition responsive to the modulation of GPR40 comprising administering to a subject in need thereof a therapeutically effective amount of a compound or composition of the invention.

[0280] In some embodiments, the disease or condition is selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia,

hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

[0281] In certain embodiments, the disease or condition is type II diabetes.

[0282] In some embodiments, the disease or condition is obesity.

[0283] In some embodiments, the disease or condition is hyptertension.

[0284] In some embodiments of administering the compounds or compositions or the invention, the compound or composition is administered orally.

[0285] In other embodiments, the compound or composition is administered parentally.

[0286] In other embodiments, the compound or composition is administered in combination with a second therapeutic agent.

[0287] In other embodiments, the second therapeutic agent is an insulin sensitizing agent, such as metformin or a thiazolidinedione, for example.

[0288] In another aspect, the invention provides methods of treating or preventing a disease or disorder responsive to modulation of GPR40 comprising administering to a subject having such a disease or disorder, a therapeutically effective amount of one or more of the subject compounds or compositions.

[0289] In yet another aspect, the invention provides methods of treating or preventing a GPR40-mediated condition, disease or disorder comprising administering to a subject having such a condition, disease or disorder, a therapeutically effective amount of one or more of the subject compounds or compositions.

[0290] In yet another aspect, the invention provides methods of modulating GPR40 comprising contacting a cell with one or more of the subject compounds or compositions.

[0291] For example, in some embodiments, a cell that constitutively expresses GPR40 is contacted with one or more of the subject compounds or compositions.

[0292] In certain embodiments, a cell to be contacted can be made to express or overexpress GPR40, for example, by expressing GPR40 from heterologous nucleic acid introduced into the cell or, as another example, by upregulating the expression of GPR40 from nucleic acid endogenous to the cell.

[0293] Depending on the disease to be treated and the subject's condition, the compounds of the invention may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (*e.g.*, transdermal, local)

routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. The invention also contemplates administration of the compounds of the invention in a depot formulation, in which the active ingredient is released over a defined time period.

[0294] In the treatment or prevention type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema or other conditions or disorders associated with GPR40, an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

[0295] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0296] The compounds of the invention can be combined or used in combination with other agents useful in the treatment, prevention, suppression or amelioration of the diseases or conditions for which compounds of the invention are useful, including type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular

disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema. Such other agents, or drugs, may be administered, by a route and in an amount commonly used therefor, simultaneously or sequentially with a compound of the invention. When a compound of the invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the invention is preferred. Accordingly, the pharmaceutical compositions of the invention include those that also contain one or more other active ingredients or therapeutic agents, in addition to a compound of the invention.

[0297] Examples of other therapeutic agents that may be combined with a compound of the invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) cholesterol lowering agents such as HMG-CoA reductase inhibitors (*e.g.*, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and other statins), bile acid sequestrants (*e.g.*, cholestyramine and colestipol), vitamin B_3 (also known as nicotinic acid, or niacin), vitamin B_6 (pyridoxine), vitamin B_{12} (cyanocobalamin), fibric acid derivatives (*e.g.*, gemfibrozil, clofibrate, fenofibrate and benzafibrate), probucol, nitroglycerin, and inhibitors of cholesterol absorption (*e.g.*, beta-sitosterol and acylCoA-cholesterol acyltransferase (ACAT) inhibitors such as melinamide), HMG-CoA synthase inhibitors, squalene epoxidase inhibitors and squalene synthetase inhibitors; (b) antithrombotic agents, such as thrombolytic agents (*e.g.*, streptokinase, alteplase, anistreplase and reteplase), heparin, hirudin and warfarin derivatives, β-blockers (*e.g.*, atenolol), β-adrenergic agonists (*e.g.*, isoproterenol), ACE inhibitors and vasodilators (*e.g.*, sodium nitroprussaide, nicardipine hydrochloride, nitroglycerin and enaloprilat); and (c) anti-diabetic agents such as insulin and insulin mimetics, sulfonylureas (*e.g.*, glyburide, meglinatide), biguanides, *e.g.*, metformin (*Glucophage*®), α-glucosidase inhibitors (acarbose), insulin sensitizers, *e.g.*, thiazolidinone compounds, rosiglitazone (*Avandia*®), troglitazone (*Rezulin*®), ciglitazone, pioglitazone (*Actos*®) and englitazone.

[0298] The weight ratio of the compound of the invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Combinations of a compound of the invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[0299] In another aspect, the present invention provides a method for modulating circulating insulin concentration in a subject, comprising administering a compound or composition of the invention.

[0300] In some embodiments, the insulin concentration is increased.

[0301] In other embodiments, the insulin concentration is decreased.

[0302] In certain embodiments, a compound, or composition comprising a compound, according to formula II wherein R^{22} comprises an alkylyl containing Si, and where R^{21}, L, Y, and W are as defined above in formula II, may be used.

[0303] In some embodiments, the Si atom is substituted with up to three alkyl groups.

[0304] In some embodiments, R^{22} is $-C\equiv C-Si(CH_3)_3$.

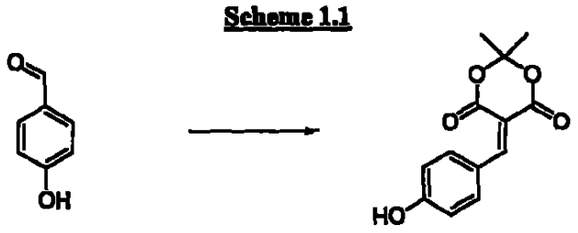
[0305] The following examples are offered by way of illustration and are not intended to limit the scope of the invention. Those of skill in the art will readily recognize a variety of noncritical parameters that could be modified to yield essentially similar results.

6. EXAMPLES

6.1 Example 1

[0306] This example illustrates the preparation of *(3S)*-3-(4-Hydroxy-phenyl)-hex-4-ynoic acid methyl ester.

Scheme 1.1



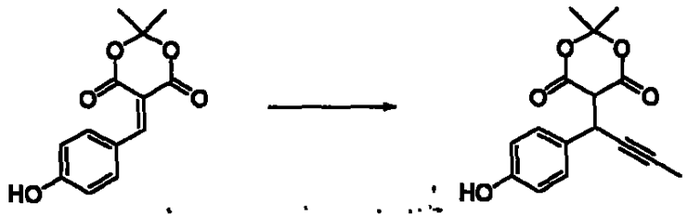
1.1

[0307] **5-(4-Hydroxy-benzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.1).** Condensation with Meldrum's acid is carried out according to the method of Bigi *et. al.* (2001) *Tetr. Lett.* 42: 5203-5205. A 2L pear-shaped flask was charged with 4-hydroxybenzaldehyde (50 g, 409 mmol) and water (400 mL). The flask was placed in a water bath at 75 °C and Meldrum's acid (62 g, 430 mmol) was added as a slurry in 400 mL of water. The reaction mixture was agitated for 2h then cooled in an ice bath for 2 hours. The product was collected by filtration and rinsed with cold water. After drying thoroughly, 95 g (94%) of adduct 1.1 was obtained as a fine yellow powder. ^{1}H NMR(500MHz)(DMSO-d_6) δ 9.75 (br s, 1H); 8.27 (s, 1H); 8.24 (d, 2H, *J*=10 Hz); 6.98 (d, 2H, *J*=10 Hz);.1.76 (s, 6H). MS ESI (pos.) m/e: 519.0 (2M + Na).

59

59

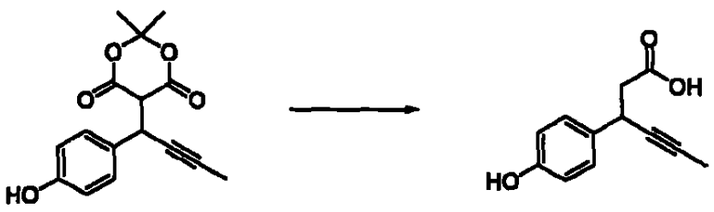
Scheme 1.2



1.1 1.2

[0308] (+/-)-5-[1-(4-Hydroxy-phenyl)-but-2-ynyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.2). An oven-dried 3L 3-neck flask equipped with a mechanical stirrer, nitrogen inlet, nitrogen outlet and placed in a room-temperature water bath. After purging with nitrogen for 20 minutes, a solution of 1-propynylmagnesium bromide in THF (0.5 N, 600 mL) was added by cannula. In a separate oven-dried and nitrogen-flushed 500 mL RB flask, compound 1.1 (35 g, 142 mmol) was dissolved in anhydrous THF (350 mL) with gentle warming. The solution of 1.1 was then added over 15 minutes. Over the course of the addition, the reaction mixture changed to a thick, yellow suspension. After the addition was complete, the reaction mixture was stirred for 15 minutes and then quenched with aqueous NH_4Cl (0.6N, 750 mL) and diluted with hexanes (800 mL). The layers were separated and the organic layer discarded. The aqueous layer was acidified to pH ~2 with saturated aqueous $KHSO_4$ and extracted with ethyl acetate (2 x 400 mL). The combined extracts were washed with saturated brine, dried over $MgSO_4$, filtered, and concentrated to a light yellow solid (37 g, 91%). ^1H NMR(500MHz)(acetone-d_6) δ 8.26 (s, 1H); 7.39 (d, 2H, J=8.5 Hz); 6.76 (d, 2H, J=8.4 Hz); 4.73 (br s, 1H); 4.46 (d, 1H, J=2.4 Hz); 1.82 (s, 3H); 1.81 (s, 3H); 1.64 (s, 3H). MS ESI (pos.) m/e: 599.0 (2M + Na).

Scheme 1.3

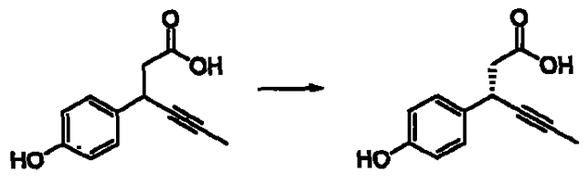


1.2 1.3

[0309] (+/-)-3-(4-Hydroxy-phenyl)-hex-4-ynoic acid (1.3). A 1L RB flask was charged with compound 1.2 (37 g), diethyl ketone (160 mL), and water (80 mL). The suspension was heated to reflux for 48h. After cooling, the aqueous layer was saturated

with $NaCl_{(s)}$ and separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated to a light brown oil which was crystallized from hot ethyl acetate:hexanes (1:2). After collecting and drying, the product was obtained as an off-white powder (20.3 g, 77%). ^{1}H NMR(500MHz)(DMSO-d_6) δ 12.2 (s, 1H); 9.27 (s, 1H); 7.12 (d, 2H, J=8.5 Hz); 6.67 (d, 2H, J=8.6 Hz); 3.87 (m, 1H); 2.54 (m, 2H); 1.82 (d, 3H, J=2.4 Hz). MS ESI (pos.) m/e: 205.1 (M + H); 227.1 (M + Na).

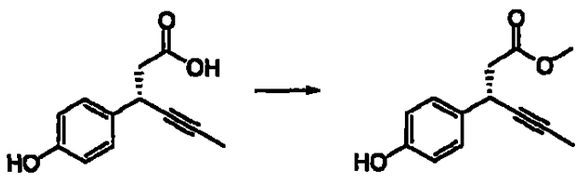
Scheme 1.4



1.3 **1.4**

[0310] **(*3S*)-3-(4-Hydroxy-phenyl)-hex-4-ynoic acid (1.4).** A 5L RB flask was charged with compound 1.3 (66.4 g, 325 mmol) and 2-propanol (1 L) and then heated to 70 °C. (*1S, 2R*)-1-amino-2-indanol (46.1 g, 309 mmol) was dissolved in 2-propanol (1 L) with gentle warming. The solution of amine was added to the dissolved carboxlic acid and the resulting solution was allowed to cool to room temperature. After 16h, the crystals were collected and dried. The salt was re-suspended in 2 L of 2-propanol and dissolved by heating to reflux. After allowing to cool to room temperature, the salt was collected after 16h. A small sample of the salt was decomposed with aqueous acid and the free carboxylic acid was analyzed by chiral HPLC (Daicel ChiralPAK AD-H column, eluant: 0.1% TFA in 90:10 hexanes:2-propanol) and was found to have 75% ee. The salt was re-suspended in 1.5 L of 2-propanol and dissolved by heating to reflux. After allowing to cool to room temperature, the salt was collected after 16h. This material was found to have 96% ee by chiral HPLC. This material was suspended in ethyl acetate (300 mL) and water (100 mL). Saturated aqueous $KHSO_4$ (100 mL) was added with vigorous mixing. After two clear layers were obtained, the layers were separated and the aqueous layer extracted with ethyl acetate (100 mL). The combined extracts were washed with saturated brine, dried over $MgSO_4$, filtered, and concentrated to a light yellow oil which crystallized on drying *in vacuo*. Compound 1.4 was obtained as an off-white solid (23.5 g, 35%).

Scheme 1.5



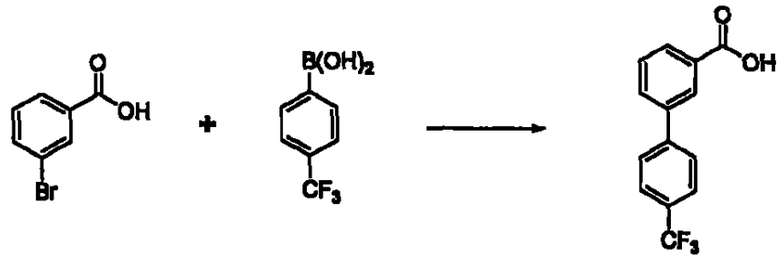
1.4 1

[0311] *(3S)*-3-(4-Hydroxy-phenyl)-hex-4-ynoic acid methyl ester (1). Phenol 1.4 (23.5 g, 115 mmol) was dissolved in acetone (230 mL) and treated with $KHCO_3$ (11.5 g, 115 mmol). After 15 minutes, methyl iodide (5 mL, 80 mmol) was added, and the reaction stirred at 40 °C for 14h. An additional portion of methyl iodide (3 mL, 48 mmol) was added and heating was continued for 24h. Potassium salts were removed by filtration and thoroughly rinsed with acetone. The filtrate was concentrated to an oil which was purified by filtration through a 1 cm plug of silica gel. Elution with 2.5% MeOH in dichloromethane followed by concentration provided phenol 1 (21.5 g, 85%) as a light yellow oil. ^{1}H NMR(500MHz)(acetone-d_6) δ 8.2 (br s, 1H); 7.20 (d, 2H, *J*=9.5 Hz); 6.77 (d, 2H, *J*=9.0 Hz); 3.98 (m, 1H); 3.60 (s, 3H); 2.65 (m, 2H); 1.78 (d, 3H, *J*=2.5 Hz). MS ESI (pos.) m/e: 219.1 (M + H); 241.1 (M + Na).

6.2 Example 2

[0312] This example illustrates the preparation of *(3S)*-3-[4-(4'-Trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-hex-4-ynoic acid sodium salt.

Scheme 2.1

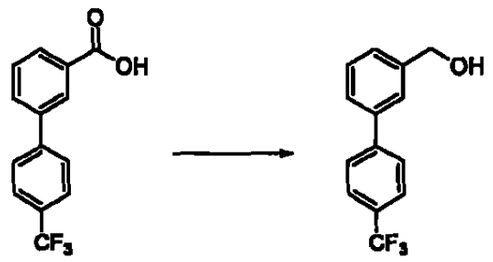


2.1

[0313] 3-(4-Trifluoromethylphenyl)-benzoic acid (2.1). The Suzuki coupling was carried out according to the method of Dyer *et al.* (2001) *Tetrahedron Letters* 42: 1765-1767. Commercially available 4-(Trifluoromethyl)phenylboronic acid (15g, 78.7 mmol) and 3-bromobenzoic acid (15.1g, 75 mmol) were suspended in 2-propanol:water (1:4, 72 mL). 10% Pd/C (1.5g) was added followed by aqueous Na_2CO_3 (39 mL, 20% by wt.). The

resulting mixture was heated at 70°C for 4 hours. The precipitate was filtered and rinsed with 20% aqueous Na_2CO_3 solution. The filtrate was diluted with water and acidified to pH=2. The white solid was filtered and dried *in vacuo*. The crude material (2.1) (19.69g) was used in the next step without further purification.

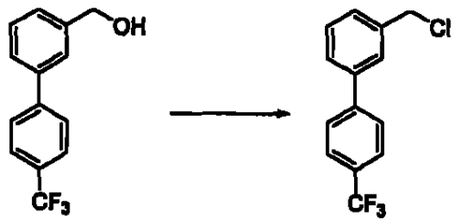
Scheme 2.2



2.1 2.2

[0314] **3-(4-Trifluoromethylphenyl)-benzyl alcohol (2.2).** The carboxylic acid 2.1 (13.3g, 50mmol) in anhydrous THF (100mL) was added dropwise to $LiAlH_4$ (2.9g, 75 mmol) in anhydrous THF (150mL) at 0°C over 30 minutes. The resulting mixture was slowly warmed to room temperature and stirred for 4 hours. The reaction was slowly quenched with water (2.9mL) at 0°C, 15% NaOH aqueous solution (2.9mL) and another portion of water (8.7mL). The mixture was dried over Na_2SO_4 and concentrated to give a white solid (11.9g). The crude product (2.2) was used in the next step without further purification.

Scheme 2.3

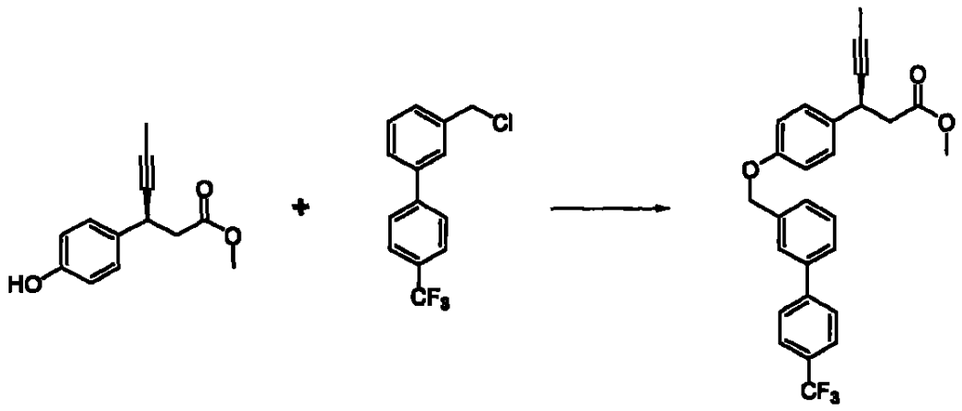


2.2 2.3

[0315] **3-(4-Trifluoromethylphenyl)-benzyl chloride (2.3).** The alcohol 2.2 (15g, 59.5mmol) was dissolved in anhydrous dichloromethane (100mL). Thionyl chloride (10mL) was slowly added dropwise to the above solution. The resulting mixture was stirred at room temperature for 24 hours. The organic solvent was removed under *vacuo*. The residue was then purified by flash chromatography (SiO_2 gel 60, eluted with 20% DCM in hexanes). Fractions containing the desired product 2.3 were combined and concentrated to

a white solid (14.0 g). HPNMR (400MHz) ($CDCl_3$) δ 7.73 (4H, s); 7.65 (1H, s); 7.58 (1H, s); 7.52-7.28 (2H, m); 4.69 (2H, s).

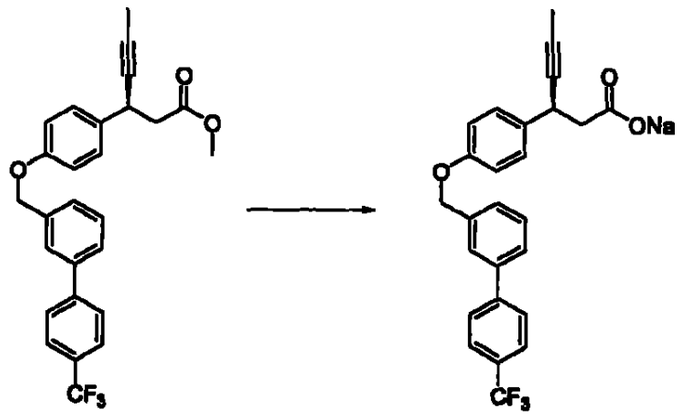
Scheme 2.4



1 2.3 2.4

[0316] *(3S)*-3-[4-(4'-Trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-hex-4-ynoic acid methyl ester (2.4). Benzyl chloride 2.3 (28.0 g, 103 mmol) and phenol 1 (21.5 g, 98 mmol) were dissolved in acetone (150 mL) and treated with Cs_2CO_3 (39.9 g, 122 mmol). The reaction was stirred at 50 ^{0}C for 16 h then filtered and concentrated to an pale yellow oil which was purified by column chromatography (silica gel, 33% to 66% dichloromethane in hexanes). Eluant containing compound 2.4 was concentrated to a colorless oil (40.0 g, 92%).

Scheme 2.4



2.4 2

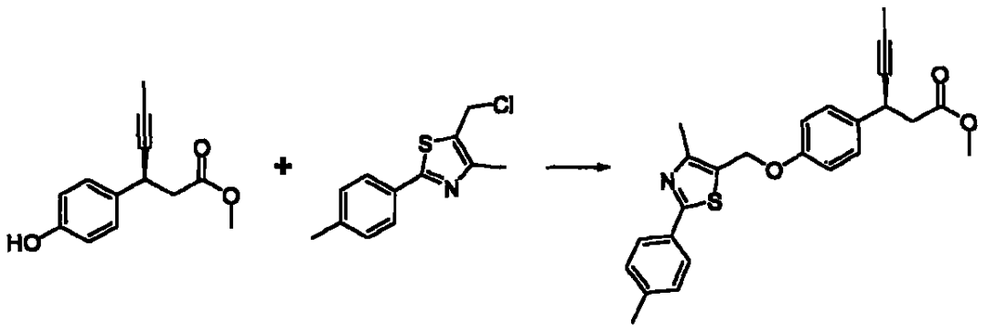
[0317] *(3S)*-3-[4-(4'-Trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-hex-4-ynoic acid sodium salt (2). Methyl ester 2.4 was dissolved in diethyl ether (50 mL).

64
64

Sodium trimethylsilanolate (0.76 g, 7 mmol) was added in one portion and the reaction mixture stirred for 48h. The precipitate was collected by filtration and recrystallized from ethyl acetate:hexanes. After drying *in vacuo*, the desired sodium salt was obtained as a white powder (1.3 g). ^{1}H NMR (500MHz) (CD_3OD) δ 7.82 (d, 2H, *J*=8.5 Hz); 7.75-7.73 (m, 3H); 7.62 (m, 1H); 7.32 (d, 2H, *J*=8.5 Hz); 6.94 (d, 2H, *J*=8.5 Hz); 5.15 (s, 2H); 4.03 (m, 1H); 2.52 (dd, 1H, *J*=8.2, 14.5 Hz); 2.45 (dd, 1H, *J*=7.0, 14.0 Hz); 1.79 (d, 3H, *J*=2.5 Hz).

6.3 **Example 3**

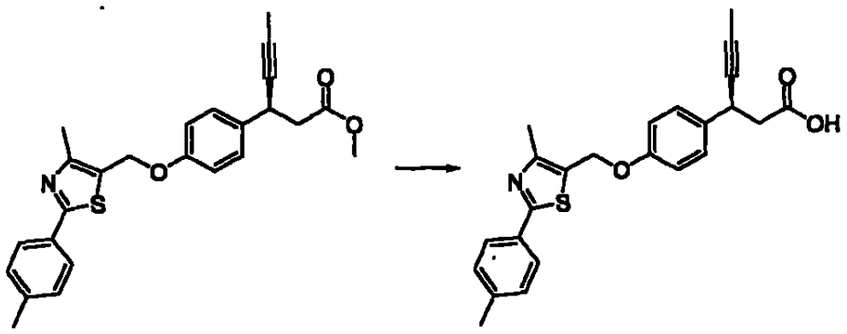
Scheme 3.1



1 3.1 3.2

[0318] *(3S)*-3-[4-(4-Methyl-2-p-tolyl-thiazol-5-ylmethoxy)-phenyl]-hex-4-ynoic acid methyl ester (3.2). Compound 3.1 was prepared according to the method described in Example 2 starting from the commercial available 4-methyl-2-(4-methylphenyl)-1,3-thiazole-5-carboxylic acid. The chloride 3.1 (250 mg, 1.1 mmol) and phenol 1 (230 mg, 1.1 mmol) were dissolved in anhydrous DMF (5 mL). Finely powdered Cs_2CO_3 (650 mg, 2.2 mmol) was then added and the reaction mixture was stirred at room temperature for 14 h. The reaction was poured into water and extracted with ethyl acetate (15mL x 3). The organic phases were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a residue which was used in the next step without further purification.

Scheme 3.1



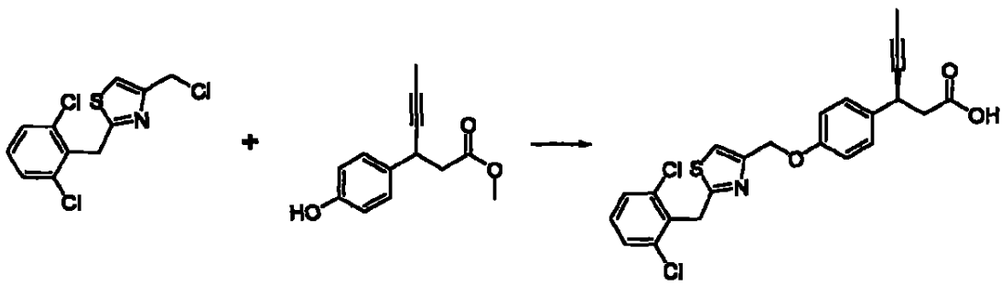
3.2 3

[0319] *(S)*-3-[4-(4-Methyl-2-p-tolyl-thiazol-5-ylmethoxy)-phenyl]-hex-4-ynoic acid (3). Ester 3.2 was dissolved in THF/MeOH/10% $NaOH_{(aq)}$ (1:1:1) solution (15mL). After stirring at room temperature over 30 minutes, the mixture was acidified with 1N HCl (aq.) until pH = 4. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried over Na_2SO_4 and concentrated. The crude residue was triturated with 20% ethyl acetate in hexanes (20 mL). The precipitate was filtered and compound 3 was acquired as a pale yellow powder (315 mg, 0.8 mmol). MS ESI m/e: 406 (M-H). ^1H NMR (500MHz) ($CDCl_3$) δ 7.86 (2H, d, *J*=7.5 Hz); 7.36 (2H, d, *J*=9 Hz); 7.26 (2H, d, *J*=8 Hz); 6.96 (2H, d, *J*=8.5 Hz); 5.18 (2H, s); 4.1 (1H, m); 2.77 (2H, m); 2.52 (3H, s); 2.42 (3H, s); 1.86 (3H, s).

6.4 Example 4

[0320] This example illustrates the preparation of 3-{4-[2-(2,6-Dichloro-benzyl)-thiazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid.

Scheme 4.1



4.1 1.3 4

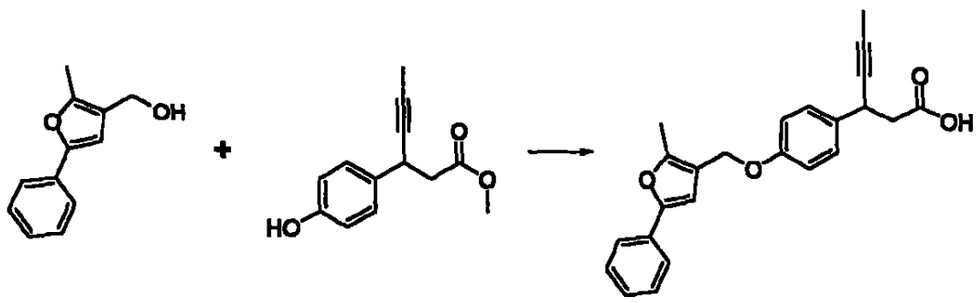
[0321] 3-{4-[2-(2,6-Dichloro-benzyl)-thiazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid (4). Preparation of thiazole 4.1 was carried out according to the method of Bordwell *et*

et al. (1990) *J. Amer. Chem. Soc.* 112: 792-797. Compound 4.1 (58 mg, 0.2 mmol) and phenol 1 (43.6 mg, 0.2 mmol) were dissolved in anhydrous DMF (2 mL) and treated with finely powdered Cs_2CO_3 (65 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for 14 hours. The reaction was poured into water and extracted with ethyl acetate (10 mL × 3). The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* and the residue dissolved in THF/MeOH/10% $NaOH_{(aq)}$ (1:1:1) solution (6 mL). The resulting mixture was stirred at room temperature for 30 minutes. The mixture was acidified with 1N $HCl_{(aq.)}$ until pH = 4. The aqueous phase was extracted with ethyl acetate. The organic phases were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was triturated with 20% ethyl acetate in hexanes (10 mL). The precipitate was filtered and acid 4 was acquired as a pale yellow powder (55 mg, 0.12 mmol). MS ESI m/e: 460 (M-H). ^{1}H NMR (400MHz) ($CDCl_3$) δ 7.40-7.19 (6H, m); 6.94-6.79 (2H, m); 5.18 (2H, s); 4.73 (2H, s); 4.1-4.06 (1H, m); 2.77 (2H, m); 1.85 (3H, s).

6.5 **Example 5**

[0322] This example illustrates the preparation of 3-[4-(2-Methyl-5-phenyl-furan-3-ylmethoxy)-phenyl]-hex-4-ynoic acid.

Scheme 5.1



5.1 1.3 5

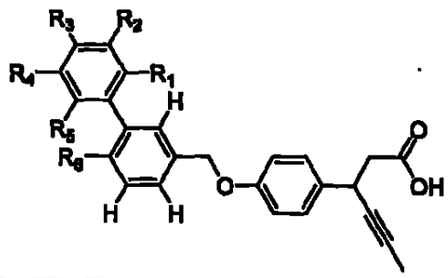
[0323] **3-[4-(2-Methyl-5-phenyl-furan-3-ylmethoxy)-phenyl]-hex-4-ynoic acid (5).** The Mitsunobu reaction was carried out according to the method of Mikó *et al.* (2003) *J. Med. Chem.* 46: 1523-1530. Commercially available 5.1 (37.6 mg, 0.2 mmol), PPh_3 (52 mg, 0.2 mmol) and phenol 1.3 (43.6 mg, 0.2 mmol) were added to anhydrous THF (3 mL). DEAD (45 µL, 0.22 mmol) was then added dropwise. The reaction mixture was stirred at room temperature over 14 hours. The reaction was then extracted with ethyl acetate (10mL × 3). The organic phases were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was dissolved in THF/MeOH/10% $NaOH_{(aq)}$ (1:1:1) solution (6 mL). The resulting mixture was stirred at room temperature over 30

minutes. The resulting mixture was stirred at room temperature for 30 minutes. The mixture was acidified with 1N $HCl_{(aq.)}$ until pH = 4. The aqueous phase was extracted with ethyl acetate. The organic phases were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was triturated in 20% ethyl acetate in hexanes (10 mL). The precipitate was filtered and compound 5 was obtained as a white powder (35 mg, 0.9 mmol). MS ESI m/e: 375 (M-H). ^1H NMR (500MHz) ($CDCl_3$) δ 7.65 (2H, d, J=8 Hz); 7.40-7.24 (5H, m); 6.96 (2H, d, J=8.5 Hz); 6.68 (1H, s); 4.88 (2H, s); 4.1 (1H, s); 2.77 (2H, m); 2.4 (3H, s); 1.86 (3H, s).

6.6 **Example 6**

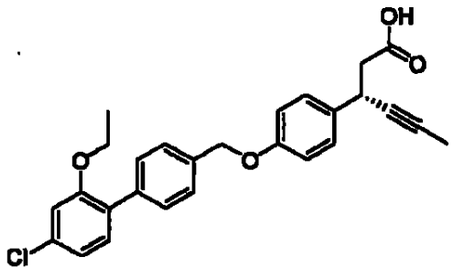
[0324] The following compounds were prepared by methods similar to those described in Example 2.

TABLE 1



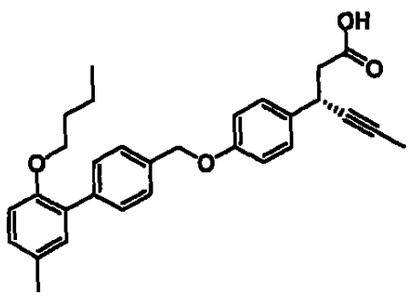
Compound	R_1	R_2	R_3	R_4	R_5	R_6
6.1	H	H	H	H	H	H
6.2	OC_2H_5	H	H	H	H	H
6.3	H	H	OC_2H_5	H	H	H
6.4	H	-OCH_2O-		H	H	H
6.5	H	H	CF_3	H	H	H
6.6	H	CN	H	H	H	H
6.7	H	H	CN	H	H	H
6.8	CF_3	H	H	H	H	H
6.9	H	CF_3	H	H	H	H
6.10	H	H	OCF_3	H	H	H
6.11	H	H	CF_3	H	H	OC_2H_5
6.12	OCH_3	H	CF_3	H	H	H

[0325] NMR and MS data for compounds 6.13 and 6.14 are as follows:



6.13

[0326] ^{1}H NMR (400MHz) ((CD$_3$)$_2$SO) δ 12.4 (s, 1H), 7.52 (d, 2H, J = 8.1 Hz), 7.48 (d, 2H, J = 8.1 Hz), 7.28-7.34 (m, 3H), 7.17 (s, 1H), 7.08 (d, 1H, J = 8.1 Hz), 6.98 (d, 2H, J = 8.2 Hz), 5.12 (s, 2H), 4.08 (q, 2H, J = 7.0 Hz), 3.95 (m, 1H), 2.50-2.60 (m, 2H), 1.78 (s, 3H), 1.27 (t, 3H, J = 7.0 Hz). $[M+H]^+$ Calculated for $C_{27}H_{25}ClO_4$: 449.1. Found 449.1.



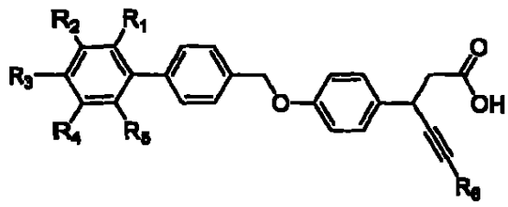
6.14

[0327] ^{1}H NMR (400MHz) ((CD$_3$)$_2$SO) δ 12.4 (s, 1H), 7.52 (d, 2H, J = 8.0 Hz), 7.46 (d, 2H, J = 8.6 Hz), 7.30 (d, 2H, J = 8.8 Hz), 7.46 (d, 2H, J = 6.0 Hz), 6.98-7.01 (m, 3H), 6.91-6.98 (m, 3H), 5.13 (s, 2H), 3.92-4.04 (m, 3H), 2.61 (d, 2H, J = 7.6 Hz), 2.29 (s, 3H), 1.79 (d, 2H, J = 2.0 Hz), 1.59-1.66 (m, 2H), 1.34-1.40 (m, 2H), 0.88 (t, 3H, J = 7.6 Hz). $[M+Na]^+$ Calculated for $C_{30}H_{32}O_4$: 471.1. Found 471.1.

6.7 Example 7

[0328] The following compounds were prepared by methods similar to those described in Example 2.

TABLE 2

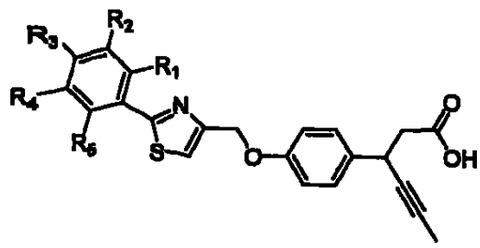


Compound	R_1	R_2	R_3	R_4	R_5	R_6
7.1	H	H	H	H	H	H
7.2	CN	H	H	H	H	H
7.3	H	H	H	H	H	CH_3
7.4	CN	H	H	H	H	CH_3
7.5	OC_2H_5	H	H	H	H	CH_3
7.6	Cl	H	H	H	H	CH_3
7.7	F	H	H	H	H	CH_3
7.8	H	OC_2H_5	H	H	H	CH_3
7.9	H	H	OC_2H_5	H	H	CH_3
7.10	H	H	CF_3	H	H	CH_3
7.11	H	-OCH_2O-		H	H	CH_3
7.12	OCH_3	OCH_3	H	H	H	CH_3
7.13	H	OCH_3	H	H	H	CH_3
7.14	H	CN	H	H	H	CH_3
7.15	H	H	CN	H	H	CH_3

6.8 Example 8

[0329] The following compounds were prepared by methods similar to those described in Example 3.

TABLE 3



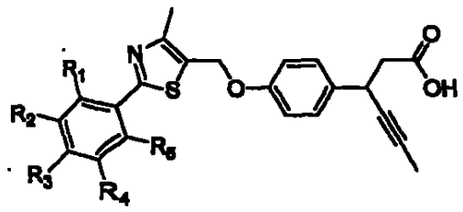
Compound	R_1	R_2	R_3	R_4	R_5
8.1	H	H	CF_3	H	H
8.2	H	H	H	H	H

Compound	R_1	R_2	R_3	R_4	R_5
8.3	H	H	Cl	H	H
8.4	H	H	OCH_3	H	H
8.5	H	H	CH_3	H	H
8.6	H	OCH_3	OCH_3	H	H
8.7	Cl	Cl	H	H	H

6.9 Example 9

[0330] The following compounds were prepared by methods similar to those described in Example 3.

TABLE 4



Compound	R_1	R_2	R_3	R_4	R_5
9.1	H	H	CF_3	H	H
9.2	H	H	CH_3	H	H
9.3	H	H	H	H	H
9.4	H	OCH_3	OCH_3	H	H
9.5	H	H	Cl	H	H
9.6	Cl	H	H	H	H

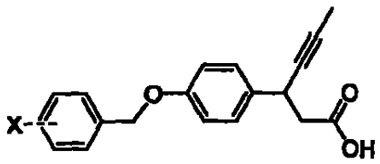
6.10 Example 10

[0331] The following compounds were prepared by methods similar to those described in Examples 3-5. The carboxylic acids corresponding to 10.2 and 10.5 were prepared according to the method of Huang *et al.* (2003) *J. Amer. Chem. Soc.* 22: 6653-6655, and Admas *et al.* (1973) *Org. Synth.* Coll. Vol. V: 107, 109, respectively.

71

71

TABLE 5

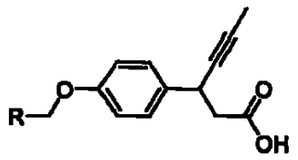


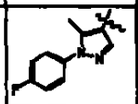
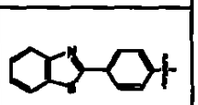
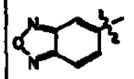
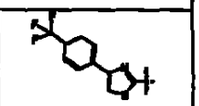
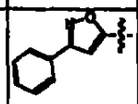
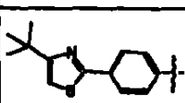
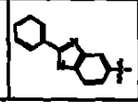
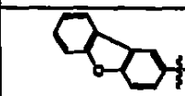
Compound	X	Compound	X
10.1	3-C(O)Ph	10.8	3-(2)-pyridyl
10.2	3-N(C_2H_5)Ph	10.9	3-(3)-pyridyl
10.3	3-Phenoxy	10.10	3-(4)-pyridyl
10.4	4-C(O)Ph	10.11	4-(2)-pyridyl
10.5	4-SO_2Ph	10.12	4-(3)-pyridyl
10.6	4-CH_2Ph	10.13	4-(4)-pyridyl
10.7	4-C_2H_4PH	10.14	4-Pyrrol-1-yl

6.11 Example 11

[0332] The following compounds were prepared by methods similar to those described in Examples 3-5.

TABLE 6

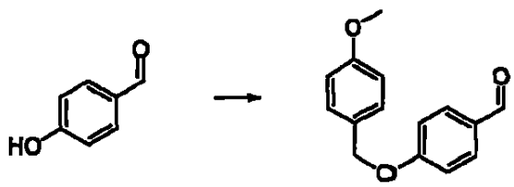


Compound	R	Compound	R
11.1		11.5	
11.2		11.6	
11.3		11.7	
11.4		11.8	

6.17 Example 12:

[0333] This example illustrates the preparation of (+/-)-3-(4-[(4-methoxyphenyl)methoxy]- phenyl)-hex-4-ynoic acid.

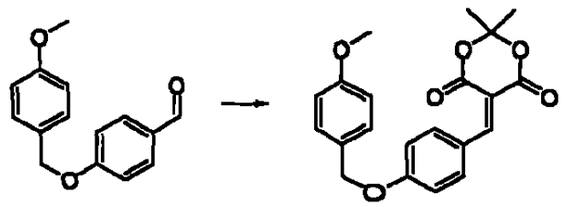
Scheme 12.1



12.1

[0334] 4-[(4-methoxyphenyl)methoxy]benzaldehyde (12.1). A 500 mL round bottom flask was charged with 4-hydroxybenzaldehyde (40 g, 328 mmol) and DMF (250 mL). 4-methoxybenzyl chloride (57.8 mL, 426 mmol) was added, followed by potassium carbonate (90 g, 656 mmol). The reaction mixture was stirred at room temperature for 5h then poured into ice water (2.5 L). The product was collected by filtration and rinsed with water. After drying thoroughly, 78 g (98%) of aldehyde 12.1 was obtained as a light yellow powder. ^{1}H NMR(400MHz)(DMSO-d_6) δ 9.88 (s, 1H); 7.88 (d, 2H, J=8.7 Hz); 7.42 (d, 2H, J=8.8 Hz); 7.21 (d, 2H, J=8.8 Hz); 6.97 (d, 2H, J=8.6 Hz); 5.16 (s, 2H); 3.77 (s, 3H). MS ESI (pos.) m/e: 243.1 (M + H).

Scheme 12.2

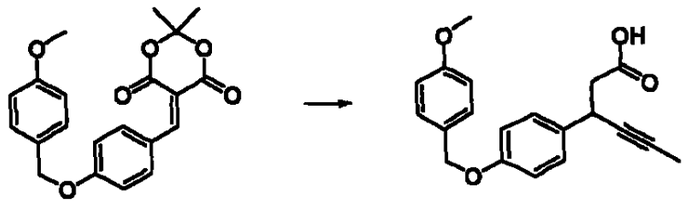


12.1 12.2

[0335] 5-[[4-[(4-methoxyphenyl)methoxy]phenyl]methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (12.2). Condensation with Meldrum's acid is carried out according to the procedure of DeWolf *et al.* (1989) *Biochemistry* 28: 3833-3842. A solution of Meldrum's acid (18 g, 124 mmol) compound 12.1 (30 g, 124 mmol) in toluene (100 mL) was treated with glacial acetic acid (4 mL) and piperidine (2 mL). The reaction mixture was stirred and heated at reflux until the removal of water with a Dean-Stark trap was complete. The reaction mixture was cooled to room temperature and the resulting solid was filtered and washed with cold toluene to yield 28g (62%) of 12.2 as a bright yellow powder.

^{1}H NMR(400MHz)(DMSO-d_6) δ 8.32 (s, 1H); 8.24 (d, 2H, *J*=8.9 Hz); 7.42 (d, 2H, *J*=8.6 Hz); 7.17 (d, 2H, *J*=9.0 Hz); 6.97 (d, 2H, *J*=8.7 Hz); 5.18 (s, 2H) 3.75 (s, 6H) 1.75 (s, 6H).

Scheme 12.3



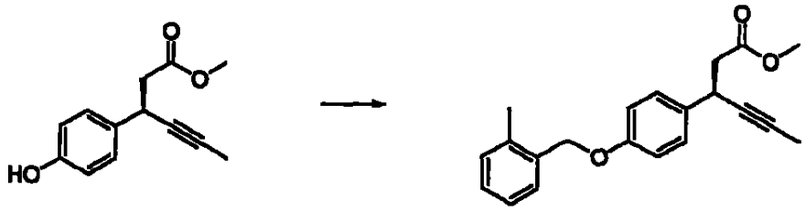
12.2 12

[0336] **(+/-)-3-(4-[(4-methoxyphenyl)methoxy]phenyl)-hex-4-ynoic acid (12).** To a stirring THF (120 mL) solution of compound **12.2** (13.8 g, 37.5 mmol) under nitrogen was added 1-propynylmagnesium bromide in THF (0.5 N, 97.5 mL) over a period of 20 minutes. After the addition was complete, the reaction mixture was stirred for 20 minutes, quenched with saturated aqueous NH_4Cl (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated to a brown oil. A solution of this brown oil in 5:1 pyridine-water (360 mL) was heated at 100 °C for 36h. The reaction mixture was cooled to room temperature and put in an ice-water bath. Concentrated HCl was carefully added to pH ~2. The resulting suspension was extracted with ethyl acetate (200 mL x 3), dried over $MgSO_4$, filtered, and concentrated to an off-white solid. Recrystalization from ethanol gave 9.5 g (78%) of compound **12** as a white powder. ^{1}H NMR(500MHz)DMSO-d_6) δ 12.2 (s, 1H); 7.37 (d, 2H, *J*=8.5 Hz); 7.27 (d, 2H, *J*=8.5 Hz); 6.95 (d, 2H, *J*=8.0 Hz); 6.94 (d, 2H, *J*=8.5 Hz); 4.99 (s, 2H); 3.95 (m, 1H); 3.76 (s, 3H); 2.60 (m, 2H); 1.78 (d, 3H, *J*=1.5 Hz). MS ESI (neg.) m/e: 323.0 (M -1).

6.13 Example 13

[0337] This example illustrates the preparation of *(3S)*-3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid sodium salt.

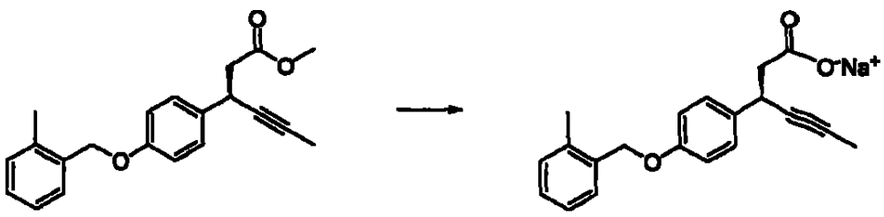
Scheme 13.1



1 13.1

[0338] (3S)-3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid methyl ester (13.1). 2-Methylbenzyl bromide (0.98 g, 5.3 mmol) and phenol 1 (0.97 g, 4.4 mmol) were dissolved in acetone (9 mL) and treated with Cs_2CO_3 (1.45 g, 4.4 mmol). The reaction was stirred at room temperature for 16 h then filtered and concentrated to an oil which was purified by radial chromatography (2 mm silica gel plate, 10% ethyl acetate in hexanes). Eluant containing compound 13.1 was concentrated to a colorless oil (1.37 g, 96%). This material was analyzed by chiral HPLC (Daicel ChiralPAK AD-H column, eluant: 0.1% TFA in 95:5 hexanes:2-propanol) and was found to have 94% ee. ^{1}H NMR(500MHz)(MeOH-d_4) δ 7.39 (d, 1H, J=7 Hz); 7.28 (d, 2H, J=8.5 Hz); 7.25-7.15 (m, 3H); 5.05 (s, 2H); 4.02 (m, 1H); 3.64 (s, 3H); 2.68 (m, 2H); 2.36 (s, 3H); 1.80 (d, 3H, J=2.5 Hz). MS ESI (pos.) m/e: 323.0 (M + H); 245.1 (M + Na).

Scheme 13.2



13.1 13

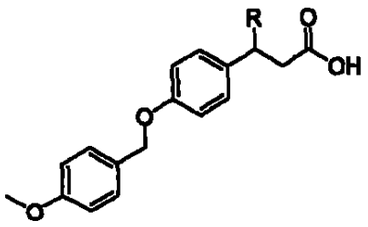
[0339] *(3S)*-3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid sodium salt (13). 2N $KOH_{(aq)}$ (3.2 mL) was added to a solution of 13.1 (1.37 g, 4.25 mmol) in methanol (30 mL). The reaction was stirred at room temperature overnight and then taken up in copious water. The aqueous solution was adjusted to pH = 2.0 with 1N $HCl_{(aq)}$ and extracted with ethyl acetate. The combined organic layers were washed with water, followed by brine. The solvent was removed under reduced pressure and the resulting residue dissolved in ethanol (4 mL) and treated with 1 equiv. of aqueous sodium bicarbonate. The solvents were removed under reduced pressure and the residue triturated with diethyl ether. After collecting by filtration and drying, sodium salt 13 (1.1 g) was obtained as a fine white powder. ^{1}H NMR(500MHz)(D_2O) δ 7.34-7.18 (m, 6H); 6.95 (d, 2H, J=6.5 Hz); 5.05 (s, 2H); 3.88 (m, 1H); 2.47 (d, 2H, J=8.5 Hz); 2.28 (s, 3H); 1.72 (d, 3H, J=2.5 Hz). MS ESI (pos.) m/e: 309.1 (M + H); 331.0 (M + Na). $[\alpha]_D$ = +20.6°.

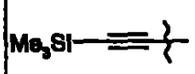
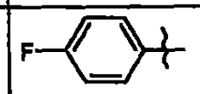
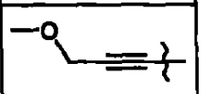
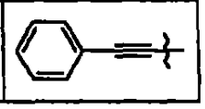
6.14 **Example 14**

[0340] The following compounds were prepared using similar methods to those described in Example 12.

75

TABLE 7



Compounds	R	Compounds	R
14.1		14.4	Me
14.2		14.5	
14.3	Et	14.6	

6.15 **Example 15**

[0341] This example illustrates the preparation of *(3S)*-3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid.

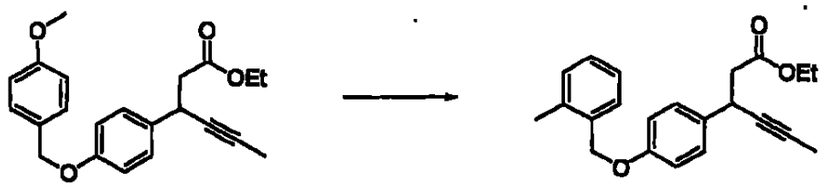
Scheme 15.1



12 15.1

[0342] **(+/-)-[4-(4-Methoxy-benzyloxy)-phenyl]-hex-4-ynoic acid ethyl ester (15.1).** A 100 mL RB flask was charged with compound 12 (3.00 g, 9.25 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.67 g, 13.9 mmol), 4-dimethylaminopyridine (1.13 g, 9.25 mmol) and dichloromethane (30 mL), the mixture was stirred into a solution. After 15 min, ethyl alcohol (absolute, 1.00 mL) was added. After 2 h, the reaction was quenched with aqueous $NaHCO_3$ (sat., 100 mL). The layers was separated, and the organic layer was washed with aqueous $NaHCO_3$ (2 X 100 mL), dried over $MgSO_4$ and concentrated to a white powder (3.19 g, 98%) which was used without further purification.

Scheme 15.2



15.1 15.2

[0343] (+/-)-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid ethyl ester (15.2). Ester 15.1 (3.19 g, 9 mmol) was taken up in glacial acetic acid (100 mL) in a 250 mL RB Flask, and the suspension was heated to reflux for 16h. The solvent was removed under reduced pressure, and the residue was re-dissolved in ethyl acetate (200 mL). The solution was washed with 1 N $HCl_{(aq)}$ (200 mL) and saturated brine (200 mL), dried over $MgSO_4$ and concentrated to a thick yellow oil, to which was added 2-methylbenyl bromide (2.57 g, 13.9 mmol), cesium carbonate (6.03 g, 18.5 mmol) and DMF (20 mL). The suspension was heated to 80 °C for overnight. After cooling, the reaction was quenched with water (200 mL) and extracted with ethyl acetate (2 X 100 mL). The combined organic layers were washed with NaHCO3 (sat. 2 X 100 mL), and NaCl (sat. 3 X 100 mL), dried over MgSO4, and concentrated to a white powder (2.41 g, 79%).

Scheme 15.3



15.2 15

[0344] (3*S*)-3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid (15). Compound 15.2 was dissolved in a mixture of 24 mL methanol and 24 mL isopropanol with the aid of sonication. The solution was filtered into a 50 mL glass vial. The racemic 15.2 was resolved with chiral normal phase HPLC using a ChiralTech AD semi-preparative column (2.0 cm X 25.0 cm), eluting isocratically with hexane/isopropanol (92:8) at a flow rate 20 mL/min. Each injection contained 50 mg of ester 15 (1 mL). The absorbance at 220 nm was used for detection. Both enantiomers were collected. After 36 injections, the separated enantiomers were dried to give white solids. Analytical chiral HPLC (Chiraltech AD-H column, 0.4 cm X 25.0 cm, 8% isopropanol/hexane, 1 mL/min) indicated both

compounds were optically pure. The enantiomers were referred to as A (retention time = 11.5 min) and B (retention time = 15.6 min).

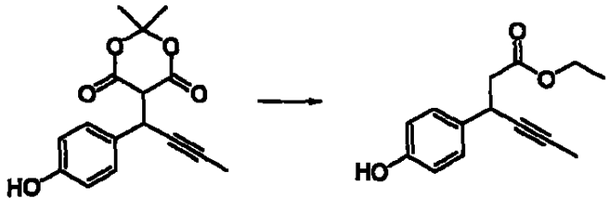
[0345] A RB flask was charged with enantiomer A (0.65 g), ethanol (10 mL) and 2N KOH (10 mL). and was stirred for 2 h at room temperature. After acidification to pH~2 with citric acid, the product was extracted into ethyl acetate (100 mL). The organic layers were washed with saturated brine(2 X 50 mL), dried over $MgSO_4$ and concentrated to a yellow oil (0.59 g, 42% overall). An aliquot (12.0 mg) was made into a 1 mL DMF solution, and optical rotation was measured. This enantiomer was assigned to (*S*) according to DeWolf Jr. *et al.* (1989) *Biochemistry* 28: 3833-3842.

[0346] ^{1}HNMR (400 MHz, acetone-d_6) δ 7.45 (d, 1H, J=7.15 Hz); 7.37 (d, 2H, J=8.66 Hz); 7.25 (d, 1H, J=1.42 Hz); 7.24 (m, 2H); 7.00 (d, 2H, J=8.74 Hz); 5.11 (s, 2H); 4.05 (m, 1H); 2.70 (m, 2H); 2.39 (s, 3H); 2.10 (s, 1H); 1.80 (d, 3H, J=2.41). MS-ESI (neg.) m/e: 307.1 (M-H); 637.2 (2M-H). $[\alpha]_D^{20}$: +16.32 (c1.2, DMF).

6.16 Example 16

[0347] This example illustrates the preparation of 3-(4-Hydroxy-phenyl)-hex-4-ynoic acid ethyl ester.

Scheme 16.1



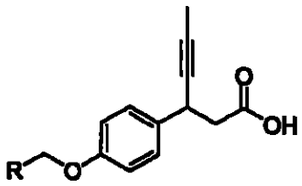
1.2 16

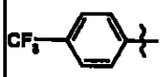
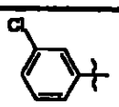
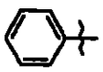
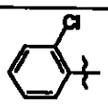
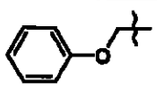
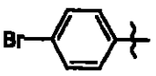
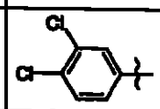
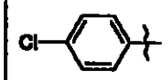
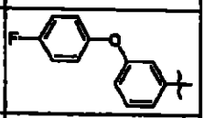
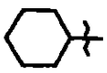
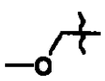
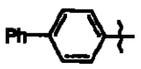
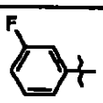
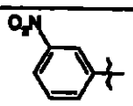
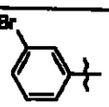
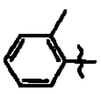
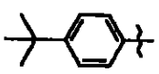
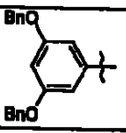
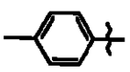
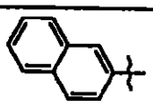
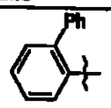
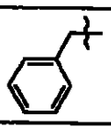
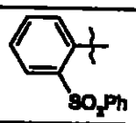
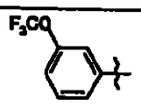
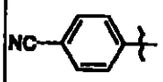
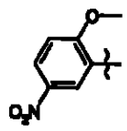
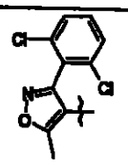
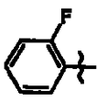
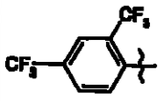
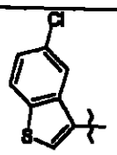
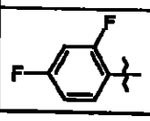
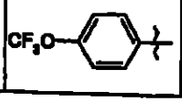
[0348] **3-(4-Hydroxy-phenyl)-hex-4-ynoic acid ethyl ester (16).** Phenol 1.2 (1.2 g, 4 mmol) was dissolved in pyridine (3 mL) and ethanol (1 mL). The mixture was heated to 90 °C for 16h and then concentrated to an oil which was purified by column chromatography (elution with 1-3% MeOH in dichloromethane). Phenol 16 (0.88 g, 91%) was obtained as an oil. ^{1}H NMR(500MHz)(acetone-d_6) δ 8.24 (s, 1H); 7.21 (d, 2H, *J*=9.5 Hz); 6.78 (d, 2H, *J*=9.0 Hz); 4.06 (m, 2H); 3.98 (m, 1H); 2.68-2.59 (m, 2H); 1.78 (d, 3H, *J*=2.5 Hz); 1.75 (t, 3H, *J*=7.0 Hz). MS ESI (pos.) m/e: 233.1 (M + H); 255.1 (M + Na).

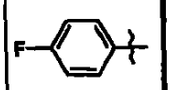
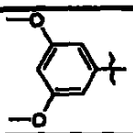
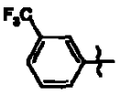
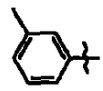
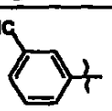
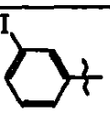
6.17 Example 17

[0349] The following compounds were prepared by methods similar to those of Examples 12 and 15.

TABLE 8



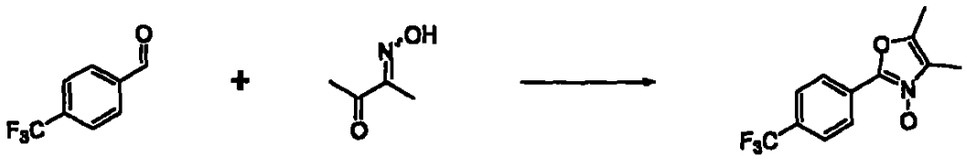
Compound	R	Compound	R	Compound	R
17.1		17.14		17.27	
17.2		17.15		17.28	
17.3		17.16		17.29	
17.4		17.17		17.30	
17.5		17.18		17.32	
17.6		17.19		17.33	
17.7		17.20		17.34	
17.8		17.21		17.35	
17.9		17.22		17.36	
17.10		17.23		17.37	
17.11		17.24		17.38	

Compound	R	Compound	R	Compound	R
17.12		17.25		17.39	
17.13		17.26		17.40	

6.18 Example 18

[0350] This example illustrates the preparation of 3-{4-[5-Methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid.

Scheme 18.1



18.1

[0351] **4,5-dimethyl-2-(4-trifluoromethyl-phenyl)-oxazole-3-oxide (18.1).** A 100 mL pear-shaped flask was charged with butane-2,3-dione monooxime (2.1 g, 20.4 mmol), 4-(trifluoromethyl)benzaldehyde (3.0 mL, 22.4 mmol), and acetic acid (20 mL). The mixture was cooled to 0° C. A solution of 4N HCl in dioxane (7.0 mL, 28.0 mmol) was added dropwise to the reaction and the resultant mixture was stirred at 0° C for 20 minutes. Diethyl ether (30 mL) was added to the reaction and the mixture was allowed to warm to room temperature overnight. The solvent was removed under reduced pressure and the resulting residue was taken up in water (300 mL). Conc. $NH_4OH_{(aq)}$ was added to adjust the pH to 9.0. The mixture was extracted with ethyl acetate (2 x 75 mL), and the combined organic layers were washed with water (100 mL), followed by saturated brine (100 mL). The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. The resulting residue was purified via radial chromatography (3% MeOH in DCM) to yield 1.8 g (35%) of 4,5-dimethyl-2-(4-trifluoromethyl-phenyl)-oxazole-3-oxide as a white solid. LC/MSD *m/e*: 258.1 (M+H); ^{1}H NMR (400 MHz) (Acetone-d_6) δ 8.68 (d, 2H, *J*=8.0 Hz), 7.89 (d, 2H, *J*=8.0 Hz), 2.45 (s, 3H), 2.16 (s, 3H).

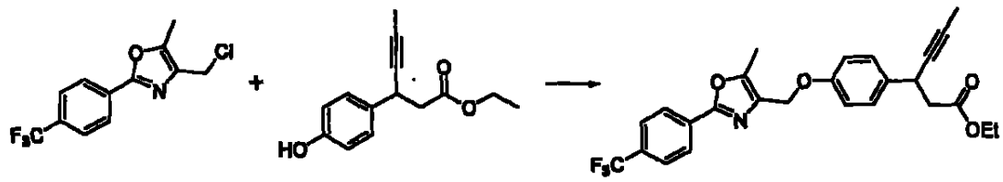
Scheme 18.2



18.1 18.2

[0352] **4-chloromethyl-5-methyl-2-(4-trifluoromethyl-phenyl)-oxazole (18.2).** Phosphorous oxychloride (0.72 mL, 7.8 mmol) was added dropwise to an oven-dried 100 mL pear-shaped flask charged with **18.1** (1.8 g, 7.00 mmol) and dichloromethane (20 mL). The reaction was refluxed under nitrogen atmosphere for 30 minutes and then cooled to room temperature. The reaction was washed with water (2 x 250 mL) and the combined aqueous layers were back extracted with DCM (2 x 25 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting residue was purified via radial chromatography (15% diethyl ether in hexanes) to yield 216 mg (15%) of 4-chloromethyl-5-methyl-2-(4-trifluoromethyl-phenyl)-oxazole as a white solid. LC/MSD *m/e*: 276.0 (M+H); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.15 (2H, d, *J*=8.0 Hz), 7.73 (2H. d, *J*=8.0 Hz), 4.59 (2H, s), 2.48 (2H, s).

Scheme 18.3

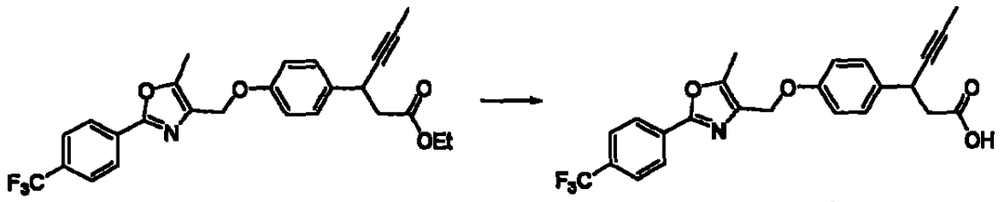


18.2 16 18.3

[0353] **3-{4-[5-Methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid ethyl ester (18.3).** Cesium carbonate (0.51 g, 1.57 mmol) was added to a solution of **18.2** (216 mg, 0.79 mmol) and phenol **16** (220 mg, 0.79 mmol) in DMF (8 mL). The reaction was stirred at room temperature overnight and then taken up in water (500 mL). The solution was adjusted to pH = 4.0 with 1N HCl(aq) and extracted with ethyl acetate (2 x 25 mL). The combined organics were washed with water, followed by brine. The solvent was removed under reduced pressure and the resulting residue was purified via radial chromatography (20% diethyl ether in hexanes) to yield 304 mg (82%) of 3-{4-[5-Methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-ynoic

acid ethyl ester. LC/MSD *m/e*: 472.0 (M+H); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.16 (2H, d, *J*=8.0 Hz), 7.73 (2H, d, *J*=8.0 Hz), 7.33 (2H, m), 6.99 (2H, m), 5.01 (2H, s), 4.14 (3H, m), 2.72 (2H, m), 2.48 (3H, s), 1.85 (3H, s), 1.26 (3H, t, *J*=8.0 Hz).

Scheme 18.4

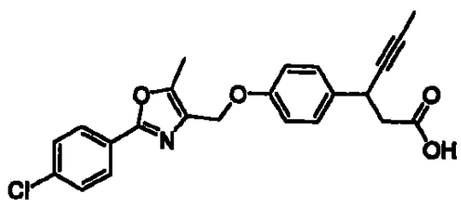


18.3 18

[0354] **3-{4-[5-Methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid (18).** 2N $KOH_{(aq)}$ was added to a solution of 18.3 (304 mg, 0.65 mmol) in ethanol (5 mL). The reaction was stirred at room temperature overnight and then taken up in copious water. The aqueous solution was adjusted to pH = 2.0 with 1N $HCl_{(aq)}$ and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with water, followed by brine. The solvent was removed under reduced pressure and the resulting residue was purified via radial chromatography (40% ethyl acetate in Hexanes + 0.1% AcOH) to yield 150 mg (52%) of compound 18 as a glass. LC/MSD *m/e*: 444.0 (M+H); ^{1}H NMR (400 MHz) (acetone) ∂ 8.21 (2H, m), 7.89 (2H, d, *J*=8.0 Hz), 7.38 (2H, m), 7.03 (2H, m), 5.06 (2H, s), 4.06 (1H, m), 2.70 (2H, m), 2.52 (3H, s), 1.81 (3H, s).

6.19 **Example 19**

[0355] Examples 19-22 were prepared using methods similar to those described in Example 18.

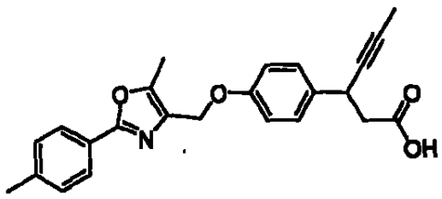


19

[0356] **3-{4-[5-Methyl-2-(4-chloro-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid (19).** LC/MSD *m/e*: 410.0 (M+H). ^{1}H-NMR (400 MHz) (acetone-d_6) δ 8.02 (2H, m), 7.49 (2H, m), 7.35 (2H, m), 7.01 (2H, m), 5.04 (2H, s), 4.09 (1H, m), 2.77 (2H, m), 2.48 (3H, s), 1.86 (3H, s).

82

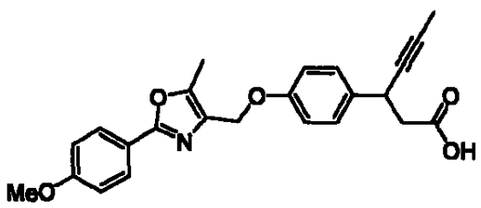
6.20 Example 20



20

[0357] 3-{4-[5-Methyl-2-(4-methyl-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid (16). LC/MSD *m/e*: 390.2 (M+H). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.96 (2H, m), 7.34 (2H, m), 6.70 (2H, m), 5.02 (2H, s), 4.09 (1H, m), 2.80 (2H, m), 2.47 (3H, s), 1.85 (3H, s).

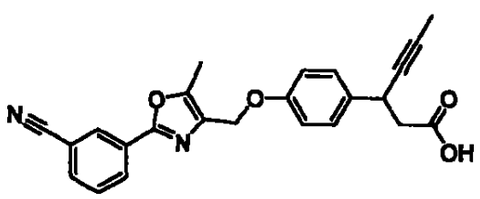
6.21 Example 21



21

[0358] 3-{4-[5-Methyl-2-(4-methoxy-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid (21). LC/MSD *m/e*: 406.1 (M+H). ^{1}H NMR (400 MHz) (acetone-d_6) δ 7.89 (2H, d, J=9.0 Hz) 7.30 (2H, m), 7.09 (2H, d, J=9.0 Hz), 7.00 (2H, m), 4.97 (3H, s), 3.90 (1H, m), 3.84 (3H, s), 2.44 (3H, s), 1.79 (3H, s).

6.22 Example 22



22

[0359] 3-{4-[5-Methyl-2-(3-cyano-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid (22). LC/MSD *m/e*: 401.2 (M+H). ^{1}H NMR (400 MHz) (acetone-d_6) δ 8.33 (2H, m), 7.91 (1H, m), 7.79 (1H, m), 7.38 (2H, m), 7.08 (2H, m), 5.06 (2H, s), 4.06 (1H, m), 2.70 (2H, m), 2.51 (3H, s), 1.81 (3H, s).

83

Example 23

[0360] The following example illustrates the synthesis of 5-{2-[4-(2-Methyl-benzyloxy)-phenyl]-pent-3-ynyl}-1*H*-tetrazole.

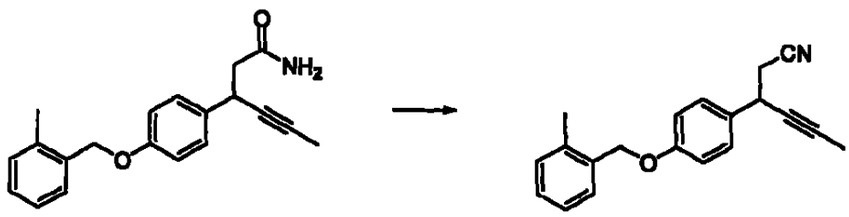
Scheme 23.1



23.1 23.2

[0361] **3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid amide (23.2).** Carbonyl diimidazole (0.46 g, 2.84 mmol) was added to a solution of 3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid (See Example 13) (0.73 g, 2.37 mmol) in anhydrous THF (10 mL). The mixture was stirred at room temperature for 2 hours. Concentrated NH_4OH (10 mL) was then added to the mixture, and the reaction was stirred at room temperature overnight. The reaction mixture was poured into water (300 mL) and the solution was adjusted to pH = 7 with conc. HCl. The aqueous layer was then extracted with 3 x 25 mL ethyl acetate. The combined organic layers were washed with water, followed by brine. The organic layer was then dried (Na_2SO_4) and concentrated under reduced pressure to yield 0.48 g (70%) of 3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid amide (23.2) as a light yellow solid. LC/MSD *m/e*: 308.4 (M+H)

Scheme 23.2



23.2 23.3

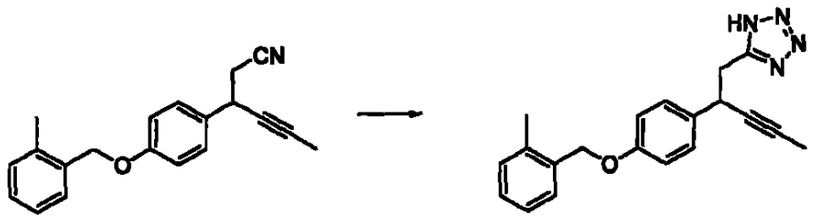
[0362] **3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynenitrile (23.3).** An oven-dried 50 mL round-bottomed flask was charged with DMF (8 mL) and a stir bar. The solution was cooled to 0 °C in an ice bath. Thionyl chloride (160 µL, 1.0 mmol) was added slowly via syringe. The mixture was stirred at 0 °C for an additional 45 minutes. Nitrile

84

84

25.2 (300 mg, 0.58 mmol) was then added to the mixture as a solution in DMF (2 mL). The reaction was stirred at 0° C for an hour, and was then allowed to gradually warm to room temperature overnight. The reaction mixture was partitioned between ice water and ethyl acetate. The aqueous layer was extracted 2 additional times with 25 mL ethyl acetate. Saturated $NaHCO_3$ was then added to the aqueous layer and the aqueous layer was extracted a third time with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ and concentrated under reduced pressure. The resulting residue was purified via radial chromatography (15% ethyl acetate in hexanes) to yield 203 mg (72%) of 3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynenitrile (**23.3**). ^{1}H NMR (400 MHz) (acetone-d_6) δ 7.44 (3H, m), 7.24 (3H, m), 7.05 (2H, m), 5.13 (2H, s), 4.09 (1H, m), 2.89 (2H, m), 2.39 (3H, s), 1.88 (3H, s).

Scheme 23.4



23.3 **23**

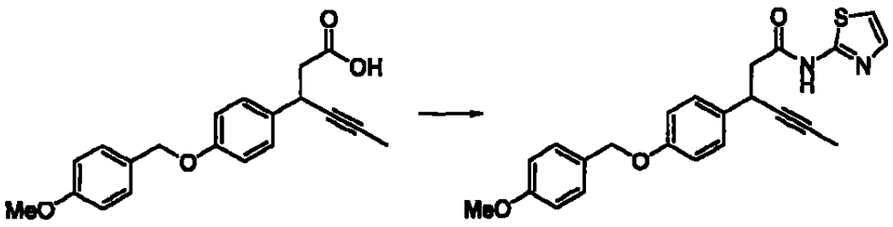
[0363] **5-{2-[4-(2-Methyl-benzyloxy)-phenyl]-pent-3-ynyl}-1*H*-tetrazole (23).** To a solution of **23.3** (200 mg, 0.51 mmol) in DMF (5 mL) was added sodium azide (35 mg, 0.54 mmol) and ammonium chloride (29 mg, 0.54 mmol). The solution was stirred at 110° C for 48 hours. The reaction mixture was poured into 50 mL of water and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were concentrated under reduce pressure, and the resulting residue was purified via HPLC to yield 5 mg (3%) of 5-{2-[4-(2-Methyl-benzyloxy)-phenyl]-pent-3-ynyl}-1*H*-tetrazole (**23**) as a film. LC/MSD *m/e*: 333.1 (M+H). ^{1}H NMR (400 MHz) (acetone-d_6) δ 7.45 (1H, m), 7.34 (2H, m), 7.25 (3H, m), 7.00 (2H, m), 5.11 (2H, s), 4.17 (1H, m), 3.37 (2H, d, *J*=7 Hz), 2.39 (3H, s), 1.79 (3H, s).

6.24 Example 24

[0364] The following example illustrates the synthesis of 3-[4-(4-Methoxy-benzyloxy)-phenyl]-hex-4-ynoic acid thiazol-2-ylamide.

85

Scheme 24.1



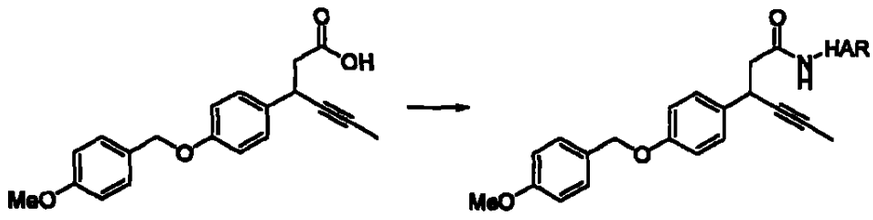
12 24

[0365] **3-[4-(4-Methoxy-benzyloxy)-phenyl]-hex-4-ynoic acid thiazol-2-ylamide (24).** A pear-shaped flask was charged with a stir bar, compound 12 (50 mg, 0.154 mmol), carbonyl diimidazole (25 mg, 0.154 mmol) and THF (4 mL). The mixture was refluxed for 1 hour, and 2-amino thiazole (16 mg, 0.154 mmol) was then added. The reaction was refluxed for 48 hours, poured into water and extracted with ethyl acetate. The organic layer was concentrated and the resulting residue was purified via HPLC to yield 1.0 mg (2%) of 3-[4-(4-Methoxy-benzyloxy)-phenyl]-hex-4-ynoic acid thiazol-2-ylamide (24) as a film. ^{1}H NMR (400 MHz) (acetone-d_6) δ 7.39 (4H, m), 7.11 (1H, s), 6.95 (3H, m), 5.03 (2H, s), 3.82 (3H, s), 2.95 (2H, m), 1.79 (3H, s).

6.25 **Example 25**

[0366] The compounds in the following table were prepared using the method described in Example 24.

TABLE 9



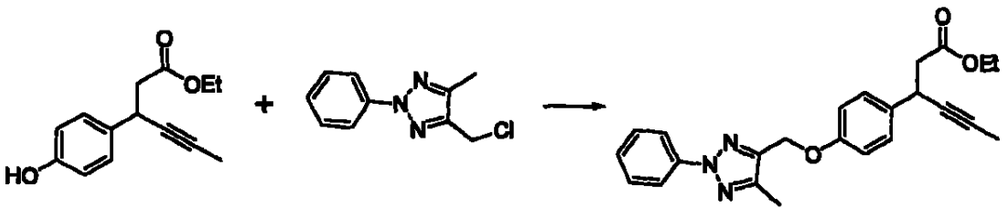
12

Compound	HAR
25.1	Tetrazole-5-yl
25.2	pyrimidin-2-yl
25.3	Pyridin-2-yl

6.26 **Example 26**

[0367] The following example illustrates the preparation of 3-[4-(5-Methyl-2-phenyl-2*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-hex-4-ynoic acid (26).

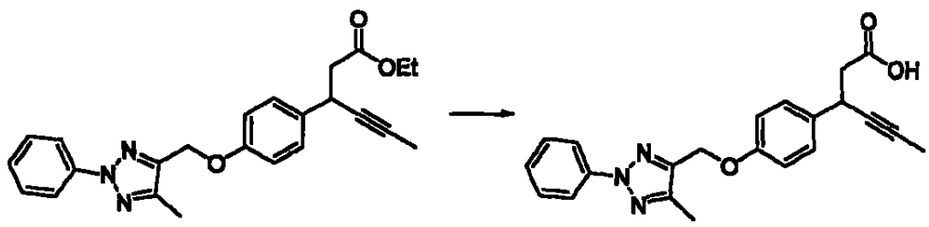
Scheme 26.1



16 **26.1** **26.2**

[0368] **3-[4-(5-Methyl-2-phenyl-2*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-hex-4-ynoic acid ethyl ester (26.2).** Cesium carbonate (107 mg, 0.33 mmol) was added to a solution of 16 (60 mg, 0.22 mmol) in DMF (5 mL). The mixture was stirred at room temperature for 5 minutes, and 4-Chloromethyl-5-methyl-2-phenyl-2*H*-[1,2,3]triazole (55 mg, 0.22 mmol) was added. The reaction was heated to 60° C and stirred overnight. The reaction mixture was then poured into copious water. 1N $HCl_{(aq)}$ was added to adjust the pH to 4.0. The aqueous layer was extracted with ethyl acetate. The organic layer was then washed with water, followed with brine. The organic layer was dried (Na_2SO_4) and concentrated. The resulting residue was purified via radial chromatography (20% ethyl acetate in hexanes) to yield 60 mg (66%) of 3-[4-(5-Methyl-2-phenyl-2*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-hex-4-ynoic acid ethyl ester (26.2). LC/MSD *m/e*: 404.2 (M+H).

Scheme 26.2



26.2 **26**

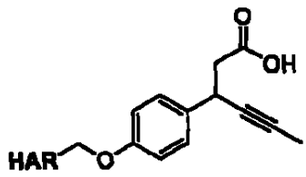
[0369] **3-[4-(5-Methyl-2-phenyl-2*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-hex-4-ynoic acid (26).** 2N KOH(aq) (1 mL) was added to a solution of **26.2** (68 mg, 0.17 mmol) in EtOH (2 mL). The reaction was stirred at room temperature overnight and then poured into water. The aqueous mixture was acidified to pH = 2 with 1N HCl(aq), and then extracted with ethyl acetate. The organic layer was washed with water, followed by brine. The organic layer was then concentrated under reduced pressure and the resulting residue was purified via radial chromatography (20% ethyl acetate in hexanes) to yield 60.3 mg (95%) of compound **26** as a colorless oil. LC/MSD *m/e*: 374.0 (M-H); ^{1}H NMR (400

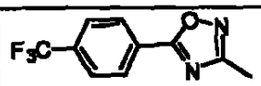
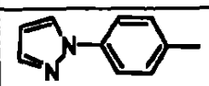
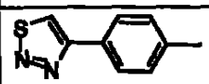
MHz) (acetone-d6) δ 8.09 (2H, d, J=8.0 Hz), 7.56 (2H, t, J=8.0 Hz), 7.40 (3H, t, J=8.0 Hz), 7.06 (2H, d, J=8.0 Hz), 5.28 (2H, s), 4.05 (1H, m), 2.70 (2H, m), 2.44 (3H, s), 1.80 (3H, s).

6.27 **Example 27**

[0370] The compounds in the following table were prepared using methods similar to those described in Example 26.

TABLE 10

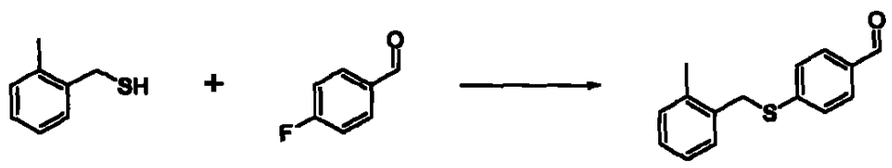


Compound	HAR
27.1	
27.2	
27.3	

6.28 **Example 28**

[0371] The following example illustrates the preparation of 3-[4-(2-Methyl-benzylsulfanyl)-phenyl]-hex-4-ynoic acid (28).

Scheme 28.1

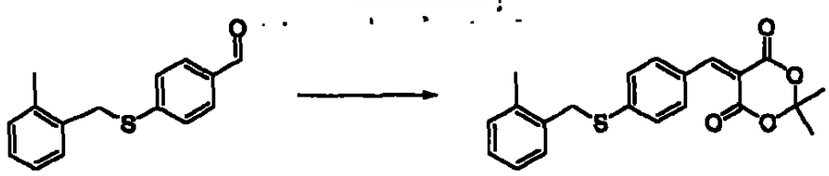


28.1

[0372] **4-(2-Methyl-benzylsulfanyl)-benzaldehyde (28.1).** 4-fluoro-benzaldehyde (1.16 g, 9.32 mmol) was added dropwise over 2 minutes to a solution of *o*-tolyl-methanethiol (1.35 g, 9.79 mmol) and Cesium carbonate (3.19 g, 9.79 mmol) in DMF (20 mL). The solution was stirred at 40 °C overnight and then poured into copious water. The pH of the solution was adjusted to 4 with 1N $HCl_{(aq)}$, and the aqueous solution was extracted with ethyl acetate (2 x 35 mL). The combined organic layers were washed with

water, followed by brine. The combined organic layers were then dried (Na_2SO_4) and the solvent removed under reduced pressure. The resulting residue was purified via radial chromatography (15% ethyl acetate in hexanes) to yield 1.29 g (54%) of 4-(2-Methyl-benzylsulfanyl)-benzaldehyde (28.1). LC/MSD *m/e*: 243.0 (M+H).

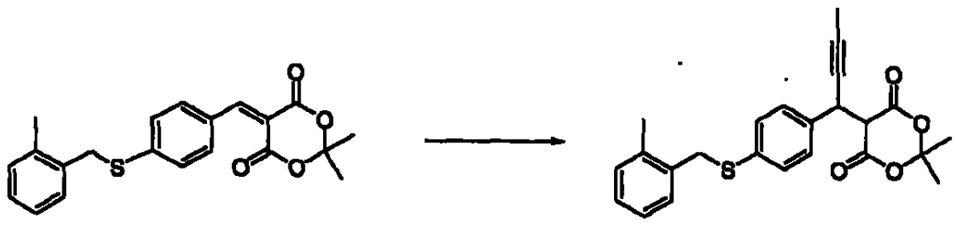
Scheme 28.2



28.1 28.2

[0373] **2,2-Dimethyl-5-[4-(2-methyl-benzylsulfanyl)-benzylidene]-[1,3]dioxane-4,6-dione (28.2).** Pyrrolidine (0.45 mL, 5.27 mmol) was added to a solution of aldehyde 28.1 in diethyl ether (20 mL) and the mixture was sonicated for 5 minutes. The mixture was then added to a solution of Meldrum's acid (0.73 g, 5.08 mmol) in diethyl ether (20 mL) and the resultant mixture was sonicated for 5 minutes, forming a solid. The solid was filtered, rinsed with diethyl ether, and then suspended in DCM (10 mL). p-Toluenesulfonic acid (0.97 g, 5.10 mmol) was then added to the suspension and the suspension was sonicated until clear. The solvent was removed under reduced pressure, and the resulting residue was taken up in diethyl ether and partitioned between water and ethyl acetate. The aqueous layer was extracted 2 additional times with ethyl acetate. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to yield 1.05 g (54%) of 2,2-Dimethyl-5-[4-(2-methyl-benzylsulfanyl)-benzylidene]-[1,3]dioxane-4,6-dione (28.2) as a yellow oil The resulting yellow oil was used without further purification. LC/MSD *m/e*: 391.1 (M+Na).

Scheme 28.3

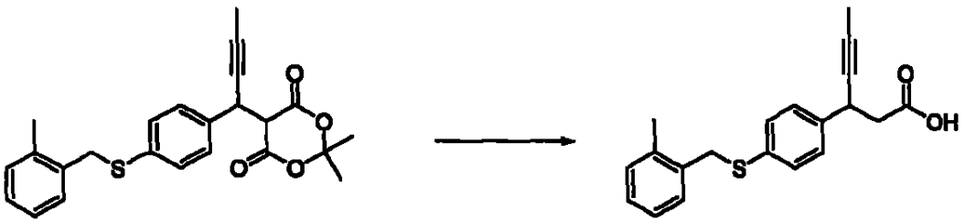


28.2 28.3

[0374] **2,2-Dimethyl-5-{1-[4-(2-methyl-benzylsulfanyl)-phenyl]-but-2-ynyl}-[1,3]dioxane-4,6-dione (28.3).** An oven-dried 100 mL pear-shaped flask, fitted with an oven-dried stir bar, was charged with a 0.5 M solution of 1-propynyl magnesium bromide in

THF (12.5 mL, 6.27 mmol) via cannula. The solution was cooled to 0° C, and then a solution of **28.2** (1.05 g, 2.85 mmol) in anhydrous THF (6 mL) was added over 3 minutes via cannula. The reaction was stirred at 0° C for 5 minutes and then stirred at room temperature for 1.5 hours. The reaction mixture was poured into saturated $NH_4Cl_{(aq)}$ and extracted with ethyl acetate. The combined organic layers were washed with water, followed by brine. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified via radial chromatography (20% ethyl acetate in hexanes) followed by recrystalization from hot ethyl acetate and hexanes to yield 162 mg (15%) of 2,2-Dimethyl-5-{1-[4-(2-methyl-benzylsulfanyl)-phenyl]-but-2-ynyl}-[1,3]dioxane-4,6-dione (**28.3**). LC/MSD *m/e*: 409.1 (M+H).

Scheme 28.4



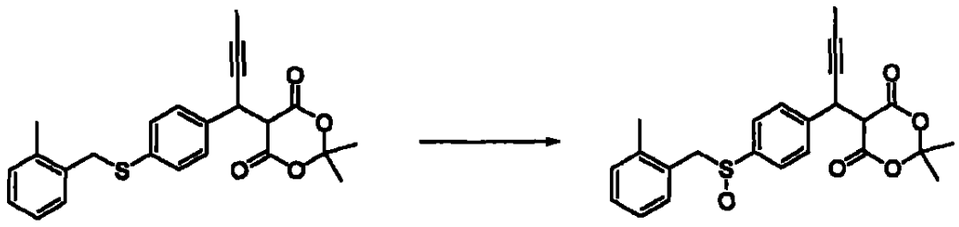
28.3 **28**

[0375] **3-[4-(2-Methyl-benzylsulfanyl)-phenyl]-hex-4-ynoic acid (28).** A solution of **28.3** (20 mg, 0.05 mmol) in 5:1 pyridine:water (6 mL) was heated to 80° C for 72 hours. The reaction was poured into 500 mL of water and the solution was acidified with 1N $HCl_{(aq)}$ (65 mL). The aqueous solution was extracted with ethyl acetate and the combined organic layers were washed with water, followed by brine. The combined organic layers were then dried (Na_2SO_4) and concentrated *in vacuo*. The resultant residue was then purified via radial chromatography (30% ethyl acetate in hexanes) to yield 18 mg (quantitative) 3-[4-(2-Methyl-benzylsulfanyl)-phenyl]-hex-4-ynoic acid (**28**). LC/MSD *m/e*: 323.1 (M-H).

6.29 Example 29

[0376] The following example illustrates the preparation of 3-(4-*o*-Tolylmethanesulfinyl-phenyl)-hex-4-ynoic acid.

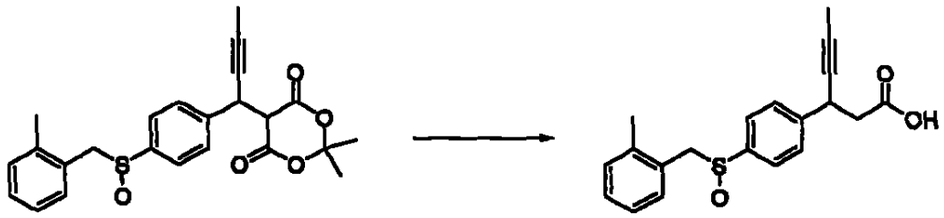
Scheme 29.1



28.3 29.1

[0377] **2,2-Dimethyl-5-[1-(4-*o*-tolylmethanesulfinyl-phenyl)-but-2-ynyl]-[1,3]dioxane-4,6-dione (29.1).** Hydrogen peroxide (20 µL, 0.05 mmol) was added to a 0° C solution of **28.3** (20 mg, 0.05 mmol) in AcOH (2 mL). The reaction was stirred at 80° C for 1.5 hours, then cooled to room temperature and stirred for 16 hours. The reaction mixture was poured into cold water and the resulting solution was acidified to pH = 2 with 6N HCl(aq). The aqueous layer was extracted with ethyl acetate and *sec*-butanol. The combined organic layers were concentrated to yield 10 mg (50%) of 2,2-Dimethyl-5-[1-(4-*o*-tolylmethanesulfinyl-phenyl)-but-2-ynyl]-[1,3]dioxane-4,6-dione (29.1). LC/MSD *m/e*: 383.0 (consistent with di-acid –H).

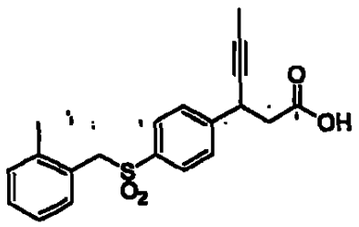
Scheme 29.1



29.1 29

[0378] **3-(4-*o*-Tolylmethanesulfinyl-phenyl)-hex-4-ynoic acid (29).** 29.1 (10.0 mg, 0.025 mmol) was hydrolyzed using the methods described in Example 28 to yield 3.0 mg (25%) of 3-(4-*o*-Tolylmethanesulfinyl-phenyl)-hex-4-ynoic acid (29). LC/MSD *m/e*: 339.1 (M-H); ^{1}H NMR (400MHz) (acetone-d_6) δ 7.60 (2H, m), 7.49 (2H, m), 7.21 (2H, m), 7.04 (2H, m), 5.63 (2H, s), 4.17 (1H, m), 2.81 (2H, m), 2.22 (3H, s), 1.88 (3H, s).

6.30 Example 30



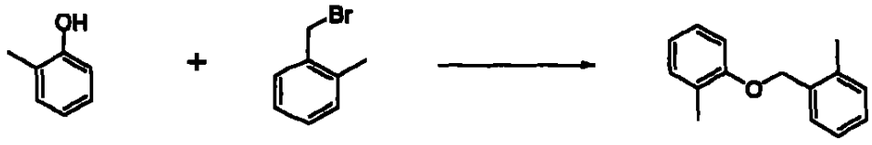
30

[0379] 3-(4-*o*-Tolylmethanesulfonyl-phenyl)-hex-4-ynoic acid (30) was prepared using methods similar to those described in Example 29.LC/MSD *m/e*: 357.2 (M+H); ^{1}H NMR (400MHz) (acetone-d_6) δ 7.69 (3H, m), 7.50 (1H, m), 7.17 (4H, m), 4.53 (2H, s), 4.22 (1H, m), 2.79 (2H, m), 2.27 (3H, s), 1.82 (3H, s).

6.31 Example 31

[0380] The following example illustrates the preparation of 3-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-hex-4-enoic acid (31).

Scheme 31.1



31.1

[0381] 2-(2-methyl-benzyloxy)toluene (31.1). α-bromo-*o*-xylene (2.0 g, 10.81 mmol) was added to a solution of 2-methyl-phenol (1.06 g, 9.82 mmol) and cesium carbonate (7.99 g, 24.55 mmol) in DMF (20 mL). The reaction was stirred at 80° C overnight. The reaction mixture was acidified with 25 mL 1N HCl(aq) and poured into copious water. The aqueous layer was extracted with ethyl acetate and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified via radial chromatography (20% ethyl acetate in hexanes) to yield 1.82 g (88%) of 2-(2-methyl-benzyloxy)toluene (31.1). LC/MSD *m/e*: 213.2 (M+H).

Scheme 31.2



31.1 31.2

[0382] 2-(2-methyl-benzyloxy)-5-bromotoluene (31.2). NBS (1.46 g, 8.23 mmol) was added to a solution of 31.1 (1.59 g, 7.48 mmol) in carbon tetrachloride (8 mL). The reaction was stirred at 60° C overnight and filtered to remove succinimide. The filtrate was concentrated *in vacuo* and purified via radial chromatography (15% diethyl ether in hexanes) to yield 0.65g (25%) of 2-(2-methyl-benzyloxy)-5-bromotoluene (31.2). LC/MSD *m/e*: 314.2 (M+Na).

Scheme 31.3



31.2 31.3

[0383] 2-Methyl-4-(2-methyl-benzyloxy)-benzaldehyde (31.3). A 2.5M solution of *n*-BuLi (2.1 mL, 5.26 mmol) in THF was added dropwise to a –78° C solution of 31.2 (1.46 g, 5.01 mmol) in THF (25 mL). The reaction was stirred at –78° C for 15 minutes and then DMF (3.3 mL) was added. Cooling was removed after 5 minutes and the reaction was allowed to warm to room temperature. The reaction was partitioned between ethyl acetate and water and the aqueous layer was extracted 1 additional time with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. The resulting residue was purified via radial chromatography (5% ethyl acetate in hexanes0 to yield 269 mg (22%) of 2-Methyl-4-(2-methyl-benzyloxy)-benzaldehyde (31.3). LC/MSD *m/e*: 241.2 (M+H).

Scheme 31.4



31.3 31.4

[0384] 4-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-but-3-en-2-one (31.4). 2N $NaOH_{(aq)}$ (0.6 mL) was added to a solution of 31.3 (100 mg, 0.42 mmol) in acetone (1 mL). The reaction was stirred at room temperature overnight and then taken up in water. The aqueous solution was acidified with 1N $HCl_{(aq)}$ (1.5 mL) and extracted with ethyl acetate. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The resultant residue was purified via radial chromatography (20% ethyl acetate in hexanes) to yield 74 mg (63%) of 4-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-but-3-en-2-one

(31.4). LC/MSD *m/e*: 281.4 (M+H); ^{1}H NMR (400 MHz) (acetone-d_6) δ 7.83 (1H, d, *J*=16), 7.70 (1H, m), 7.46 (1H, m), 7.25 (3H, m), 6.96 (2H, m), 6.63 (1H, d, *J*=16 Hz).

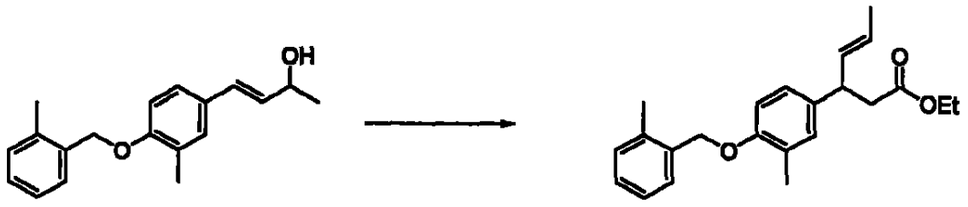
Scheme 31.5



31.4 **31.5**

[0385] **4-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-but-3-en-2-ol (31.5).** $NaBH_4$ (20 mg, 0.51 mmol) was added to a 0.4 M solution of $CeCl_3$ in MeOH (0.65 mL, 0.26 mmol), **31.4** (74 mg, 0.26 mmol), and THF (1 mL). The reaction was stirred, uncapped, until gas evolution ceased. The reaction was quenched with water (1.5 mL) and partitioned between water and diethyl ether. The aqueous layer was extracted 2 times with diethyl ether and the combined organic layers were washed with brine and concentrated *in vacuo* to yield 69 mg (93%) of 4-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-but-3-en-2-ol (**31.5**). LC/MSD *m/e*: 266.3 (M-OH); ^{1}H NMR (400 MHz) (DMSO-d_6) δ 7.44 (2H, m), 7.25 (3H, m0, 6.86 (2H, m), 6.75 (1H, m), 6.08 (1H, m), 5.11 (2H, s), 4.40, (1H, m), 2.38 (3H, s), 2.32 (3H, s), 1.29 (3H, m).

Scheme 31.6



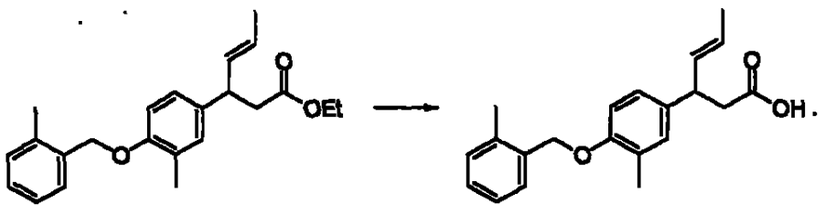
31.5 **31.6**

[0386] **3-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-hex-4-enoic acid ethyl ester (31.6).** Propionic acid (cat.) was added to a solution of **31.5** (69 mg, 0.24 mmol) in 1,1,1-triethoxy-ethane (440 µL, 2.4 mmol). The reaction was stirred at 105° C overnight. The solvent was removed under reduced pressure and the resulting residue was purified via radial chromatography (5% ethyl acetate in hexanes) to yield 33 mg (39%) of 3-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-hex-4-enoic acid ethyl ester (**31.6**). LC/MSD *m/e*: 375.0 (M+Na).

94

94

Scheme 31.7



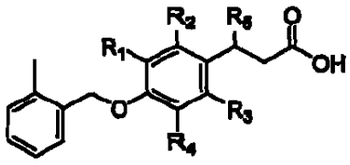
31.6 31

[0387] **3-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-hex-4-enoic acid (31).** The hydrolysis of **31.6** (33 mg, 0.094 mmol) was carried out using methods similar to those described in Example 26 to yield 5.7 mg (19%) of 3-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-hex-4-enoic acid (31). ^{1}H NMR (400 MHz) (acetone) δ 7.44 (2H, m), 7.25 (3H, m), 6.86 (2H, m), 6.73 (1H, m), 6.10 (1H, m), 5.64 (2H, s), 4.42 (1H, m), 2.38 (3H, s), 2.32 (3H, s), 1.29 (3H, d, J=7.0 Hz).

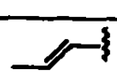
6.32 **Example 32**

[0388] The following compounds were made using methods similar to those described in Examples 28 and 31.

TABLE 11



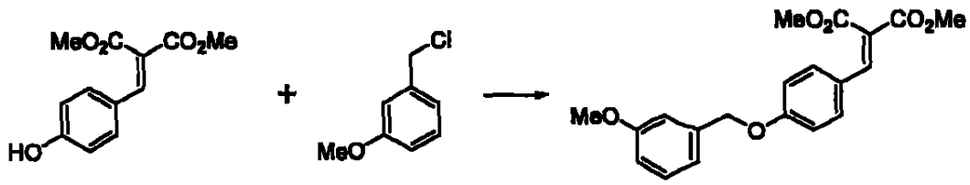
32

Compound	R1	R2	R3	R4	R5
32.1	Me	H	Me	H	
32.2	H	Ph	H	H	
32.3	Me	Me	H	H	
32.4	Ph	H	H	H	

Example 33

[0389] The following example illustrates the preparation 3-[4-(3-Methoxy-benzyloxy)-phenyl]-5-methyl-hex-4-enoic acid (33).

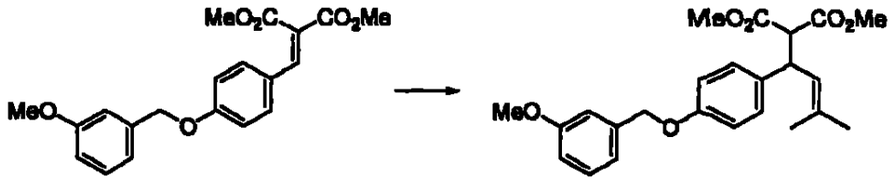
Scheme 33.1



33.1

[0390] 2-[4-(3-Methoxy-benzyloxy)-benzylidene]-malonic acid dimethyl ester (33.1). K_2CO_3 was added to a solution of 4-hydroxybenzylidene-malonic acid dimethyl ester (6.95 mmol) and 4-methyoxybenzyl chloride (7.64 mmol) in DMF (15 ml). It was stirred at room temperature overnight. The reaction was poured into water, and the product was extracted with ethyl acetate twice. The organic layer was washed with water and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified using silica gel column chromatography (hexane/ethyl acetate = 2/1) to give compound 33.1 as a white solid (3.2 mmol).

Scheme 33.2



33.1 33.2

[0391] 2-{1-[4-(3-Methoxy-benzyloxy)-phenyl]-3-methyl-but-2-enyl}-malonic acid dimethyl ester (33.2). 2-methyl-1-propenylmagnesium bromide (3 mL, 0.5 M in THF) was added dropwise to a solution of compound 33.1 (1.0 mmol) in THF. The reaction mixture was stirred at room temperature for 1hr and then quenched with saturated $NH_4Cl_{(aq)}$ and the aqueous layer extracted with ethyl acetate twice. The combined organic layers were washed with water and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified using silica gel column chromatography (hexane/ethyl acetate = 2/1) to give compound 33.2 as a white solid (0.93 mmol).

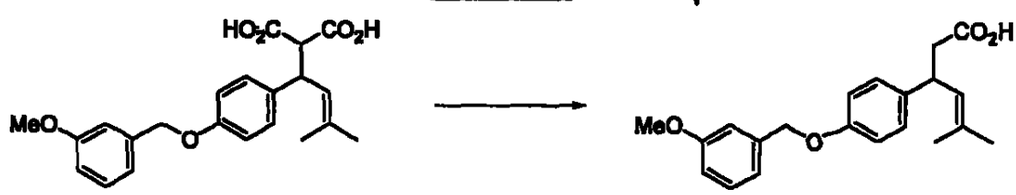
Scheme 33.3



33.2 33.3

[0392] **2-{1-[4-(3-Methoxy-benzyloxy)-phenyl]-3-methyl-but-2-enyl}-malonic acid (33.3).** To a solution of compound 33.2 (0.50g, 1.21 mmol) in THF (5 ml), methanol (5 ml) and water (2.5 ml) was added lithium hydroxide monohydrate (1.17g, 28 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was acidified with 1N HCl to pH 2-3, and then extracted with ethyl acetate twice. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was used for the next reaction without purification.

Scheme 33.4



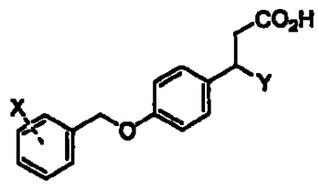
33.3 33

[0393] **3-[4-(3-Methoxy-benzyloxy)-phenyl]-5-methyl-hex-4-enoic acid (33).** A suspension of compound 33.3 (0.136 mmol) in toluene was refluxed for 16 h. After removing the solvent, the residue was purified using silica gel column chromatography (TFA/ Dichloromethane/ ethyl acetate = 1/5/40) to give compound 33 as a white solid (0.088 mmol). MS ESI m/e: 339 (M-H) ^{1}H NMR (500MHz) (DMSO-d_6) δ 11.97 (1H, s); 7.31 (1H, t, J=10 Hz); 7.14 (2H, d, J=11 Hz); 6.99 (2H, m); 6.87 (3H, m); 5.22 (1H, m); 5.03 (2H, s); 3.75 (1H, m); 3.75 (3H, s); 2.44-2.53 (2H, m); 1.63 (3H, s); 1.62 (3H, s).

6.34 **Example 34**

[0394] The following compounds were made using the method described in Example 33.

TABLE 12



Compound	X	Y
34.1	4-Methoxy	1-Propenyl
34.2	4-Methoxy	3-Propenyl
34.3	4-Methoxy	Vinyl
34.4	4-Methoxy	2-Propenyl
34.5	4-Methoxy	2-Methyl-1-propenyl
34.6	4-Methoxy	1-Methyl-1-propenyl
34.7	4-Methoxy	Thiophen-2-yl
34.9	2-Methoxy	2-Methyl-1-propenyl
34.10	3-Methoxy	1-Propynyl
34.11	3-Ethoxy	2-Methyl-1-propenyl

[0395] Compound 34.1. MS ESI m/e: 325 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.05 (1H, s); 7.36 (2H, d, J=10 Hz); 7.16 (2H, d, J=10 Hz); 6.94 (2H, d, J=10 HZ); 6.90 (2H, d, J=5 Hz); 5.48-5.58 (1H, m); 5.39-5.43 (1H, m); 4.98 (2H, s); 3.99-4.03 (1H, m); 3.76 (3H, s); 2.46-2.60 (2H, m); 1.64 (3H, d, J=5 HZ).

[0396] Compound 34.2. MS ESI m/e: 325 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 11.98 (1H, s); 7.38 (2H, d, J=10 Hz); 7.13 (2H, m); 6.95 (2H, m); 6.09 (2H, m); 5.63 (1H, m); 4.97 (2H, s); 4.92 (2H, d, J=10 Hz); 3.76 (3H, s); 3.03 (1H, m); 2.28-2.56 (4H, m).

[0397] Compound 34.3. MS ESI m/e: 311 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.06 (1H, s); 7.37 (2H, d, J=10 Hz); 7.14 (2H, d, J=10 Hz); 6.92-6.95 (4H, m); 5.92 (1H, m); 5.00 (2H, m); 4.98 (2H, s); 3.76 (3H, s); 3.35 (1H, m); 2.54-2.64 (2H, m).

[0398] Compound 34.4. MS ESI m/e: 325 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.03 (1H, s); 7.37 (2H, d, J=10 Hz); 7.09-7.19 (4H, m); 6.91-6.99 (4H, m); 4.97 (2H, s); 3.76 (3H, s); 3.63 (1H, m); 2.57-2.71 (2H, m); 2.09 (3H, s).

[0399] Compound 34.5. MS ESI m/e: 339 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 11.97 (1H, s); 7.36 (2H, d, J=10 Hz); 7.14 (2H, d, J=10 Hz); 6.94 (2H, d, J=10 Hz); 6.89 (2H, d, J=5 Hz); 5.24 (2H, d, J=10 Hz); 3.85-3.90 (1H, m); 3.76 (3H, s); 2.44-2.57 (2H, m); 1.68 (3H, s); 1.63 (3H, d, J=10 Hz).

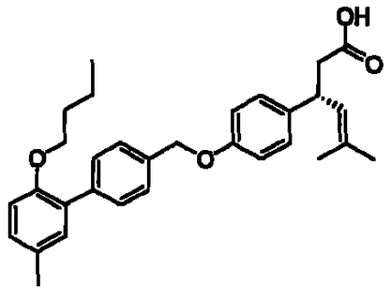
[0400] Compound 34.6. MS ESI m/e: 339 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 11.97 (1H, s); 7.37 (2H, d, J=8.5 Hz); 7.10 (2H, d, m); 6.90-6.95 (4H, m); 5.23 (1H, d, J=6.5 Hz); 4.97 (2H, s); 4.29 (1H, m); 3.76 (3H, s); 2.47-2.75 (2H, m); 1.71 (3H, d, J=6 Hz); 1.56 (3H, s).

[0401] Compound 34.7. MS ESI m/e: 367 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.18 (1H, s); 7.37 (2H, d, J=5 Hz); 7.32 (1H, m); 7.21 (2H, d, J=10 Hz); 6.92-6.95 (6H, m); 4.98 (2H, s); 4.58 (1H, m); 3.76 (3H, s); 3.01 (1H, m); 2.94 (1H, m).

[0402] Compound 34.9. MS ESI m/e: 339 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 11.99 (1H, s); 7.37 (2H, m); 7.14 (2H, d, J=10 Hz); 7.04 (2H, d, J=10 Hz); 6.96 (1H, t, J=10 Hz); 6.88 (2H, d, J=10 Hz); 5.24 (2H, d, J=10 Hz); 5.00 (2H, s); 3.87 (1H, m); 3.87(3H, s); 2.45-2.55 (2H, m); 1.63 (3H, s).

[0403] Compound 34.10. MS ESI m/e: 323 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.10 (1H, s); 7.25-7.32 (3H, m); 7.01 (2H, d, J=9 Hz); 6.94 (2H, d, J=10 Hz); 6.88 (1H, m); 5.05 (2H, s); 3.92-3.95 (1H, m); 3.75 (3H, s); 2.58 (2H, d, J=10 Hz); 1.77 (3H, s).

[0404] Compound 34.11. MS ESI m/e:353.0 (M-H).



34.12

[0405] ^{1}H NMR (400MHz) ($(CD_3)_2SO$) δ 11.95 (s, 1H), 7.49 (d, 2H, J = 8.2 Hz), 7.15 (d, 2H, J = 8.6 Hz), 7.08-7.10 (m, 2H), 6.91-6.98 (m, 3H), 5.25 (d, 1H, 9.0 Hz), 5.07 (s, 2H), 3.78-3.94 (m, 3H), 2.44-2.59 (m, 2H), 2.26 (s, 3H), 1.55-1.63 (m, 8H), 1.30-1.38 (m, 2H), 0.85 (t, 3H, J = 7.3 Hz). $[M+1]^+$ Calculated for $C_{31}H_{36}O_4$: 473.3. Found 473.5.

6.35 Example 35

[0406] The following example illustrates the preparation 3-[4-(3-Methoxy-benzyloxy)-phenyl]-5-methyl-hex-4-enoic acid.

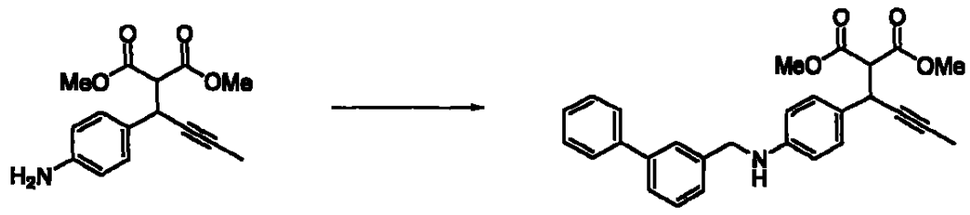
Scheme 35.1



35.1 35.2

[0407] **2-[1-(4-Amino-phenyl)-but-2-ynyl]-malonic acid dimethyl ester (35.2).** Tin chloride dihydrate (46 mmol) was added to solution of compound 35.1 (15.3 mmol, prepared from commercially available dimethyl-4-nitrobenzylidinemalonate and 1-propynylmagnesium bromide according to the method in Example 33) in ethanol (200 ml). The mixture was stirred at 70 °C for 17 h. After removing solvent under reduced pressure, aqueous sodium carbonate solution was added and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with water and brine, dried over Na_2SO_4, concentrated *in vacuo*. The resulting residue was filtered through short plug of silica gel, eluting with ethyl acetate. The eluant was concentrated to obtain compound 35.2 (12.8 mmol).

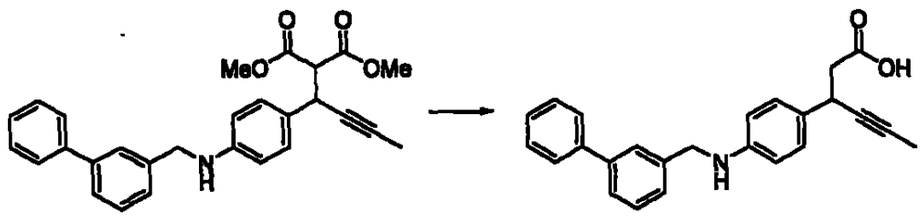
Scheme 35.2



35.2 35.3

[0408] **2-(1-{4-[(Biphenyl-3-ylmethyl)-amino]-phenyl}-but-2-ynyl)-malonic acid dimethyl ester (35.3).** A mixture of compound 35.2 (1.0 mmol), 3-(bromomethyl)biphenyl (1.3 mmol) and K_2CO_3 (2.0 mmol) in DMF (10 ml) was stirred at 90 °C for 19 h. After diluting with ethyl acetate, the mixture was washed with aqueous Na_2CO_3 and then with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified using silica gel column chromatography (hexane/ethyl acetate = 2/1) to give compound 35.3.

Scheme 35.3



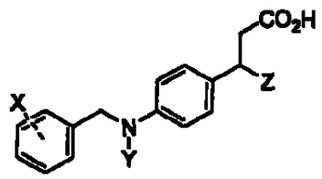
35.3 35

[0409] 3-{4-[(Biphenyl-3-ylmethyl)-amino]-phenyl-hex-4-ynoic acid (35). Compound 35 was prepared from compound 35.3 by hydrolysis with base and decarboxylation as described in Example 33. MS ESI m/e: 368 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.63-7.66 (2H, m); 7.51(1H, m); 7.34-7.44 (6H, m); 7.05 (2H, d, J=10 Hz); 6.60 (2H, d, J=10 Hz); 4.33 (2H, s); 3.79-3.83 (1H, m); 2.44-2.53 (2H, m); 2.09 (1H, s); 1.74 (3H, s).

6.36 Example 36

[0410] The following compounds were prepared according to the methods described in Example 35.

TABLE 13

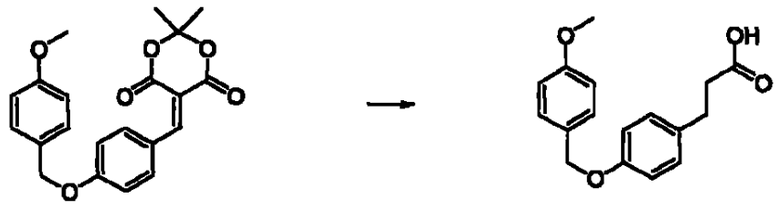


Compound	X	Y	Z
36.1	3-Methoxy	H	1-Propynyl
36.2	3-Methoxy	3-Methoxy-benzyl	1-Propynyl
36.3	4-Phenyl	H	1-Propynyl
36.4	4-(2-cyanophenyl)	H	1-Propynyl

6.37 Example 37

[0411] This example illustrates the preparation of (+/-)-3-(4-[(4-methoxyphenyl)methoxy]- phenyl)-propanoic acid.

Scheme 37.1



12.2 37

[0412] (+/-)-3-(4-[(4-methoxyphenyl)methoxy]phenyl)-propanoic acid (37). To a stirring ethyl acetate (100mL) solution of 5-[[4-[(4-methoxyphenyl)methoxy]phenyl]-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (200 mg, 0.543 mmol) was added EtOH (4 mL), followed by $NaBH_4$ (62 mg, 1.63 mmol). The reaction mixture was stirred at room temperature for 15 minutes, quenched with water (5 mL), extracted with EtOAc (10 mL). The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated to a white solid. A solution of this white solid in 3:1 pyridine-water (5 mL) was heated at 100 °C for 24h. The reaction mixture was cooled to room temperature and put in an ice-water bath. Concentrated HCl was carefully added to pH ~2. The resulting suspension was extracted with ethyl acetate (10mL x 3), dried over $MgSO_4$, filtered, and concentrated to an off-white solid. Preparative HPLC gave compound 37 as a white solid. MS ESI (neg.) m/e: 285.0 (M -1).

6.38 Example 38

[0413] This example illustrates the preparation of (+/-)-3-(4-[(4-methoxyphenyl)methoxy]- phenyl)-3-cyano-propanoic acid.



38

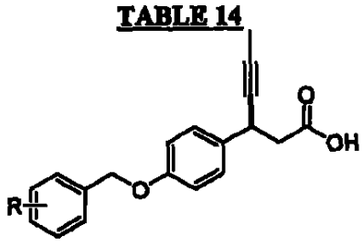
[0414] (+/-)-3-(4-[(4-methoxyphenyl)methoxy]phenyl)-3-cyano-propanoic acid (38). To a stirred DMF (10mL) solution of 2-[4-[(4-Methoxyphenyl)methoxy]phenyl]-acetonitrile (500 mg, 1.97 mmol) was added ethyl bromoacetate (330 µL, 2.96 mmol), followed by K_2CO_3 (820 mg, 5.9 mmol). The reaction mixture was stirred at room temperature for 2h, poured into ice water (100 mL), filtered, and dried to a white solid. 20 mg of this white solid in 1:1 THF/1N NaOH in MeOH (4 mL) was stirred for 5h. The reaction mixture was concentrated, diluted with water (10mL), washed with EtOAc (5mL x

2). The aqueous layer was acidified with 3N HCl to pH ~2, extracted with EtOAc (10mL x 2), dried over $MgSO_4$, filtered, and concentrated to a white solid. MS ESI (neg.) m/e: 310.0 (M -1).

6.39 **Example 39**

[0415] The following compounds were prepared by the methods described in Example 15 using the enantiomer with the shorter retention time from the chiral HPLC resolution.

TABLE 14



Compounds	R	Compounds	R
15	2-CH_3	39.4	4-(2-CN)Ph
39.1	3-CH_3	39.5	3-CF_3
39.2	3-CF_3O	39.6	4-Br
39.3	3-Cl	39.7	4-CH_3O

[0416] **(3*S*)-3-[4-(3-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid (39.1).** MS-ESI (neg.) m/e: 307.1 (M-H). $[\alpha]^{20}$: +21.26 (c0.188, DMF).

[0417] **(3*S*)-3-[4-(3-Trifluoromethoxy-benzyloxy)-phenyl]-hex-4-ynoic acid (39.2).** MS-ESI (neg.) m/e: 377.0 (M-H). $[\alpha]^{20}$: +18.30 (c0.259, DMF).

[0418] **(3*S*)-3-[4-(3-chlorobenzyloxy)-phenyl]-hex-4-ynoic acid (39.3).** MS-ESI (neg.) m/e: 327.1 (M-H). $[\alpha]^{20}$: +14.36 (c0.440, DMF).

[0419] **(3*S*)-3-[4-(2'-Cyano-biphenyl-4-ylmethoxy)-phenyl]-hex-4-ynoic acid (39.4).** MS-ESI (neg.) m/e: 394.1 (M-H). $[\alpha]^{20}$: +16.07 (c0.331, DMF).

[0420] **(3*S*)-3-[4-(2-Tirfluoromethyl-benzyloxy)-phenyl]-hex-4-ynoic acid (39.5).** MS-ESI (neg.) m/e: 361.1 (M-H). $[\alpha]^{20}$: +12.80 (c0.285, DMF).

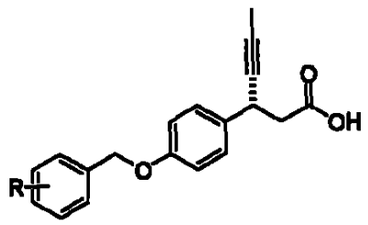
[0421] **(3*S*)-3-[4-(4-Bromobenzyloxy)-phenyl]-hex-4-ynoic acid (39.6).** MS-ESI (neg.) m/e: 371.0, 373.0 (M-H). $[\alpha]^{20}$: +19.19 (c0.238, DMF).

[0422] **(3*S*)-3-[4-(4-Methoxy-benzyloxy)-phenyl]-hex-4-ynoic acid (39.7).** MS-ESI (neg.) m/e: 323.0 (M-H). $[\alpha]^{20}$: +23.30 (c0.329, DMF).

6.40 Example 40

[0423] The following compounds were prepared by the methods described in Example 15 using the enantiomer with longer retention time from the chiral HPLC resolution.

TABLE 15



Compounds	R	Compounds	R
40.1	2-CH_3	40.4	3-CF_3
40.2	3-Cl	40.5	4-CH_3O
40.3	4-(2-CN)Ph		

[0424] **(3*R*)-3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid (40.1).** ^{1}HNMR (400 MHz, acetone-d_6) δ 7.45 (d, 1H, J=7.11 Hz); 7.37 (d, 2H, J=8.58 Hz); 7.26 (d, 1H, J=1.62 Hz); 7.22-7.27 (m, 2H); 7.00 (d, 2H, J=8.76 Hz); 5.11 (s, 2H); 4.05 (m, 1H); 3.33 (s, 1H); 2.69 (m, 2H); 2.38 (s, 3H); 1.80 (d, 3H, J=2.44). MS-ESI (neg.) m/e: 307.1 (M-H). $[\alpha]^{20}$: -19.78 (c0.286, DMF).

[0425] **(3*R*)-3-[4-(3-chlorobenzyloxy)-phenyl]-hex-4-ynoic acid (40.2).** MS-ESI (neg.) m/e: 327.0 (M-H). $[\alpha]^{20}$: -20.50 (c0.158, DMF).

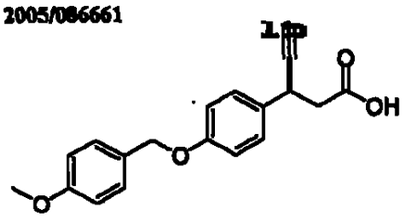
[0426] **(3*R*)-3-[4-(2'-Cyano-biphenyl-4-ylmethoxy)-phenyl]-hex-4-ynoic acid (40.3).** MS-ESI (neg.) m/e: 394.1 (M-H). $[\alpha]^{20}$: -25.04 (c0.143, DMF).

[0427] **(3*R*)-3-[4-(2-Tirfluoromethyl-benzyloxy)-phenyl]-hex-4-ynoic acid (40.4).** MS-ESI (neg.) m/e: 361.0 (M-H). $[\alpha]^{20}$: -14.69 (c0.286, DMF).

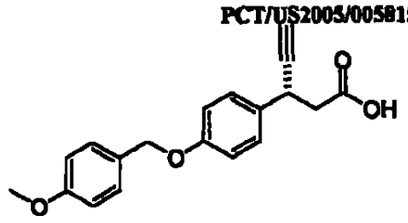
[0428] **(3*R*)-3-[4-(4-Methoxy-benzyloxy)-phenyl]-hex-4-ynoic acid (40.5).** MS-ESI (neg.) m/e: 323.0 (M-H). $[\alpha]^{20}$: -27.20 (c0.324, DMF).

6.41 Example 41

[0429] The following compounds were prepared by the methods similar to those of Example 15.



41.1



41.2

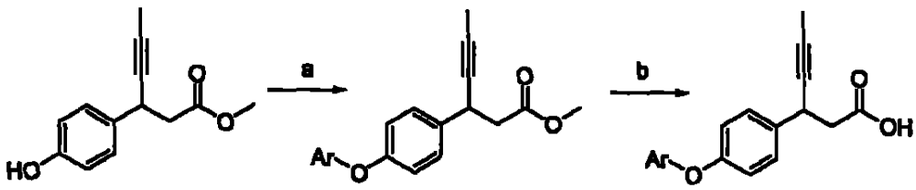
[0430] **(3*S*)-3-[4-(4-Methoxy-benzyloxy)-phenyl]-pent-4-ynoic acid (41.1).** MS-ESI (pos.) m/e: 333.1 (M+H). $[\alpha]^{20}$: +11.80 (c0.166, DMF).

[0431] **(3*R*)-3-[4-(4-Methoxy-benzyloxy)-phenyl]-pent-4-ynoic acid (41.2).** MS-ESI (pos.) m/e: 333.1 (M+H). $[\alpha]^{20}$: -10.20 (c0.206, DMF).

6.42 **Example 42**

[0432] Scheme 42.1 presents a general procedure for preparation of diaryl ether compounds.

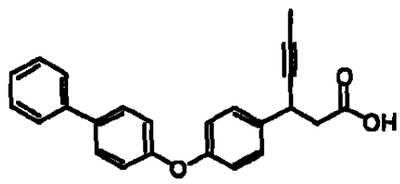
Scheme 42.1



Scheme 42.1. a. $ArB(OH)_2$, $CuO(Ac)_2$, Et_3N, DCM, 4A MS, r.t., 16h; b. LiOH/THF, MeOH, and water, r.t., 2h.

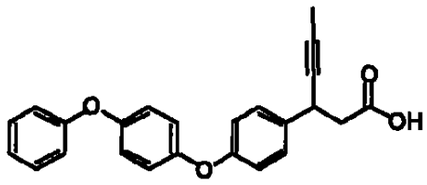
42.1 42.2 42.3

[0433] General procedure for preparation of diaryl ether compounds: A flask is charged with phenol (1.0 equiv.), $Cu(OAc)_2$ (1.0 equiv.), arylboronic acid (1.0-3.0 equiv.), powdered 4 Å molecular sieves. The reaction mixture was diluted with CH_2Cl_2 to yield a solution approximately 0.1 M in phenol, and Et_3N (5.0 equiv.) is added. After stirring the heterogeneous reaction mixture for 16h at 25 °C under ambient atmosphere, the resulting slurry is filtered and the diaryl ether is isolated from the organic filtrate by flash chromatography. The resulted ester was then hydrolyzed with LiOH (2.0 equiv.) in a 1:1:1 mixture of MeOH, THF, and water for 2h at 25 °C. The reaction mixture was acidified with 1N HCl, extracted with CH_2Cl_2 and concentrated to give the pure acid.



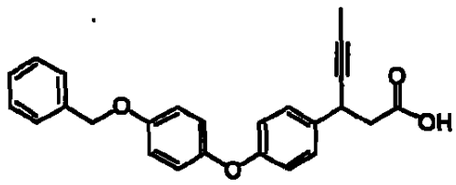
42.4

[0434] 3-[4-(Biphenyl-4-yloxy)-phenyl]-hex-4-ynoic acid (42.4). MS ESI m/e: 357.0 (M + H). ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.60-7.57 (4H, m); 7.46 (2H, dd, *J*=8.0, 8.0 Hz); 7.39 (2H, d, *J*=8.5 Hz); 7.36 (1H, d, *J*=7.3 Hz); 7.09 (2H, d, *J*=8.6 Hz); 7.04 (2H, d, *J*=8.6 Hz); 4.2-4.1 (1H, m); 2.87 (1H, dd, *J*=15.8, 8.6 Hz); 2.77 (1H, dd, *J*=15.8, 6.7 Hz); 1.88 (3H, d, *J*=2.3 Hz).



42.5

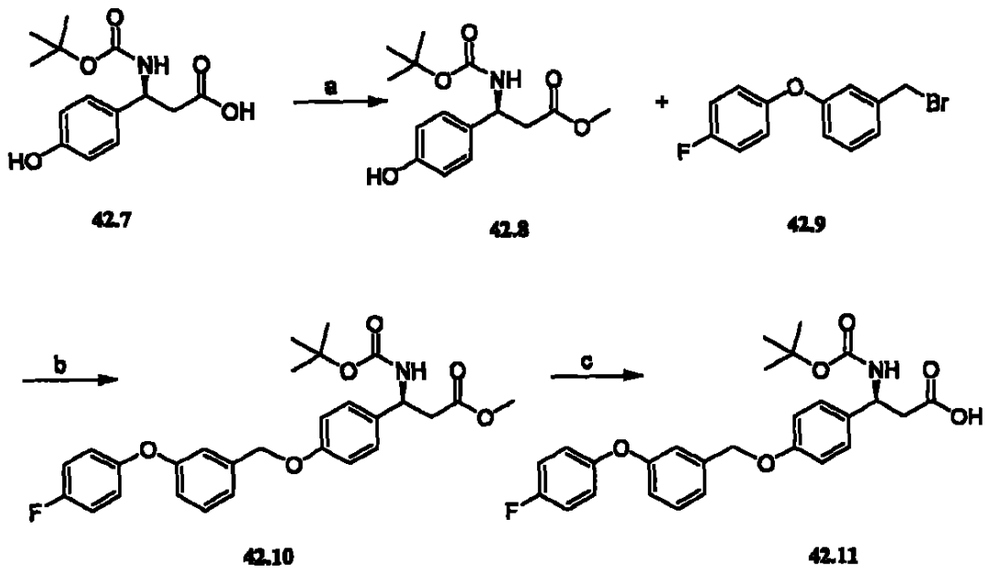
[0435] 3-[4-(4-Phenoxy-phenoxy)-phenyl]-hex-4-ynoic acid (42.5). MS ESI m/e: 373.0 (M + H). ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.37-7.32 (5H, m); 7.12 (2H, dd, *J*=8.0, 8.0 Hz); 7.03 (2H, d, *J*=7.5 Hz); 7.02 (2H, s); 6.97 (2H, d, *J*=8.6 Hz); 4.1 (1H, m); 2.85 (1H, dd, *J*=15.8, 8.6 Hz); 2.75 (1H, dd, *J*=15.8, 6.7 Hz); 1.87 (3H, d, *J*=2.3 Hz).



42.6

[0436] 3-[4-(4-Benzyloxy-phenoxy)-phenyl]-hex-4-ynoic acid (42.6). MS ESI m/e: 387.0 (M + H). ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.47 (2H, d, *J*=7.2 Hz); 7.42 (2H, dd, *J*=7.5, 7.5 Hz); 7.37 (1H, d, *J*=7.3 Hz); 7.33 (2H, d, *J*=8.7 Hz); 6.98 (4H, br. s); 6.93 (2H, d, *J*=9.7 Hz); 5.07 (2H, s); 4.10 (1H, m); 2.84 (1H, dd, *J*=15.7, 8.5 Hz); 2.75 (1H, dd, *J*=15.7, 6.7 Hz); 1.86 (3H, d, *J*=2.3 Hz).

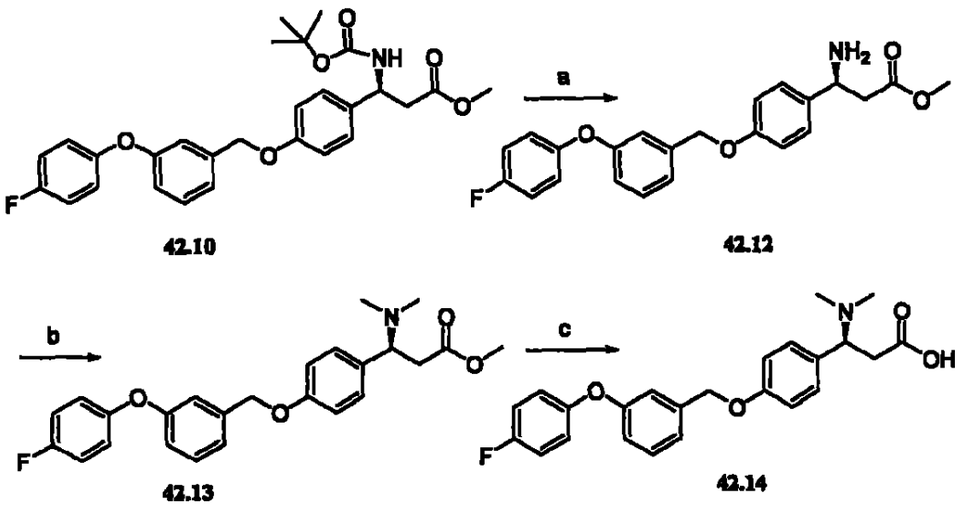
Scheme 42.2



Scheme 42.2. a. $TMSCHN_2$, MeOH, benzene, r.t., 1h; b. K_2CO_3, DMF, r.t., overnight; c. LiOH/THF, MeOH, and water, r.t., 2h.

[0437] **(*S*)-3-*tert*-Butoxycarbonylamino-3-{4-[3-(4-fluoro-phenoxy)-benzyloxy]-phenyl}-propionic acid (42.11).** 3-Boc-amino-3(4-hydroxyphenyl)-propanoic acid (42.7) (703 mg, 2.5 mmol) in 25mL of MeOH/Benzene (4:1) was slowly added 2.5 mL of 2M solution of trimethylsilyldiazomethane in hexane at 25 °C. The reaction mixture was stirred for 1h and concentrated in vacuo to give the methyl ester. MS ESI m/e: 296.0 (M + H). To a solution of the methyl ester 42.8 (2.5 mmol) and 4-fluorophenoxybenzyl bromide 42.9 (700 mg, 2.5 mmol) in DMF (10 mL), was added K_2CO_3 (414 mg, 3 mmol) and the resulting mixture was stirred overnight (14~16h) at 25 °C. The solution was diluted with water (20mL0 and extracted with EtOAc twice (20 mL). The organic extraction was concentrated and the product was purified by flash chromatography. MS ESI m/e: 518.0 (M + Na). The methyl ester 42.10 (39mg, 0.08 mmol) was hydrolyzed with LiOH (10 mg, 0.25 mmol) in a 1.5 mL of 1:1:1 mixture of MeOH, THF, and water for 2h at 25 °C. The reaction mixture was acidified with 1N HCl, extracted with CH_2Cl_2 and concentrated to give the pure acid (42.11). MS ESI m/e: 504.0 (M + Na). ^1H NMR (400MHz) ($CDCl_3$) δ 8.5 (1H, br. s); 7.34 (1H, dd, *J*=8.0, 8.0 Hz); 7.24 (2H, d, *J*=8.8 Hz); 7.16 (1H, d, *J*=7.7 Hz); 7.07-6.98 (5H, m); 6.93 (2H, d, *J*=11.7 Hz); 6.92 (1H, d); 5.3 (1H, br. s); 5.03 (2H, s); 3.0-2.8 (2H, m); 2.1-1.9 (1H, m); 1.44 (9H, s).

Scheme 42.3

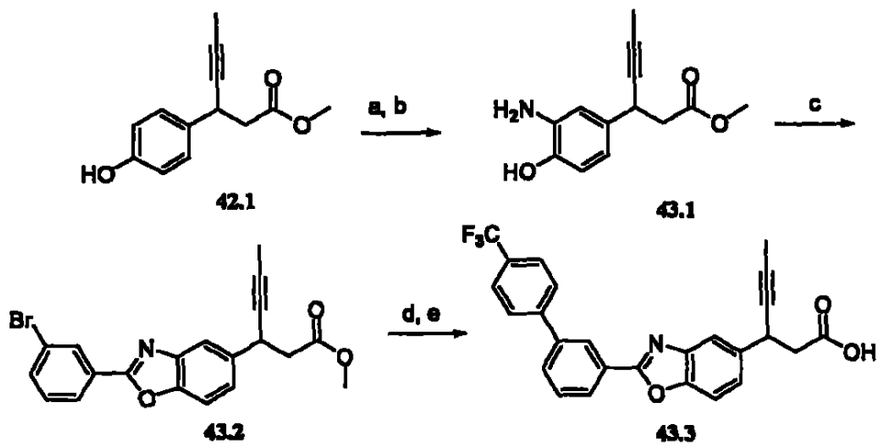


Scheme 42.3. a. TFA, DCM, r.t., 1h; b. formaldehyde, $NaBH(OAc)_3$, AcOH, DMF, r.t., overnight; c. LiOH/THF, MeOH, and water, r.t., 2h.

[0438] **3-Dimethylamino-3-{4-[3-(4-fluoro-phenoxy)-benzyloxy]-phenyl}-propionic acid (42.14).** (*S*)-3-*tert*-Butoxycarbonylamino-3-{4-[3-(4-fluoro-phenoxy)-benzyloxy]-phenyl}-propionic acid methyl ester (**42.10**) (1.0 g, 2 mmol) was treated with 10 mL of 10% TFA solution in CH_2Cl_2 at 25 °C for 1h. The solvent was concentrated in vacuo to give the free amine (**42.12**). MS ESI m/e: 418.0 (M + Na). The amine (60 mg, 0.15 mmol) was treated with excess formaldehyde (2 equiv.), $NaBH(OAc)_3$ (85 mg, 0.4 mmol) and catalytic amount of AcOH in DMF overnight (14~16h) at 25 °C. The product was purified by reverse phase HPLC. MS ESI m/e: 424.1 (M + H). The methyl ester was hydrolyzed with LiOH (19mg, 0.45 mmol) in a 3 mL of 1:1:1 mixture of MeOH, THF, and water for 2h at 25 °C. The reaction mixture was acidified with 1N HCl, extracted with CH_2Cl_2 and concentrated to give the pure acid (**42.14**) (23 mg). MS ESI m/e: 410.2 (M + H). ^{1}H NMR (500MHz) ($CDCl_3$) δ 9.46 (1H, br. s); 7.72 (1H, d, *J*=16.0 Hz); 7.51 (2H, d, *J*=8.7 Hz); 7.36 (1H, dd, *J*=8.0, 8.0 Hz); 7.17 (2H, d, *J*=7.0 Hz); 7.08-6.98 (5H, m); 6.94 (1H, d, *J*=8.2 Hz); 6.34 (1H, d, *J*=16.0 Hz); 5.10 (2H, s); 3.4-2.9 (2H, m); 2.73 (6H, s); 2.1-1.9 (1H, m).

6.43 Example 43

Scheme 43.1



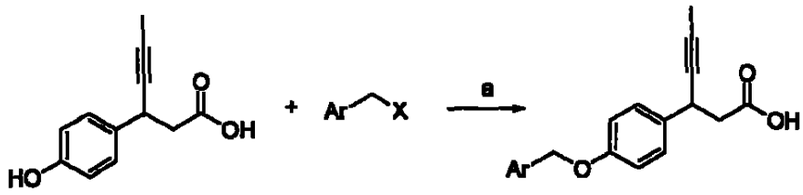
Scheme 43.1. a. HNO_3, HOAc, 80 °C, 3h; b. $SnCl_2$, EtOAc/EtOH, 70 °C, 3h; c. 3-bromobenzaldehyde, DDQ, DMF, r.t., 2h; d. 4-trifluoromethylbezeneboronic acid, $Pd(PPh_3)_4$, DME, Na_2CO_3, 80 °C, 14h; e. LiOH/THF, MeOH, and water, r.t., 2h.

[0439] **3-[2-(4'-Trifluoromethyl-biphenyl-3-yl)-benzooxazol-5-yl]-hex-4-ynoic acid (43.3).** 3-(4-Hydroxy-phenyl)-hex-4-ynoic acid methyl ester (1.32 g, 6 mmol) was treated with HNO_3 (0.30 mL, 7.2 mmol) in AcOH (10 mL) at 80 °C for 3h. The solvent was concentrated in vacuo and 3-(3-nitro-4-hydroxy-phenyl)-hex-4-ynoic acid methyl ester (613 mg, 2.3 mmol) was isolated from flash chromatography. MS ESI m/e: 264.0 (M + H). The nitro group was then reduced with $SnCl_2$ (2.62 g, 11.6 mmol) in EtOH (10 mL0 and EtOAc (10 mL) at 70 °C for 3h. The reaction mixture was cooled to 25 °C, washed with saturated aqueous Na_2CO_3, water, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was then purified by reverse phase HPLC to give 3-(3-amino-4-hydroxy-phenyl)-hex-4-ynoic acid methyl ester (174 mg, 0.74 mmol). MS ESI m/e: 234.0 (M + H). 3-(3-amino-4-hydroxy-phenyl)-hex-4-ynoic acid methyl ester (174 mg, 0.74 mmol) and 3-bromobenzaldehyde (278 mg, 1.5 mmol) in DMF (3 mL) was treated with DDQ (204 mg, 0.9 mmol) for 2h at 25 °C. The producted was purified by reverse phase HPLC. MS ESI m/e: 398.0 (M + H). 3-[2-(3-Bromo-phenyl)-benzooxazol-5-yl]-hex-4-ynoic acid methyl ester (19.6 mg, 0.05 mmol) and trifluorophenylboronic acid (38 mg, 0.2 mmol) in DME (1 mL) and 0.2 mL of 2M solution of aqueous Na_2CO_3 was treated with $Pd(PPh_3)_4$ at 80 °C for 14h. The product was isolated from flash chromatography. MS ESI m/e: 464.0 (M + H). The methyl ester (7.8 mg, 0.017 mmol) was hydrolyzed with LiOH (4mg, 0.1 mmol) in a 1 mL of 1:1:1 mixture of MeOH, THF, and water for 2h at 25 °C. The reaction mixture was acidified with 1N HCl, extracted with CH_2Cl_2 and concentrated to give the pure acid (7.6 mg). MS ESI m/e: 450.1 (M + H). ^1H NMR (500 MHz) ($CDCl_3$) δ

8.52 (1H, s); 8.36 (1H, d, J=7.8 Hz); 7.91 (1H, s); 7.83 (2H, d, J=8.2 Hz); 7.82 (1H, s); 7.78 (2H, dd, J=8.0, 8.0 Hz); 7.67 (1H, dd, J=7.8, 7.8 Hz); 7.58 (2H, d, J=8.4 Hz); 7.46 (1H, dd, J=8.4, 1.5 Hz); 4.29 (1H, m); 2.94 (1H, dd, J=15.8, 8.1 Hz); 2.84 (1H, dd, J=15.8, 6.9 Hz); 1.89 (3H, d, J=2.3 Hz).

6.44 **Example 44**

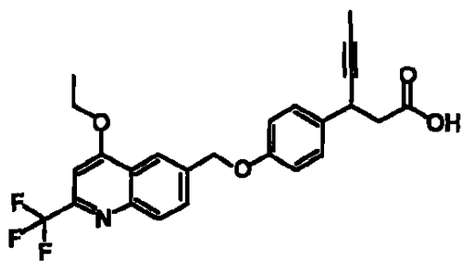
Scheme 44.1



Scheme 44.1. a. NaOH, EtOH, water, r.t., 3h (X = Br, Cl).

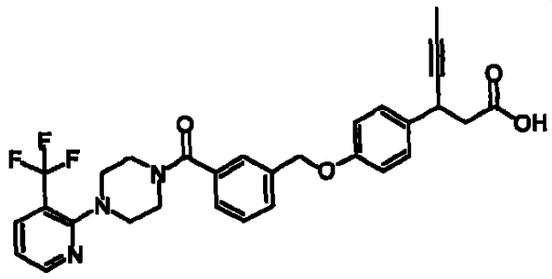
44.1 44.2

[0440] General procedure for the preparation of aryl benzyl ethers: 3-(4-Hydroxy-phenyl)-hex-4-ynoic acid in EtOH (0.4M) was added 1N NaOH solution (3 equiv.) in water at 25 °C and stirred fro 5 minutes at 70 °C. $ArCH_2X$ (X = Br, Cl, 1 equiv.) in EtOH (0.2M) was slowly added, stirred for 3h at 70 °C. The reaction mixture was acidified with 1N HCl and purified from reverse phase HPLC.



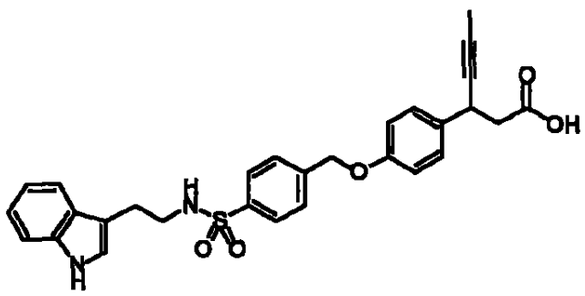
44.3

[0441] **3-[4-(4-Ethoxy-2-trifluoromethyl-quinolin-6-ylmethoxy)-phenyl]-hex-4-ynoic acid (44.3).** MS ESI m/e: 458.0 (M + H). ^{1}H NMR (400 MHz) (DMSO-d_6) δ 12.6 (1H, br. s); 8.31 (1H, s); 8.12 (1H, d, J=8.7 Hz); 7.95 (1H, dd, J=8.7, 1.3 Hz); 7.41 (1H, s); 7.31 (2H, d, J=8.5 Hz); 7.03 (2H, d, J=8.5 Hz); 5.36 (2H, s); 4.47 (2H, q, J=8.0 Hz); 3.96 (1H, m); 2.62 (2H, d, J=7.6 Hz); 1.79 (3H, d, J=1.9 Hz); 1.21 (3H, t, J=8.0 Hz).



44.4

[0442] **3-(4-{3-[4-(3-Trifluoromethyl-pyridin-2-yl)-piperazine-1-carbonyl]-benzyloxy}-phenyl)-hex-4-ynoic acid.** MS ESI m/e: 552.0 (M + H). ^{1}H NMR (400 MHz) (DMSO-d_6) δ 12.5 (1H, br. s); 8.57 (1H, d, *J*=3.5 Hz); 8.12 (1H, dd, *J*=7.9, 1.6 Hz); 7.56-7.48 (3H, m); 7.41 (1H, d, *J*=7.5 Hz); 7.30-7.25 (3H, m); 6.98 (2H, d, *J*=8.7 Hz); 5.16 (2H, s); 3.95 (1H, m); 3.2 (4H, m); 2.60 (2H, d, *J*=7.6 Hz); 2.52 (4H, m); 1.77 (3H, d, *J*=2.4 Hz).



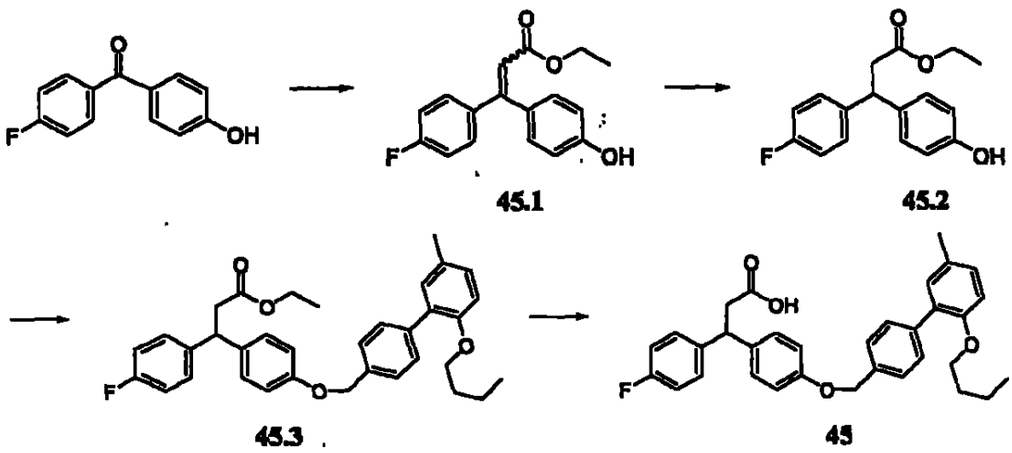
44.5

[0443] **3-(4-{4-[2-(1*H*-Indol-3-yl)-ethylsulfamoyl]-benzyloxy}-phenyl)-hex-4-ynoic acid.** MS ESI m/e: 517.2 (M + H). ^{1}H NMR (400 MHz) (DMSO-d_6) δ 12.5 (1H, br. s); 10.82 (1H, s); 7.83 (2H, d, *J*=8.3 Hz); 7.77 (1H, dd, *J*=7.8, 7.8 Hz); 7.39 (1H, d, *J*=8.0 Hz); 7.32 (1H, d, *J*=8.0 Hz); 7.29 (2H, d, *J*=8.7 Hz); 7.13 (1H, d, *J*=2.2 Hz); 7.06 (1H, dd, *J*=7.0, 8.0 Hz); 6.97 (2H, d, *J*=8.7 Hz); 5.19 (2H, s); 3.95 (1H, m); 3.02 (2H, t, *J*=7.6 Hz); 2.81 (2H, t, *J*=7.6 Hz); 2.61 (2H, d, *J*=8.0 Hz); 1.78 (3H, d, *J*=2.4 Hz).

6.45 **Example 45**

[0444] This example illustrates the preparation of (+/-)-3-[4-(2'-butoxy-5'-methyl-biphenyl-4-ylmethoxy)-phenyl]-3-(4-fluorophenyl)-propionic acid (45).

Scheme 45.1



[0445] **Ethyl 3-(4-fluorophenyl)-3-(4-hydroxyphenyl)-acrylate (45.1).** A solution of lithium hexamethyldisilazide (23.1 mL, 1M in THF) was added to a stirred solution of ethyl (trimethylsilyl)acetate (2.53 mL, 13.9 mmol) in THF (15 mL) in 10 min. at –78 °C. The reaction mixture was further stirred at this temperature for 20 min. A solution of (4-fluorophenyl)-(4-hydroxyphenyl)-methanone (2 g, 9.2 mmol) in THF (30 mL) was slowly added to the reaction mixture. The reaction mixture was brought to 0 °C in 5 h. The reaction mixture was quenched with saturated ammonium chloride solution, extracted into ethyl acetate and washed with dilute ammonium chloride solution. The organic layer was dried over magnesium sulfate. The solvent was removed under vacuum and product was purified flash chromatography on silica gel, giving **45.1** as an oil (1.405 g).

[0446] **3-(4-Fluorophenyl)-3-(4-hydroxyphenyl)-propionic acid ethyl ester (45.2).** A solution of **45.1** (385 mg) in ethanol (12 mL) and ethyl acetate (10 mL) was stirred with 10% Pd-C (50 mg) under a hydrogen atmosphere at room temperature for 3 h. The reaction mixture was filtered and concentrated to provide **45.2** (350 mg).

[0447] **3-[4-(2'-Butoxy-5'-methyl-biphenyl-4-ylmethoxy)-phenyl]-3-(4-fluorophenyl)-propionic acid ethyl ester (45.3).** A mixture of **45.2** (48 mg, 0.166 mmol), 4'-Bromomethyl-2-butoxy-5-methyl-biphenyl (67 mg, 0.2 mmol) and cesium carbonate (81 mg, 0.25 mmol) in DMF (2 mL) was stirred at room temperature overnight. The reaction mixture was diluted with water, acidified with dilute HCl, extracted into ethyl acetate, washed with water and dried over magnesium sulfate. The residue obtained after concentration was flash chromatographed on silica gel to obtain **45.3** (71 mg).

[0448] **(+/-)-3-[4-(2'-Butoxy-5'-methyl-biphenyl-4-ylmethoxy)-phenyl]-3-(4-fluorophenyl)-propionic acid (45).** A mixture of **45.3** (56 mg, 0.1 mmol) and 2N $NaOH_{(aq)}$ solution (0.31 mL, 0.62 mmol) in THF (3 mL) was stirred at room temperature overnight.

The reaction mixture was concentrated, treated with dilute HCl, and extracted into ethyl acetate. The organic layer washed with water and concentrated to yield product which was purified by flash chromatography to give compound 45 (40 mg). ^{1}H NMR (500 MHz, $CDCl_3$, ppm), δ 0.9 (t, 3H), 1.4 (m, 2H), 1.65 (m, 2H), 2.35 (s, 3H), 3.05 (m, 2H), 3.9 (t, 2H), 4.5 (t, 1H), 5.05 (s, 2H), 6.8-7.5 (m, 15H). MS ESI (neg.) m/e: 511.0 (M-H).

6.46 Example 46

[0449] The following compounds were prepared according to methods analogous to those described in Example 45: 3-(4-fluorophenyl)-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-propionic acid (46.1), 3-(4-fluorophenyl)-3-[4-(4-methyl-2-p-tolyl-thiazol-5-ylmethoxy)-phenyl]-propionic acid (46.2) and 3-(4-fluorophenyl)-3-{4-[2-(3-trifluoromethyl-phenoxy)-ethoxy]-phenyl}-propionic acid (46.3).

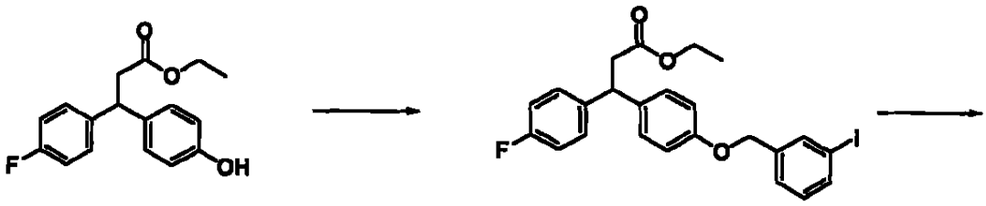
[0450] Starting from (4-hydroxyphenyl)-phenyl-methanone, the following compounds were prepared according to methods analogous to those described in Example 45: 3-[4-(2-methyl-benzyloxy)-phenyl]-3-phenyl-propionic acid (46.4), 3-[4-(2'-butoxy-5'-methyl-biphenyl-4-ylmethoxy)-phenyl]-3-phenyl-propionic acid (46.5), 3-[4-(4-methyl-2-p-tolyl-thiazol-5-ylmethoxy)-phenyl]-3-phenyl-propionic acid (46.6), 3-phenyl-3-{4-[2-(3-trifluoromethyl-phenoxy)-ethoxy]-phenyl}-propionic acid (46.7), 3-[4-(2'-cyano-biphenyl-4-ylmethoxy)-phenyl]-3-phenyl-propionic acid (46.8) and 3-phenyl-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-propionic acid (46.9).

[0451] Starting from (4-hydroxyphenyl)-pyridin-4-yl-methanone, the following compounds were prepared according to methods analogous to those described in Example 45: 3-[4-(2'-butoxy-5'-methyl-biphenyl-4-ylmethoxy)-phenyl]-3-pyridin-4-yl-propionic acid (46.10) and 3-pyridin-4-yl-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-propionic acid (46.11).

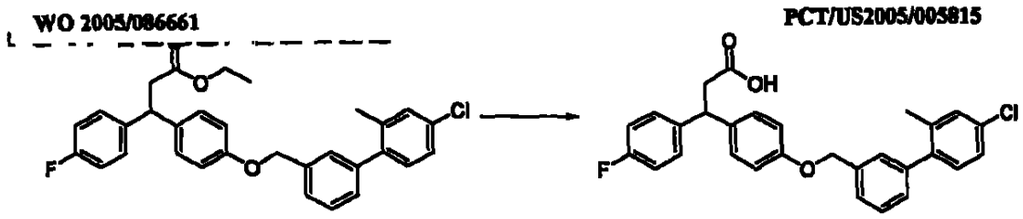
6.47 Example 47

[0452] This example illustrates the preparation of (+/-)-3-(4-[3-(4-chloro-2-methylphenyl) benzyloxy]phenyl)-3-(4-fluorophenyl)-propanoic acid (47).

Scheme 47.1



45.2 47.1



47.2 47

[0453] **Ethyl 3-(4-(3-iodobenzyloxy)phenyl)-3-(4-fluorophenyl)propanoate (47.1).** Cs_2CO_3 (4.89g 15mmol) and 1-(bromomethyl)-3-iodobenzene (4.45g, 15mmol) were added successively to a dry DMF (20 mL) solution of 45.2 (2.88g, 10mmol). The reaction mixture was stirred at room temperature overnight, diluted with ethyl acetate (200mL), washed with water (100 mL x 2) and brine (100 mL), and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash chromatography to give compound 47.1 as a colorless oil. MS ESI (pos.) m/e: 505.0 (M+H).

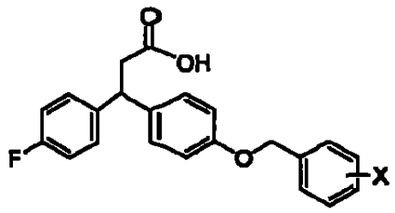
[0454] **3-(4-[3-(4-Chloro-2-methylphenyl)benzyloxy]phenyl)-3-(4-fluorophenyl)-propanoate (47.2).** CsF (96 mg, 0.6mmol), 4-chloro-2-methylphenylboronic acid (102 mg, 0.6 mmol) and $Pd(PPh_3)_4$ (70 mg, 0.06mmol) were added successively to a dry 1,2-dimethoxyethane (DME, 2 mL) solution of 47.1 (108 mg, 0.2 mmol) with stirring under a nitrogen atmosphere. The reaction mixture was stirred at 80 °C overnight. The solvent was removed under nitrogen flow and the residue was dissolved in CH_2Cl_2 (2 mL) and purified by flash chromatography. Compound 47.2 was obtained as a colorless oil. MS ESI (pos.) m/e 503.0 (M+1).

[0455] **(+/-)-3-{4-[3-(4-Chloro-2-methylphenyl)phenyl]-methoxyl)phenyl}-3-(4-fluorophenyl)-propanoic acid (47).** LiOH (48 mg, 2 mmol) was added to the THF-H_2O (1/1, 4mL) solution of compound 47.2 (104 mg, 0.2 mmol). The reaction mixture was stirred at room temperature overnight. 1N $HCl_{(aq)}$ was added to acidify the mixture to pH 3 at 0 °C. The mixture was extracted with ethyl acetate (20 mL x 2), washed with water and brine, dried over Na_2SO_4, and purified by flash chromatography to obtain compound 47 (82 mg) as colorless oil. ^1H NMR (400 MHz)($CDCl_3$) δ 2.22 (s, 3H), 3.05 (dd, J = 7.8, 1.1 Hz, 2H), 4.49 (t, J = 8.0 Hz, 1H), 5.09 (s, 2H), 6.92-7.43 (m, 12H). MS ESI (neg.) m/e 473.0 (M-H).

6.48 Example 48

[0456] The following compounds were prepared according to the methods described in Example 47.

Table 16

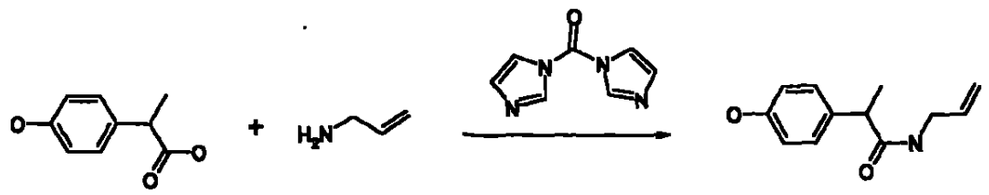


Compound	X
48.1	4-iodo
48.2	3-iodo
48.3	4-(3-benzyloxyphenyl)
48.4	4-(3-butoxyphenyl)
48.5	4-(5-ethoxy-2-fluorophenyl)
48.6	4-(2-ethoxy-6-fluorophenyl)
48.7	4-(2-butoxy-5-fluorophenyl)
48.8	4-(3-isopropoxyphenyl)
48.9	4-(2-fluoro-5-propoxyphenyl)
48.10	4-(4-chloro-2-methylphenyl)
48.11	4-(4-methoxy-2-methylphenyl)
48.12	4-(4-methoxy-2,6-dimethylphenyl)
48.13	4-(2,4,6-trimethylphenyl)
48.14	4-(4-chloro-2-ethoxyphenyl)
48.15	4-(4-fluoro-2-ethoxyphenyl)
48.16	4-(2-isopropoxyphenyl)
48.17	3-(2,5-dimethylphenyl)
48.18	3-(3-benzyloxyphenyl)
48.19	3-(5-ethoxy-2-fluorophenyl)
48.20	3-(4-chloro-2-methylphenyl)
48.21	3-(2-ethoxy-5-methylphenyl)
48.22	3-(4-chloro-2-ethoxyphenyl)
48.23	3-(2-butoxy-5-methylphenyl)
48.24	3-(2-butoxy-5-fluorophenyl)
48.25	3-(4-ethoxyphenyl)
48.26	3-(5-fluoro-2-methoxyphenyl)
48.27	3-(3-isopropoxyphenyl)

6.49 Example 49

[0457] This example illustrates the preparation of (+/-)-3-(4-(3-(4-(trifluoromethyl)phenyl) benzyloxy)phenyl)-4-(diethylamino)-3-methyl-4-oxobutanoic acid.

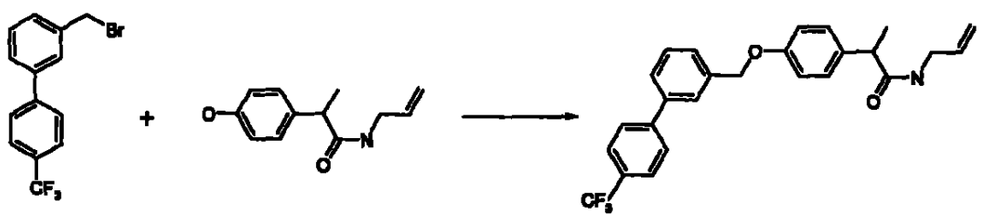
Scheme 49.1



49.1

[0458] *N*-Allyl-2-(4-hydroxyphenyl)propanamide (49.1). *N,N'*-Carbonyldiimidazole (22.65g, 140mmol) was added to commercially available 2-(4-hydroxyphenyl)propionic acid (21g, 127mmol) in THF (100mL). Gentle warming and gas evolution was observed. The resulting mixture was stirred for 3 h. Allylamine (10.9 g, 190.5 mmol) and Et_3N (19.2 mL, 190.5 mmol) were added dropwise, and the mixture was stirred overnight. The reaction was quenched with water (200mL) and the organic phase was extracted with ethyl acetate (50 mL×3). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography (elution with ethyl acetate). Phenol 49.1 was obtained as a white solid. MS ESI m/e: 206 (M-H).

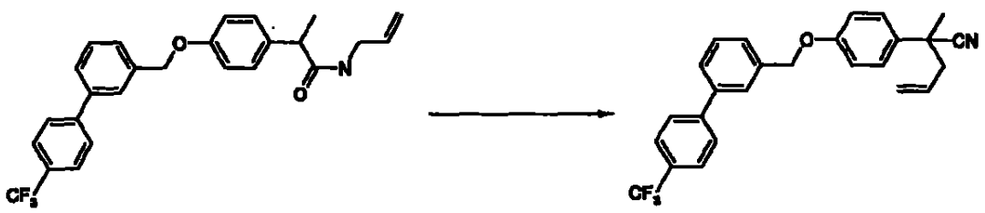
Scheme 49.2



49.2 49.1 49.3

[0459] 2-(4-(3-(4-(Trifluoromethyl)phenyl)benzyloxy)phenyl)-*N*-allylpropanamide (49.3). Cs_2CO_3 (23.1g, 71mmol) was added to a mixture of compound 49.2 (20.33g, 64.5mmol) and phenol 49.1 (13.23g 64.5mmol) in DMF (50mL). The resulting mixture was stirred overnight. The reaction was quenched with water (500mL). The organic phase was extracted with ethyl acetate (75mL×3). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting residue was purified *via* flash chromatography (10% Acetone in dichloromethane) to yield 15.9 g of 49.3. MS ESI m/e: 440 (M-H).

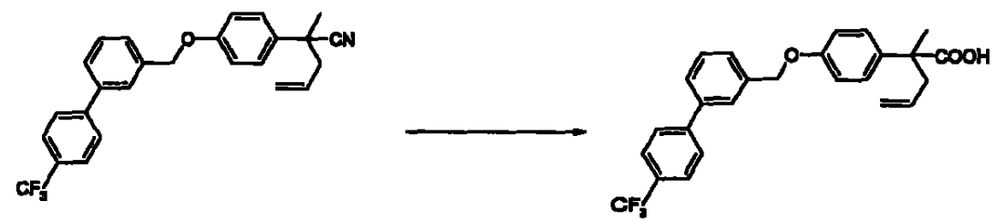
Scheme 49.3



49.3 **49.4**

[0460] **2-(4-(3-(4-(Trifluoromethyl)phenyl)benzyloxy)phenyl)-2-methylpent-4-enenitrile (49.4).** The 3-aza-claisen reaction was carried out according to the method of Walters *et al.* (1991) *Tetrahedron Lett.* 2: 179-182. Amide **49.3** (15.9g, 36.2mmol) and PPh_3 (21g, 80mmol) were dissolved in anhydrous dichloromethane (160 mL). Et_3N (12g, 119.5mmol) and CCl_4 (18.4g, 119.5mmol) were added dropwise. The resulting mixture was stirred at room temperature overnight. The reaction was quenched with saturated brine (250 mL). The organic phase was extracted with ethyl acetate (50mL×3). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified *via* flash chromatography (25% ethyl acetate in hexanes) to yield 12.3 g of **49.4**. ^1H NMR (400MHz) ($CDCl_3$) δ 7.73 (4H, s); 7.70 (1H, s); 7.61-7.51 (3H, m); 7.41 (2H, d, *J*=8.9Hz); 7.05 (2H, d, *J*=8.9Hz); 5.76-5.72 (1H, m); 5.21-5.17 (4H, m); 2.71-2.59 (2H, m); 1.72 (3H, s).

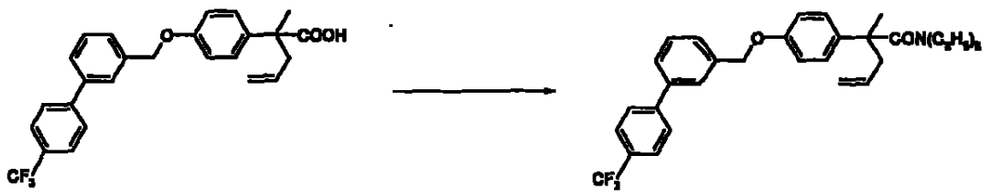
Scheme 49.4



49.4 **49.5**

[0461] **2-(4-(3-(4-(Trifluoromethyl)phenyl)benzyloxy)phenyl)-2-methylpent-4-enoic acid (49.5).** **49.4** was added to a mixture of ethylene glycol (8 mL), H_2O (0.25 mL) and KOH (750 mg). The resulting mixture was heated to 190°C for 6 h. The reaction mixture was cooled to room temperature. The aqueous phase was extracted with ethyl acetate (10 mL×3). The extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified *via* flash chromatography (10% acetone in dichloromethane) to yield 632 mg of **49.5**. MS ESI m/e: 441 (M-H).

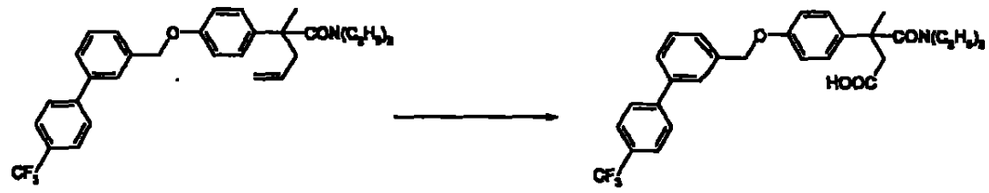
Scheme 49.5



49.5 **49.6**

[0462] **2-(4-(3-(4-(Trifluoromethyl)phenyl)benzyloxy)phenyl)-*N,N*-diethyl-2-methylpent-4-enamide (49.6).** Oxalyl chloride (57.7mg, 0.45mmol) was added dropwise to **49.5** (100 mg, 0.23 mmol) in anhydrous dichloromethane (4 mL). The resulting mixture was refluxed in a sealed tube at 50 °C overnight. The dichloromethane was removed under a stream of N_2. Anhydrous ether (2 mL) was added dropwise, followed by diethyl amine (50 mg, 0.69 mmol) and Et_3N (70 mg, 0.69 mmol). The mixture was refluxed overnight. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified *via* flash chromatography (25% ethyl acetate in hexanes). 82 mg of **49.6** was obtained. MS ESI m/e: 496 (M-H). ^{1}H NMR (500MHz) ($CDCl_3$) δ 7.72 (4H, s); 7.69 (1H, s); 7.6-7.5 (3H, m); 7.14 (2H, d, *J*=8.5Hz); 7.05 (2H, d, *J*=8.5Hz); 5.7-5.6 (1H, m); 5.15 (2H, s); 5.03-5 (2H, m); 3.5-3.2 (2H, m); 3.0-2.9 (2H, m); 2.74-2.64 (2H, m); 1.62 (3H, s); 1.13 (3H, s); 0.72 (3H, s).

Scheme 49.6



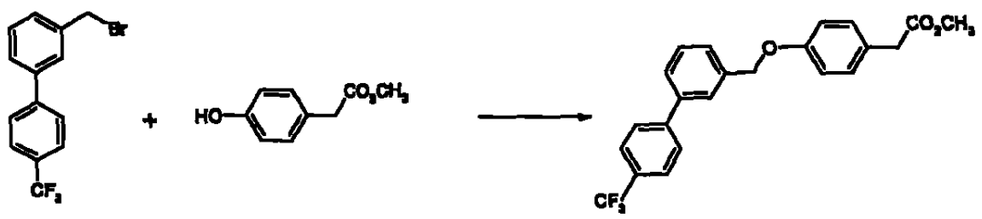
49.6 **49**

[0463] **(+/-)-3-(4-(3-(4-(Trifluoromethyl)phenyl)benzyloxy) phenyl)-4-(diethylamino)-3-methyl-4-oxobutanoic acid (49).** The oxidation reaction was carried out according to the method of Henry *et al.* (1993) *J. Org. Chem.* 58: 4745. A catalytic amount of OsO_4 was added to a solution of **49.6** (50 mg, 0.1 mmol) in acetone (4 mL), followed by an excess of Jones reagent (0.25 mL). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (2 mL), and the aqueous phase was extracted with dichloromethane (2 mL×3). The combined organic extracts were dried over $MgSO_4$ and removed under reduced pressure. The resulting residue was purified on reversed phase HPLC. MS ESI m/e: 514 (M-H).

6.50 Example 50

[0464] This example illustrates the preparation of 3-{4-[4'-(1,1-difluoro-ethyl)-biphenyl-3-ylmethoxy]-phenyl}-*N,N*-dimethyl-succinamic acid.

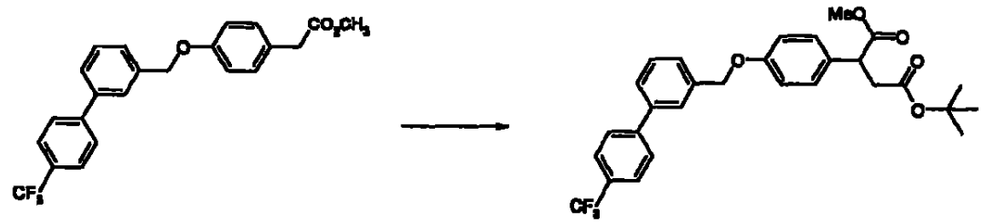
Scheme 50.1



49.2 50.1

[0465] **[4-(4'-Trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-acetic acid methyl ester (50.1).** Compound **49.2** (15.8 g, 50.1 mmol) was added to methyl 4-hydroxyphenylacetate (8.3 g 50 mmol) in DMF (30 mL), followed by Cs_2CO_3 (17.9 g, 55 mmol). The resulting mixture was stirred overnight. The reaction was quenched with water (300 mL). The organic phase was extracted with ethyl acetate (50 mL × 3). The combined organic phase was rinsed with saturated brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product (16.3 g) was used in the next step without further purification. MS ESI (pos.) m/e: 423 (M+Na).

Scheme 50.2

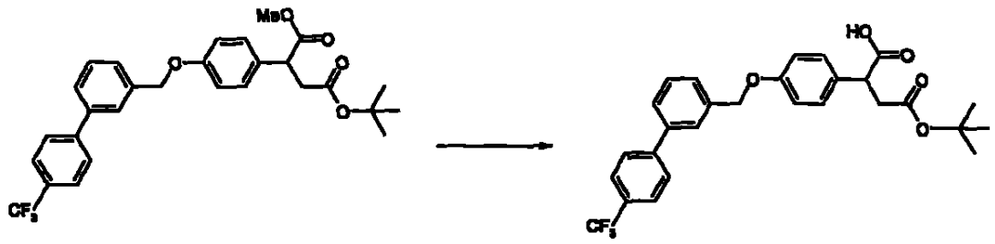


50.1 50.2

[0466] **2-{4-[4'-Trifluoromethyl-biphenyl-3-ylmethoxy]-phenyl}-succinic acid 4-*tert*-butyl ester 1-methyl ester (50.2).** Compound **50.1** (4 g, 10mmol) in THF (12 mL) was added dropwise to LDA in THF (1M, 12 mL) at –78°C. The resulting mixture was stirred for 30 min. before *tert*-butyl bromoacetate (2.15 g, 11 mmol) in THF (2 mL) was added over 10 min. The reaction mixture was stirred for 2 h at –78 °C and allowed to warm slowly to 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (20 mL). The organic phase was extracted with ethyl acetate (25 mL×3). The organic extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified *via* flash chromatography (50% ethyl acetate in hexanes) to yield 3.3 g of **50.2**. MS ESI (pos.) m/e: 537 (M+Na). ^1H NMR (400MHz) ($CDCl_3$) δ 7.72 (4H, s);

7.68 (1H, s); 7.58-7.49 (3H, m); 7.25-7.24 (2H, m); 6.98-6.97 (2H, m); 5.14 (2H, s); 4.04-4.0 (1H, m); 3.7 (3H, s); 3.1 (1H, m); 2.63 (1H, m); 1.42 (9H, s).

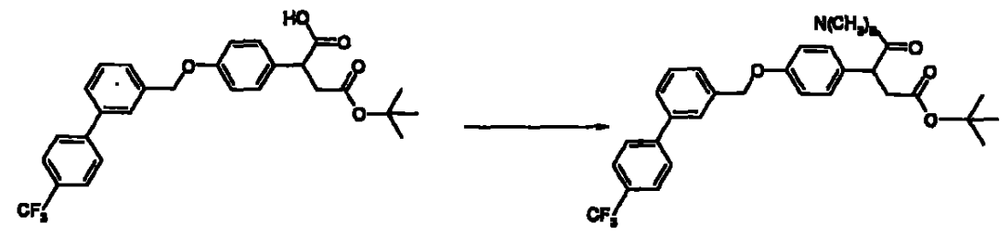
Scheme 50.3



50.2 **50.3**

[0467] **2-{4-[4'-Trifluoromethyl-biphenyl-3-ylmethoxy]-phenyl}-succinic acid 4-*tert*-butyl ester (50.3).** Lithium hydroxide (121mg, 5mmol) was added to a solution of **50.2** in MeOH/THF/H_2O (1:1:1, 90mL). The resulting mixture was stirred at room temperature overnight. The organic solvent was removed under reduced pressure. The reaction mixture was extracted with dichloromethane (10 mL×3). The organic extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified *via* flash chromatography (50% ethyl acetate in hexanes) to yield acid **50.3** (860 mg). MS ESI (pos.) m/e: 523 (M+Na). ^{1}H NMR (400MHz) ($CDCl_3$) δ 7.72 (4H, s); 7.67 (1H, s); 7.59-7.47 (3H, m); 7.29-7.25 (2H, m); 6.98-6.97 (2H, m); 5.14 (2H, s); 4.04-4.0 (1H, m); 3.1-3.053 (1H, m); 2.64-2.60 (1H, m); 1.4 (9H, s).

Scheme 50.4

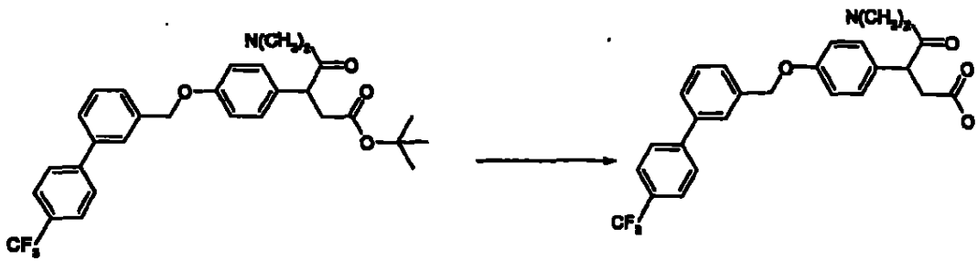


50.3 **50.4**

[0468] **3-{4-[4'-Trifluoromethyl-biphenyl-3-ylmethoxy]-phenyl}-*N,N*-dimethyl-succinamic acid *tert*-butyl ester (50.4).** A solution of compound **50.3** (50mg, 0.1mmol) in dichloromethane (2mL) was treated with 1-hydroxybenzotriazole (15 mg, 0.11mmol) and EDC (21 mg, 0.11mmol) sequentially. The resulting mixture was stirred for 1 h. before dimethylamine (9 mg, 0.2mmol) was added dropwise. The reaction was quenched 30 min. later with water (5 mL). The reaction mixture was extracted with dichloromethane (2 mL×3). The organic extracts were combined, dried over $MgSO_4$ and concentrated under

reduced pressure to yield amide 50.4 (48 mg). The product was used in the next step without further purification. MS ESI (pos.) m/e: 527 (M^+).

Scheme 50.5



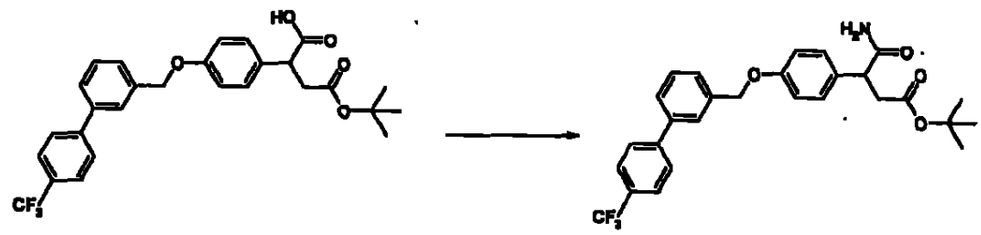
50.4 **50**

[0469] **(+/-)-3-[4-[4'-Trifluoromethyl-biphenyl-3-ylmethoxy]-phenyl]-*N,N*-dimethyl-succinamic acid (50).** Ester 50.4 (48mg, 0.09mmol) was dissolved in dichloromethane/TFA solution (3:1, 2 mL). The resulting mixture was stirred at room temperature for 2 h. The solvent removed under reduced pressure, and the product was purified on reserve phase HPLC to yield acid 50 (30mg). MS ESI (pos.) m/e: 472 (M+H). ^{1}H NMR (400MHz) ($CDCl_3$) δ 7.72 (4H, s); 7.67 (1H, s); 7.59-7.28 (3H, m); 7.2 (2H, d, *J*=8.6Hz); 7.0 (2H, d, *J*=8.6Hz); 5.13 (2H, s); 4.24-4.21 (1H, m); 3.20-3.13 (1H, m); 3.0 (3H, s); 2.95 (3H, s); 2.76-2.71 (1H, m).

6.51 Example 51

[0470] This example illustrates the preparation of 3-(4-methyl-thiazol-2-yl)-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-propionic acid.

Scheme 51.1

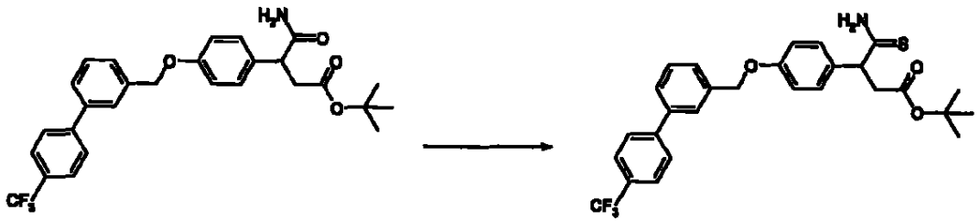


50.3 **51.1**

[0471] **3-[4-(4'-Trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-succinamic acid *tert*-butyl ester (51.1).** 1-hydroxybenzotriazole (225 mg, 1.65 mmol) and EDC (315 mg, 1.65 mmol) were added sequentially to compound 50.3 (750 mg, 1.5 mmol) in dichloromethane (25 mL). The resulting mixture was stirred for 1 h before ammonium hydroxide (25% in water, 630 mg, 4.5 mmol) was added dropwise. The reaction was quenched after 30 min. with water (10 mL). The reaction mixture was extracted with dichloromethane (10 mL×3). The organic extracts were combined, dried over $MgSO_4$ and

concentrated under reduced pressure. The product was purified *via* flash chromatography (50% ethyl acetate in hexanes) to yield **51.1** (720 mg) as a white solid. MS ESI (pos.) m/e: 500 (M+H). ^{1}H NMR (400MHz) ($CDCl_3$) δ 7.72 (4H, s); 7.68 (1H, s); 7.57-7.48 (3H, m); 7.29-7.25 (2H, m); 7.0-6.97 (2H, d, *J*=6,8Hz); 5.14 (2H, s); 3.91-3.88 (1H, m); 3.19-3.13 (1H, m); 2.60-2.55 (1H, m); 1.4 (9H, s).

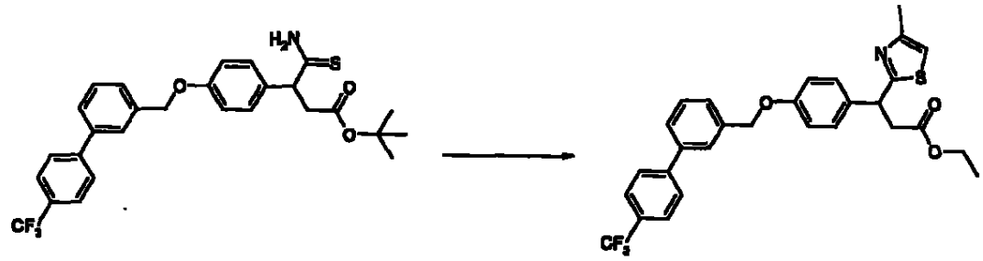
Scheme 51.2



51.1 **51.2**

[0472] **3-Thiocarbamoyl-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-propionic acid *tert*-butyl ester (51.2).** Lawesson's reagent (81 mg, 0.2 mmol) was added to a solution of compound **51.1** (50 mg, 0.1 mmol) in THF (2mL). The resulting mixture was stirred at room temperature for 6 h. The reaction was quenched with water (5 mL). The reaction mixture was extracted with dichloromethane (3 mL×3). The organic extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified *via* flash chromatography (50% ethyl acetate in hexanes) to yield compound **51.2** (40 mg) as a clear film. MS ESI (pos.) m/e: 516 (M+H). ^{1}H NMR (400MHz) ($CDCl_3$) δ 7.72 (4H, s); 7.67 (1H, s); 7.51-7.48 (3H, m); 7.31-7.28 (2H, m); 7.0-6.97 (2H, m); 5.14 (2H, s); 4.25-4.22 (1H, m); 3.51-3.46 (1H, m); 2.78-2.72 (1H, m); 1.38 (9H, s).

Scheme 51.3

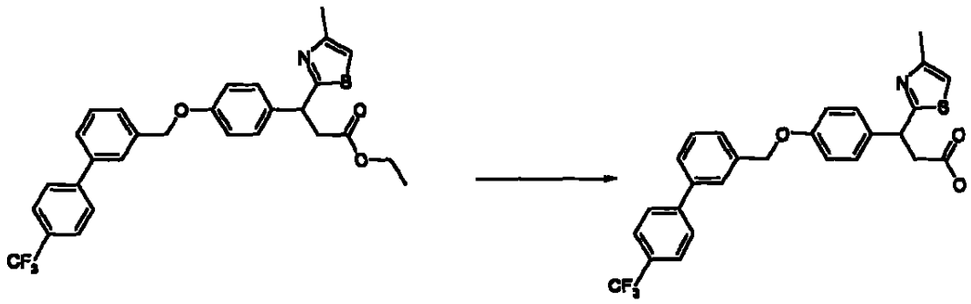


51.2 **51.3**

[0473] **Ethyl 3-(4-Methyl-thiazol-2-yl)-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-propanoate (51.3).** A solution of **51.2** (100 mg, 0.19 mmol) in EtOH (3 mL) was treated with chloroacetone (88mg, 0.95mmol). The resulting mixture was refluxed for 5 h. Aqueous HCl (6N, 25μL) was added into above reaction mixture and the

reaction was heated at 50 °C overnight. The solvent was removed under reduced preasure. The product was purified *via* flash chromatography (50% ethyl acetate in hexanes) to yield 51.3 (50mg). MS ESI (pos.) m/e: 526 (M+H).

Scheme 51.4



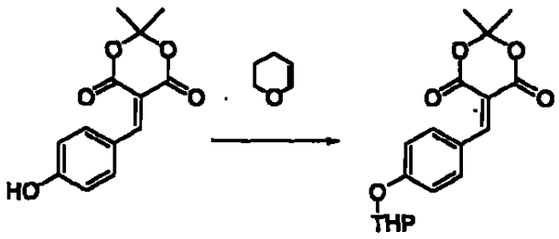
51.3 51

[0474] **(+/-)-3-(4-Methyl-thiazol-2-yl)-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-propionic acid (51).** Compound 51.3 (50 mg, 0.1 mmol) was dissolved in MeOH/THF/H_2O (1:1:1, 3 mL). The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to PH=4 and extracted with dichloromethane (3 mL×3). The product was purified on reverse phase HPLC to yield compound 51 (40 mg). MS ESI (pos.) m/e: 498 (M+H). ^{1}H NMR (400MHz) (DMSO) δ 7.92 (2H, d, *J*=8.1Hz); 7.84 (3H, d, *J*=8.8Hz); 7.71 (1H, t, *J*=5.1Hz); 7.54 (2H, d, *J*=7Hz); 7.29 (2H, d, *J*=8.7Hz); 7.09 (1H, s); 7.01 (2 H, d, *J*=8.7Hz); 5.18 (2H, s); 4.66 (1H, m); 3.2 (1H, m); 2.93 (1H, m); 2.33 (3H, s).

6.52 Example 52

[0475] This example illustrates the preparation of (+/-)-3-(4-((4-methyl-2-p-tolylthiazol-5-yl)methoxy)phenyl)-3-(thiophen-2-yl)propanoic acid.

Scheme 52.1

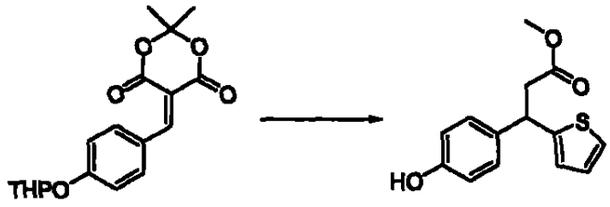


1.1 52.1

[0476] **2,2-Dimethyl-5-[4-(tetrahydro-pyran-2-yloxy)-benzylidene]-[1,3]dioxane-4,6-dione (52.1).** Protection of the phenol with dihydropyran was carried out based on the method given in Miyashita *et al.* (1977) *J. Org. Chem.* 42: 3772. Compound

1.1 (500 g, 2 mol) was dissolved in dichloromethane (4 L). 3,4-Dihydro-2H-pyran (250 g, 3 mol) was added to the suspension followed by PPTS (5 g, 20 mmol). The reaction mixture heated to a gentle reflux (3.5 h). HPLC showed ~90% completion of the reaction. The reaction was concentrated under reduced pressure to ~2L of volume. 1 L of acetone was added, and 2 L of solvent was removed under reduced pressure. 1 L of acetone was added, and 1 L of solvent was removed under reduced pressure. 0.5 L of acetone was added, and 0.5 L of solvent was removed under reduced pressure. The resulting slurry of very fine, light yellow crystals was filtered and rinsed sequentially with two 500 mL portions of acetone. The product was dried in a vacuum oven at 50 °C until no further solvent collected in the traps. Compound 52.1 (528 g) was obtained as fine, light yellow crystals. ^{1}H NMR(400MHz)(DMSO-d_6) δ 8.29 (s, 1H); 8.18 (d, 2H, J=8.9 Hz); 7.13 (d, 2H, J=8.9 Hz);. 5.67 (m, 1H); 3.70 (m, 1H); 3.60 (m, 1H).1.9-1.5 (m, 12H). MS ESI (pos.) m/e: 355.1 (M + Na).

Scheme 52.2

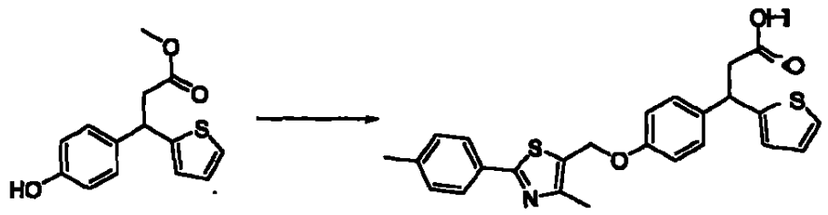


52.1 **52.2**

[0477] **(+/-)-Methyl 3-(4-hydroxyphenyl)-3-(thiophen-2-yl)propanoate (52.2).** A 500 mL flask was equipped with a magnetic stir bar, nitrogen inlet, nitrogen outlet and placed in a room temperature water bath. Compound 52.1 (5.00 g, 15.1 mmol) was added to the flask along with anhydrous THF (150 mL). After purging with nitrogen for 30 min, a solution of thiophene-2-yl-magnesium bromide in THF (1 M, 18.1 mL) was added by cannula. After the addition was complete, the reaction mixture was stirred for 1.5 h and quenched with aqueous NH_4Cl (1 M, 100 mL) diluted with ethyl acetate (100 mL). The aqueous layer was acidified to pH ~2 with Conc. HCl and extracted with ethyl acetate (150 mL x 2). The extract was washed with brine and concentrated. The residue was dissolved in 100 mL of 10:1 DMF-water heated to 100°C for 8 h. The reaction was cooled and the diluted with 500 mL water and extracted with ethyl acetate (150 mL x 3). The organic was dried with $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was dissolved in MeOH (200 mL) and 5 drops of conc. H_2SO_4 were added and the solution was refluxed for 24 h. The solution was concentrated to a residue on a rotary evaporator and purified using flash column chromatography with 30% ethyl acetate/hexanes as the eluant.

The fractions were combined and concentrated to afford 2.69 g (10.3 mmol) of 52.2 as a viscous oil.

Scheme 52.3



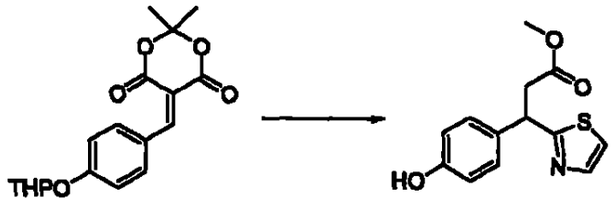
52.2 52

[0478] **(+/-)-3-(4-((4-Methyl-2-p-tolylthiazol-5-yl)methoxy)phenyl)-3-(thiophen-2-yl)propanoic acid (52).** Thiazole chloride 3.1 (108 mg, 0.457 mmol) and phenol 52.2 (100 mg, 0.381 mmol) were dissolved in DMF (1 mL) and treated with Cs_2CO_3 (371 mg, 1.14 mmol). The reaction was stirred at 50°C for 16 h diluted with water (15 mL) and methylene chloride (15 mL). The organic layer was washed with water, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, 33% to 66% ethyl acetate in hexanes). Eluant containing desired compound was concentrated dissolved in a THF/MeOH/2N $LiOH_{(aq)}$ (1:1:1) solution (2 mL). The mixture was stirred at room temperature for 90 min., and the solution was poured into 0.65 N HCl $_{(aq.)}$ (2 mL). The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. After filtration and drying, 156 mg (0.323 mmol) of carboxylic acid 52 was obtained. ^1H NMR (400MHz) ($CDCl_3$) δ 7.77 (d, 2H, J = 8.1 Hz), 7.23-7.30 (m, 5H), 6.89-6.97 (m, 4H), 5.24 (s, 2H), 4.58 (t, 1H, J = 7.8 Hz), 3.02 (m, 1H), 2.92 (m, 1H), 2.40 (s, 3H), 2.33 (s, 3H).

6.53 **Example 53**

[0479] This example illustrates the preparation of (+/-)-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-3-(thiazol-2-yl)-propionic acid.

Scheme 53.1

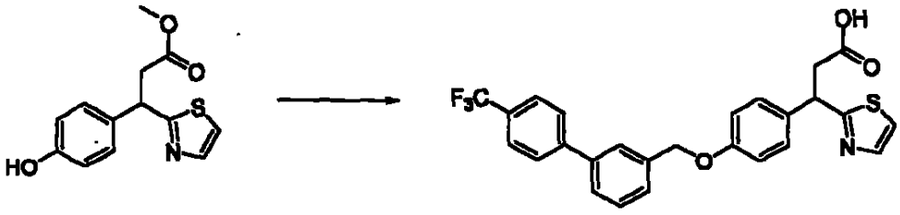


52.1 53.1

[0480] **(+/-)-Methyl 3-(4-hydroxyphenyl)-3-(thiazol-2-yl)propanoate (53.1).** A 500 mL flask was equipped with a magnetic stir bar, nitrogen inlet, nitrogen outlet and

placed in a room temperature water bath. Compound 52.1 (5.00 g, 15.1 mmol) was added to the flask along with anhydrous THF (150 mL). After purging with nitrogen for 30 min, a solution of thiozole-2-yl-magnesium bromide in THF (1 M, 18.1 mL) was added by cannula. After the addition was complete, the reaction mixture was stirred for 1.5 h, quenched with aqueous NH_4Cl (1 M, 100 mL) diluted with ethyl acetate (100 mL). The aqueous layer was acidified to pH ~2 with conc. HCl and extracted with ethyl acetate (150 mL x 2). The extract was washed with brine and concentrated. The residue was dissolved in 100 mL of 10:1 DMF-water and heated to 100 °C for 8 h. The reaction was cooled and the diluted with 500 mL water and extracted with ethyl acetate (150 mL x 3). The organic was dried with $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was dissolved in MeOH (200 mL) and 5 drops of Conc. H_2SO_4 were added and the solution was refluxed for 24 h. The solution was concentrated to a residue on a rotary evaporator and purified using flash column chromatography with 50% ethyl acetate/hexanes as the eluant. The fractions were combined and concentrated to afford 1.90 g (7.25 mmol) of 53.1 as a viscous oil.

Scheme 53.2



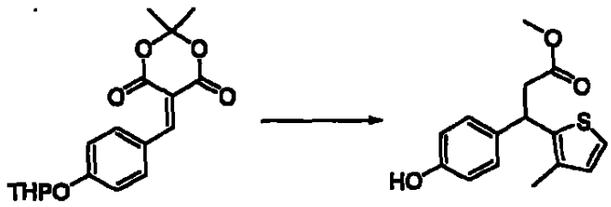
53.1 53

[0481] **(+/-)-3-[4-(4'-Trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-3-(thiazol-2-yl)-propionic acid (53).** Benzyl chloride 2.3 (123 mg, 0.456 mmol) and phenol 53.1 (100 mg, 0.380 mmol) were dissolved in acetone (1 mL) and treated with Cs_2CO_3 (371 mg, 1.14 mmol). The reaction was stirred at 50 °C for 16 h, filtered and concentrated. The residue was purified by column chromatography (silica gel, 30% to 70% ethyl acetate in hexanes). Eluant containing desired compound was concentrated and dissolved in a THF/MeOH/2N $LiOH_{(aq)}$ (1:1:1) solution (2 mL). The mixture was stirred at room temperature for 90 min., and the solution was poured into 0.65 N $HCl_{(aq.)}$ (2 mL). The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. After filtration and drying, 150 mg (0.311 mmol) of carboxylic acid 53 was obtained. ^1H NMR (400MHz) ($CDCl_3$) δ 7.47-7.77 (m, 9H), 7.24-7.27 (m, 3H), 6.99-7.00 (m, 2H), 5.14 (s, 2H), 4.78 (dd, 1H, J = 6.8, 4.4 Hz), 3.47 (dd, 1H, J = 12.8, 6.8 Hz), 3.09 (dd, 1H, J =12.8, 4.4 Hz).

6.54 Example 54

[0482] This example illustrates the preparation of (+/-)-3-[4-(4'-Trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-3-(3-methylthiophen-2-yl)-propionic acid.

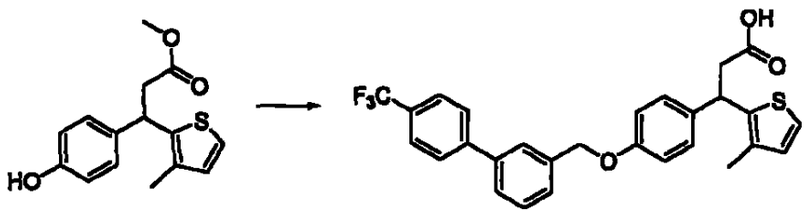
Scheme 54.1



52.1 54.1

[0483] **(+/-)-Methyl 3-(4-hydroxyphenyl)-3-(3-methylthiophen-2-yl)propanoate (54.1).** A 500 mL flask was equipped with a magnetic stir bar, nitrogen inlet, nitrogen outlet and placed in a room temperature water bath. Compound 52.1 (5.00 g, 15.1 mmol) was added to the flask along with anhydrous THF (150 mL). After purging with nitrogen for 30 min, a solution of 3-methylthiophen-2-yl-magnesium bromide in THF (1 M, 18.1 mL) was added by cannula. After the addition was complete, the reaction mixture was stirred for 1.5 h, quenched with aqueous NH_4Cl (1 M, 100 mL) and diluted with ethyl acetate (100 mL). The aqueous layer was acidified to pH ~2 with Conc. HCl and extracted with ethyl acetate (150 mL x 2). The extract was washed with brine and concentrated. The residue was dissolved in 100 mL of 10:1 DMF-water and heated to 100 °C for 8 h. The reaction mixture was cooled, diluted with 500mL water, and extracted with ethyl acetate (150 mL x 3). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was dissolved in MeOH (200 mL) and 5 drops of Conc. H_2SO_4 were added and the solution was refluxed for 24 h. The solution was concentrated to a residue on a rotary evaporator and purified using flash column chromatography with 30% ethyl acetate/hexanes as the eluant. The fractions were combined and concentrated to afford 2.33 g (7.25 mmol) of 54.1 as a viscous oil.

Scheme 54.2



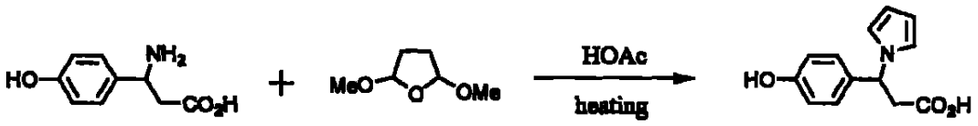
54.1 54

[0484] (+/-)-3-[4-(4'-Trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-3-(3-methylthiophen-2-yl)-propionic acid (54). Benzyl chloride 2.3 (113 mg, 0.434 mmol) and phenol 54.1 (100 mg, 0.362 mmol) were dissolved in acetone (1 mL) and treated with Cs_2CO_3 (371 mg, 1.14 mmol). The reaction was stirred at 50 °C for 16 h, filtered and concentrated. The residue was purified by column chromatography (silica gel, 30% to 60% ethyl acetate in hexanes). Eluant containing desired compound was concentrated and dissolved in a THF/MeOH/2N $LiOH_{(aq)}$ (1:1:1) solution (2 mL). The mixture was stirred at room temperature for 90 min., the solution was poured into 0.65 N $HCl_{(aq.)}$ (2 mL). The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. After filtration and drying, 154 mg (0.311 mmol) of carboxylic acid 54 was obtained. ^1H NMR (400MHz) ($CDCl_3$) δ 7.43-7.70 (m, 8H), 7.21 (d, 2H, J = 8.6 Hz), 7.05 (d, 1H, J = 5.0 Hz), 6.92 (d, 2H, J = 8.6 Hz), 6.76 (d, 1H, 5.0 Hz), 5.09 (s, 2H), 4.74 (t, 1H, J = 7.8 Hz), 3.05 (d, 2H, J = 7.8 Hz), 2.15 (s, 3H).

6.55 Example 55

[0485] This example illustrates the preparation of methyl 3-(4-hydroxyphenyl)-3-(1*H*-pyrrol-1-yl)propanoate.

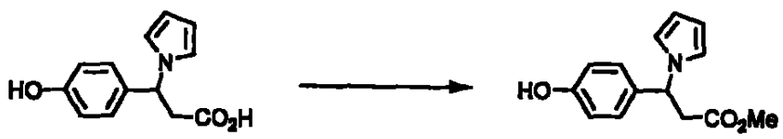
Scheme 55.1



55.1

[0486] 3-(4-Hydroxyphenyl)-3-(1*H*-pyrrol-1-yl)propanoic acid (55.1). At 100 °C, 2,5-dimethoxytetrahydrofuran (8.5 mmol) was added to a mixture of 3-amino-3-(4-hydroxyphenyl) propanoic acid (7.7 mmol) and sodium acetate (46 mmol) in acetic acid (34 mL). After stirring for 1 h, acetic acid was removed under reduced pressure. The residue was extracted with ethyl acetate (300 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified *via* column chromatography (10% methanol in dichloromethane) to compound 55.1. LC-MS (neg.) m/e: 230.2 (M-H).

Scheme 55.2



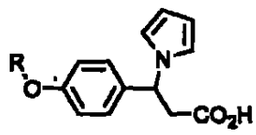
55.1 55

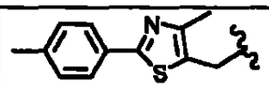
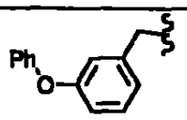
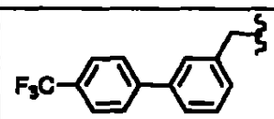
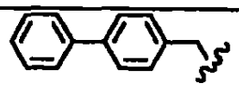
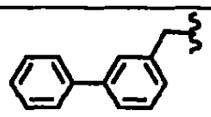
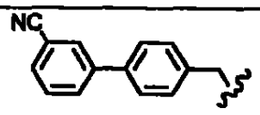
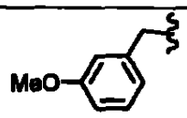
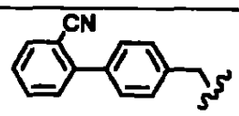
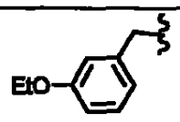
[0487] (*R*)-Methyl 3-(4-hydroxyphenyl)-3-(1*H*-pyrrol-1-yl)propanoate (55). Trimethysilyldiazomethane (8 mL, 2M in diethyl ether, 16 mmol) was added to a solution of compound 55.1 (7 mmol) in methanol (25 mL). After 10 min., the solvent was removed to yield methyl compound 55. MS ESI (pos.) m/e: 246.1 (M+H).

6.56 Example 56

[0488] The following compounds were prepared from compound 55 according to the methods described in Example 18.

Table 17



Compound	R	Compound	R
56.1		56.6	
56.2		56.7	
56.3		56.8	
56.4		56.9	
56.5			

[0489] Compound 56.1. MS ESI (neg.) m/e: 431 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.3 (1H, s); 7.81 (2H, d, J=8 Hz); 7.30 (4H, m); 6.99 (2H, d, J=9Hz); 6.92 (2H, m); 5.98 (2H, m); 5.56 (1H, t, J=8Hz), 5.29 (2H, s); 3.18 (2H, m); 2.44 (3H, s); 2.38 (3H, s).

[0490] Compound 56.2. MS ESI (neg.) m/e: 464 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.92 (2H, m); 7.84 (3H, m); 7.72 (1H, d, J=8Hz); 7.53 (2H, m); 7.26 (2H, d, J=9Hz); 7.00 (2H, d, J=9Hz), 6.91 (2H, m); 5.55 (1H, d, J=8Hz); 5.19 (2H, s); 3.16 (2H, m).

[0491] Compound 56.3. MS ESI (neg.) m/e: 396 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.37 (1H, s); 7.65-7.77 (4H, m); 7.41-7.51 (5H, m); 67.27 (2H, m); 7.01 (2H, d, J=5Hz)); 6.92 (2H, m); 5.99(2H, m), 5.56 (1H, m); 5.18 (2H, s), 3.21 (2H, m).

[0492] Compound 56.4. MS ESI (neg.) m/e: 350 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.4 (1H, s); 7.30-7.34 (1H, t, J=8Hz); 7.26 (2H, d, J=9Hz); 7.01 (2H, m); 6.96 (2H, d, J=9Hz)); 6.90-6.92 (3H, m); 5.98 (2H, m), 5.55 (1H, t, J=8Hz); 5.07(2H, s); 3.78 (3H, s); 3.21(2H, m).

[0493] Compound 56.5. MS ESI (neg.) m/e: 364 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.24-7.31 (3H, m); 6.99 (2H, m); 6.88 (3H, m); 5.97 (2H, s); 5.55 (1H, m); 5.06(2H, s), 4.04 (2H, q, J=7Hz); 3.16 (2H, m); 1.34 (3H, t, J=7Hz).

[0494] Compound 56.6. MS ESI (neg.) m/e: 412 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.40-7.43 (3H, m); 7.16-7.26 (4H, m); 7.08 (1H, s); 7.03 (2H, d, J=8Hz)); 6.90-6.97 (5H, m); 5.98(2H, s), 5.54 (1H, t, J=8Hz); 5.09 (2H, s); 3.17 (2H, m)

[0495] Compound 56.7. MS ESI (neg.) m/e: 396 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.70-7.71 (4H, m); 7.41-7.55 (4H, m); 7.39 (1H, m); 7.25 (2H, d, J=8Hz)); 6.98 (2H, d, J=9Hz); 6.89 (2H, s), 5.97 (2H, s); 5.55 (1H, t, J=8Hz); 5.12 (2H, s); 3.10 (2H, m).

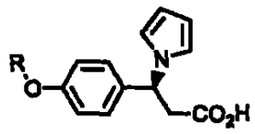
[0496] Compound 56.8. MS ESI (neg.) m/e: 421 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 8.19 (1H, s); 8.05 (1H, d, J=8Hz); 7.87 (1H, d, J=8Hz); 7.80 (2H, d, J=8Hz); 7.71 (1H, t, J=8Hz); 7.56 (2H, d, J=8Hz); 7.26 (2H, d, J=8Hz); 6.98 (2H, d, J=8Hz); 6.90 (2H, d, J=8Hz); 5.98 (2H, m); 5.55 (2H, t, J=8Hz)); 5.17 (2H, s); 3.13 (2H, m).

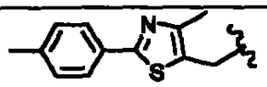
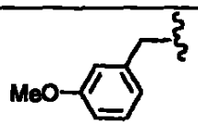
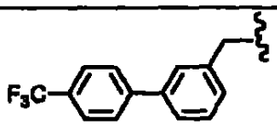
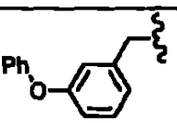
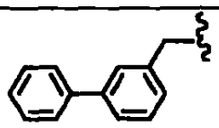
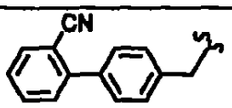
[0497] Compound 56.9. MS ESI (neg.) m/e: 421 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.99 (1H, d, J=8Hz); 7.84 (1H, t, J=8Hz); 7.68 (1H, d, J=8Hz); 7.58-7.64 (5H, m); 7.17 (2H, d, J=8Hz); 6.96 (2H, d, J=8Hz); 6.81 (2H, m); 5.95 (2H, m); 5.55 (1H, t, J=7Hz); 5.18 (2H, s); 2.73 (2H, d, J=7Hz).

6.57 **Example 57**

[0498] The following compounds were prepared according to the methods described in Examples 55 and 56.

Table 18



Compound	R	Compound	R
57.1		57.4	
57.2		57.5	
57.3		57.6	

[0499] Compound 57.1. MS ESI (neg.) m/e: 431 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.81 (2H, m); 7.28-7.32 (4H, m); 7.00 (2H, d, J=8Hz); 6.92 (2H, s); 5.99 (2H, s); 5.57 (1H, m); 5.30 (2H, s); 3.23 (2H, m); 2.44(3H, s); 2.38 (3H, s).

[0500] Compound 57.2. MS ESI (neg.) m/e: 464 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.93 (2H, d, J=8Hz); 7.83-7.86 (3H, m); 7.72 (1H, d, J=8Hz); 7.56 (2H, m); 7.27 (2H, d, J=9Hz); 7.01 (2H, d, J=9Hz); 6.91 (2H, m); 5.98 (2H, s); 5.55 (1H, d, J=8Hz); 3.14 (2H, m).

[0501] Compound 57.3. MS ESI (neg.) m/e: 396 (M-H). ^{1}H NMR (500MHz) ($CDCl_3$) δ 7.63-7.76 (4H, m); 7.39-7.59 (5H, m); 7.15 (2H, d, J=8Hz); 6.77 (2H, s); 6.19 (2H, s); 5.64 (1H, s); 5.13 (2H, s); 3.22-3.26 (2H, m).

[0502] Compound 57.4. MS ESI (neg.) m/e: 350 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.33 (1H, t, J=8Hz); 7.25 (2H, d, J=8Hz); 7.01 (2H, m); 6.95 (2H, d, J=9Hz); 6.90 (3H, m); 5.98 (2H, s); 5.55 (1H, t, J=8Hz); 5.07 (2H, s); 3.78 (3H, s); 3.16 (2H, m).

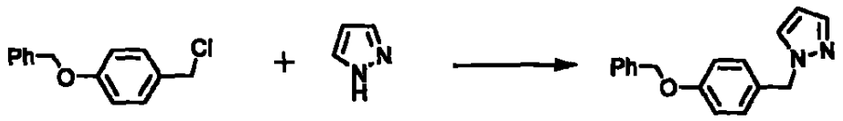
[0503] Compound 57.5. MS ESI (neg.) m/e: 412 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.40-7.43 (3H, m); 7.24-7.26 (3H, m); 7.20 (1H, m); 7.10 (1H, s); 7.03 (2H, d, J=9Hz); 6.90-6.93 (5H, m); 5.98 (2H, m); 5.55 (1H, m); 5.10 (2H, s); 3.18 (2H, m).

[0504] Compound 57.6. MS ESI (neg.) m/e: 421 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.99 (1H, d, J=8Hz); 7.81(1H, m); 7.68 (1H, d, J=8Hz); 7.61-7.65 (5H, m); 6.92 (2H, m); 5.99 (2H, s); 5.56 (1H, t, J=8Hz); 5.20(2H, s); 3.19 (2H, m).

6.58 Example 58

[0505] This example illustrates the preparation of (+/-)-3-(4-(Benzyloxy)phenyl)-3-(1*H*-pyrazol-1-yl)propanoic acid (58.3).

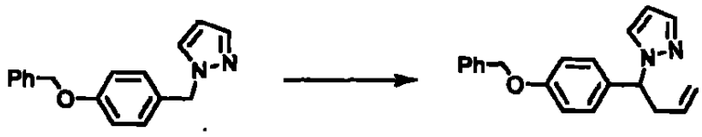
Scheme 58.1



58.1

[0506] 1-(4-(Benzyloxy)benzyl)-1*H*-pyrazole (58.1). After a mixture of pyrazole (7.73 mmol) and potassium hydroxide (7.73 mmol) in DMF (35 mL) was stirred at room temperature for 30 min., a solution of 1-(benzyloxy)-4-(chloromethyl)benzene (6.44 mmol) in DMF (7 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight and the product obtained from a standard aqueous work up. Column chromatography (1:2 ethyl acetate / hexane) of the residue yielded compound 58.1 as a white solid. LC-MS ESI (pos.) m/e: 265 (M+H); ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.79 (1H, m); 7.46 (3H, m); 7.40 (2H, m); 7.36 (1H, m); 7.21 (2H, d, J=9Hz)); 5.27 (2H, s); 5.11 (2H, m).

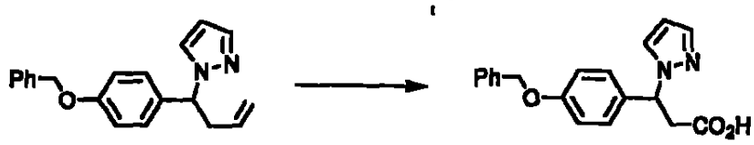
Scheme 58.2



58.1 58.2

[0507] 1-(4-(Benzyloxy)phenyl)but-3-anyl)-1*H*-pyrazole (58.2). To a solution of compound 58.1 (3.41 mmol) in THF (30 mL) at –78 °C was added dropwise n-butyllithium in hexanes (3.75 mmol). The mixture was stirred for 10 min. followed by addition of allyl bromide (3.75 mmol). The reaction mixture was allowed to warm to room temperature overnight, quenched by addition of water. After extraction with ethyl acetate, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (1:3 ethyl acetate/hexane) of the residue yielded compound 58.2 as a white solid. LC-MS ESI (pos.) m/e: 305 (M+H).

Scheme 58.3



58.2 58.3

[0508] 3-(4-(benzyloxy)phenyl)-3-(1*H*-pyrazol-1-yl)propanoic acid (58.3). A solution of $KMnO_4$ (1.68 mmol) in water (19 mL) was added dropwise to a mixture of compound 58.2 (1.08 mmol), $NaIO_4$ (2.2 mmol), acetone (6mL), and acetic acid (6mL). After stirring at room temperature for 1 h, ethylene glycol (2 mL) was added and stirred for additional 1 h. MnO_2 was removed by filtration through silica gel (eluting with 1:9 methanol: dichloromethane). After concentration under reduced pressure, the residue was purified by column chromatography (1:9 methanol: dichloromethane), yielding compound 58.3 (243 mg, 0.75 mmol). LC-MS ESI (pos.) m/e: 323 (M+H).

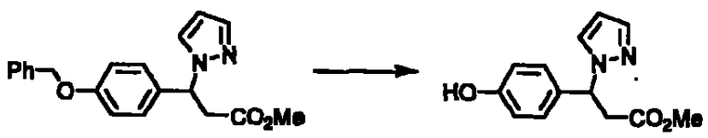
Scheme 58.4



58.3 58.4

[0509] Methyl 3-(4-(benzyloxy)phenyl)-3-(1H-pyrazol-1-yl)propanoate (58.4). Compound 58.3 was esterified similarly to the method discussed in connection with Scheme 55.2.

Scheme 58.5



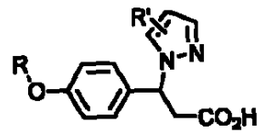
58.4 58

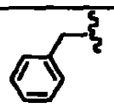
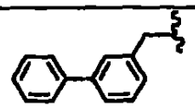
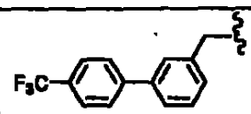
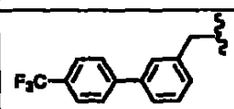
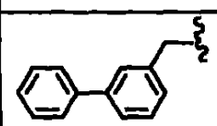
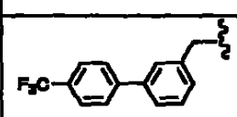
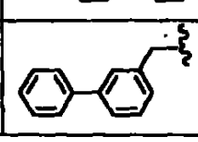
[0510] (+/-)-Methyl 3-(4-hydroxyphenyl)-3-(1*H*-pyrazo-1-l)propanoate (58). A mixture of compound 58.4 (0.37 mmol) and a small amount of Pd-C in methanol (8 mL) was stirred at room temperature under hydrogen atmosphere for 20 min. After filtration and concentration, the residue was purified by column chromatography. Compound 58 was obtained (81 mg, 0.33 mmol). LC-MS ESI (pos.) m/e: 247 (M+H).

6.59 Example 59

[0511] The following compounds were prepared from compound 58 according to the methods described in Example 18.

Table 19



Compound	R	R'
59.1		H
59.2		H
59.3		H
59.4		3-Methyl
59.5		3-Methyl
59.6		5-Methyl
59.7		5-Methyl

[0512] Compound 59.1. MS ESI (neg.) m/e: 321 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.84 (1H, d, J=2Hz); 7.40-7.50 (5H, m); 7.35 (1H, m); 7.27(2H, d, J=9Hz); 6.97 (2H, d, J=9Hz); 6.24 (1H, s); 5.79 (1H, m); 5.06 (2H, s); 3.3(1H, m); 3.12 (1H, m).

[0513] Compound 59.2. MS ESI (neg.) m/e: 397 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.85 (1H, s); 7.64-7.77 (4H, m); 7.41-7.50 (6H, m); 7.29(2H, d, J=8Hz); 7.01 (2H, d, J=9Hz); 6.24 (1H, s); 5.80 (1H, m); 5.18 (2H, s); 3.3(1H, m); 3.12 (1H, m).

[0514] Compound 59.3. MS ESI (neg.) m/e: 465 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.93 (2H, d, J=8Hz); 7.85 (4H, m); 7.73 (1H, d, J=7Hz); 7.54(2H, m); 7.29 (1H, s); 7.28 (2H, m); 7.00 (2H, m); 6.23(1H, s); 5.80 (1H, m); 5.20 (2H, s); 3.3(1H, m); 3.14 (1H, m).

[0515] Compound 59.4. MS ESI (neg.) m/e: 479 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.92 (2H, m); 7.82-7.86 (3H, m); 7.72 (1H, m); 7.52-7.56 (2H, m); 7.36 (1H, s); 7.20 (2H, d, J=9Hz); 6.99 (2H, d, J=9Hz); 6.02 (1H, m); 5.69 (1H, m); 5.14 (2H, s); 3.3 (1H, m); 2.98 (1H, m); 2.24 (3H, s).

[0516] Compound 59.5. MS ESI (neg.) m/e: 411 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.63-7.73 (4H, m); 7.36-7.52 (6H, m); 7.20 (2H, d, J=8Hz); 6.99 (2H, d, J=8Hz); 6.01 (1H, s); 5.70 (1H, m); 5.17 (2H, s); 3.3 (1H, m); 2.99 (1H, m); 2.24 (3H, s).

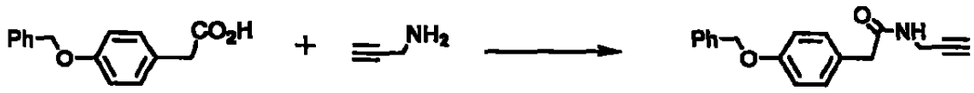
[0517] Compound 59.6. MS ESI (neg.) m/e: 479 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.93 (2H, m); 7.84 (3H, m); 7.71 (2H, m); 7.55 (2H, m); 7.26(2H, d, J=9Hz); 7.00 (2H, d, J=9Hz); 6.00 (1H, s); 5.69 (1H, m); 5.19 (2H, s); 3.3 (1H, m); 3.05 (1H, m); 2.15 (3H, s).

[0518] Compound 59.7. MS ESI (neg.) m/e: 411 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.64-7.74 (5H, m); 7.39-7.52 (5H, m); 7.26 (2H, d, J=9Hz); 6.99 (2H, d, J=9Hz); 5.99 (1H, s); 5.68 (1H, m); 5.17 (2H, s); 3.3 (1H, m); 3.06 (1H, m); 2.15 (3H, s).

6.60 Example 60

[0519] This example illustrates the preparation of ethyl 3-(4-hydroxyphenyl)-3-(5-methyloxazol-2-yl)propanoate.

Scheme 60.1



60.1

[0520] **2-(4-(Benzyloxy)phenyl)-*N*-(prop-2-ynyl)acetamide (60.1).** A mixture of 4-(benzyloxy)phenylacetic acid (20.7 mmol), 1-hydroxybenzotrizole hydrate (37 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (37 mmol), propargylamine (20.7mmol) and *N*-methylmorpholine (62 mmol) in DMF (60 mL) were stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (400 mL), washed with 1N HCl, water, saturated Na_2CO_3 solution, brine and dried over Na_2SO_4. After removing solvent under reduced pressure, the residue was triturated with dichloromethane. Compound 60.1 was obtained as a white solid after filtration and drying. LC-MS ESI (pos.) m/e: 280 (M+H).

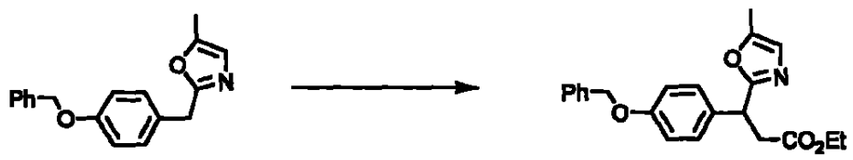
Scheme 60.2



60.1 60.2

[0521] **2-(4-Benzyloxy)benzyl)-5-methyl oxazole (60.2).** A mixture of compound **60.1** (10.1 mmol), $AuCl_3$ (1 mmol) in dichloromethane (100 mL) was stirred at room temperature overnight. Additional dichloromethane (100 L) was added and the reaction mixture was washed with $NaHCO_3$ solution and saturated brine. After drying over Na_2SO_4 and concentration under reduced pressure, the residue was purified by column chromatography (1:2 ethyl acetate-hexanes) to obtain compound **60.2**. LC-MS ESI (pos.) m/e: 280 (M+H).

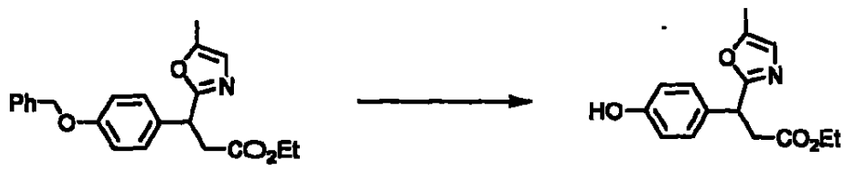
Scheme 60.3



60.2 60.3

[0522] **Ethyl 3-(4-(benzyloxy)phenyl)-3-(5-methyloxazol-2-yl)propanoate (60.3).** Compound **60.3** was obtained from compound **60.2** according to the method of Example 58.

Scheme 60.4



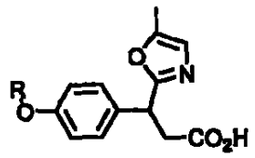
60.3 60

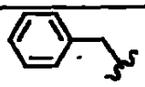
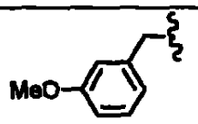
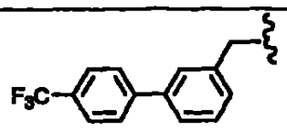
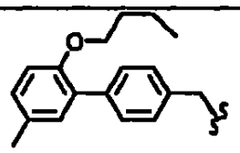
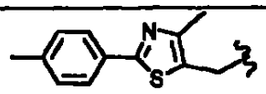
[0523] **(+/-)-Ethyl 3-(4-hydroxyphenyl)-3-(5-methyloxazol-2-yl)propanoate (60).** Compound **60** was obtained from compound **60.3** according to the method of Example 58.

6.61 Example 61

[0524] The following compounds were prepared from compound **60** according to the methods described in Example 18.

Table 20



Compound	R	Compound	R
61.1		61.4	
61.2		61.5	
61.3			

[0525] Compound 61.1. MS ESI (neg.) m/e: 336 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.41-7.46 (4H, m); 7.36 (1H, m); 7.17 (2H, d, J=9Hz); 6.97 (2H, d, J=9Hz); 6.73 (1H, s); 5.09 (2H, s); 4.44 (1H, m); 3.08 (1H, m); 2.71 (1H, m); 2.22 (3H, s).

[0526] Compound 61.2. MS ESI (neg.) m/e: 480 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.91-7.93 (2H, m); 7.82-7.85 (3H, m); 7.72 (2H, d, J=7Hz); 7.54 (2H, m); 7.18 (2H, d, J=8Hz); 6.99 (2H, d, J=8Hz); 6.72 (1H, s); 5.17 (2H, s); 4.44 (1H, m); 3.08 (1H, m); 2.74 (1H, m); 2.21 (3H, s).

[0527] Compound 61.3. MS ESI (neg.) m/e: 447 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.80 (2H, d, J=8Hz); 7.30 (2H, d, J=8Hz); 7.19 (2H, d, J=8Hz); 7.00 (2H, d, J=8Hz); 6.73 (1H, s); 5.27 (2H, s); 4.44 (1H, m); 3.10 (1H, m); 2.73 (1H, m); 2.43 (3H, s); 2.34 (3H, s); 2.21 (3H, s).

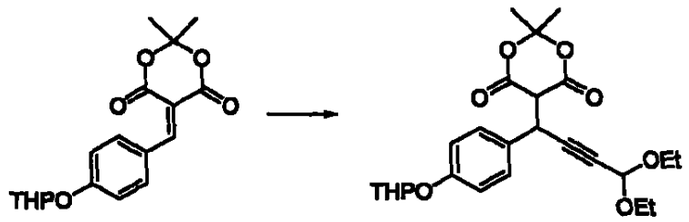
[0528] Compound 61.4. MS ESI (neg.) m/e: 366 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.32 (1H, t, J=8Hz); 7.16 (2H, d, J=8Hz); 7.00(2H, m); 6.96 (2H, m); 6.89 (1H, m); 6.72 (1H, s); 5.05 (2H, s); 4.42 (1H, m); 3.76 (3H, s); 3.06 (1H, m); 2.76 (1H, m); 2.21 (3H, s).

[0529] Compound 61.5. MS ESI (pos.) m/e: 500 (M+H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.50 (2H, d, J=8Hz); 7.44 (2H, d, J=8Hz); 7.11-7.18 (4H, m); 6.97 (3H, m); 6.71 (1H, s); 5.10 (2H, s); 4.43 (1H, m); 3.93 (2H, t, J=7Hz); 3.06 (1H, m); 2.70 (1H, m); 2.20 (3H, s); 1.61 (2H, m);1.36 (2H, m); 0.86 (3H, t, J=7Hz).

6.62 Example 62

[0530] This example illustrates the preparation 3-(4-(3-(4-(trifluoromethyl)phenyl) benzyloxy)phenyl)-3-(isoxazol-5-yl)propanoic acid (62).

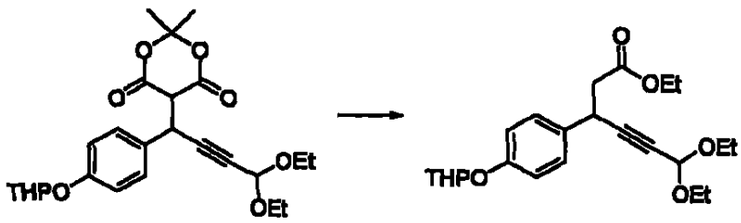
Scheme 62.1



52.1 62.1

[0531] 5-(4,4-Diethoxy-1-(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)but-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (62.1). Propiolaldehyde diethyl acetal (5 g, 39 mmol) in anhydrous THF (65 mL) was cooled to –5 °C and treated with ethylmagnesium bromide (39 mmol in 14 mL of anhydrous THF) dropwise over 10 min. After 45 min., the solution of Grignard reagent was added to compound 52.1 in anhydrous THF (50 mL). After stirring 1 h, the reaction was quenched with saturated $NH_4Cl_{(aq)}$ (20 mL) and diluted with hexanes (100 mL). After mixing vigorously, the layers were separated and the organic layer discarded. The aqueous layer was acidified and extracted twice with diethyl ether. The combined organic layers were washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was used immediately without further purification. MS ESI (pos.) m/e: 478.3 $(M+NH_4)^+$.

Scheme 62.2

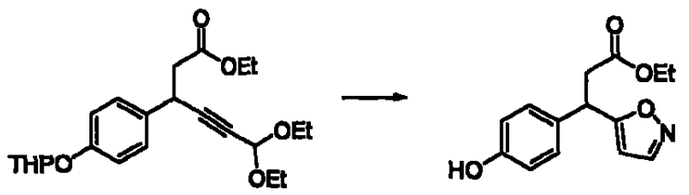


62.1 62.2

[0532] Ethyl 6,6-diethoxy-3-(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)hex-4-ynoate (62.1). Ethanolysis and decarboxylation was carried out according to the method of Example 16. Ester 62.2 was obtained as a light yellow oil (8 g).

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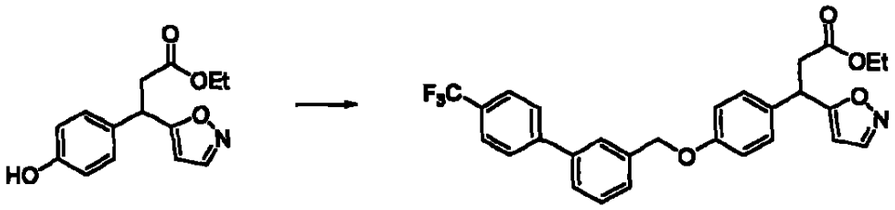
Scheme 62.3



62.2 62.3

[0533] **Ethyl 3-(4-hydroxyphenyl)-3-(isoxazol-5-yl)propanoate (62.3).** Compound 62.2 (1 g, 2.5 mmol) and hydroxylamine hydrochloride (0.43 g, 6.2 mmol) were dissolved in a mixture of ethanol (10 mL) and water (1 mL). After refluxing 2 h, the reaction mixture was diluted with 200 mL of water and extracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with saturated brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 5% methanol in dichloromethane eluant). Compound 62.3 was obtained as a thick oil (0.38 g). ^{1}H NMR (500MHz) ($CDCl_3$) δ 8.14 (d, J=1.5 Hz, 1H); 7.12 (d, J=8.5 Hz, 2H); 6.77 (d, J=8.5, 2H); 5.98 (d, J=1.0 Hz, 1H); 5.30 (s, 1H); 4.64 (t, J= 8.0 Hz, 1H); 4.06 (m, 2H); 3.15 (dd, J=16, 7.5 Hz, 1H); 2.95 (dd, J=16, 8.0 Hz, 1H); 1.17 (t, J= 7.2 Hz, 3H).

Scheme 62.4

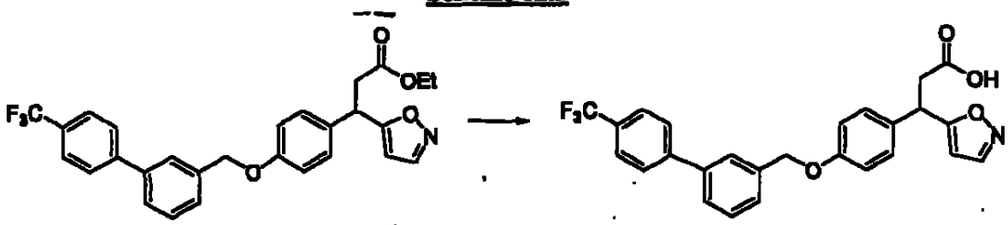


62.3 62.4

[0534] **Ethyl 3-(4-(3-(4-(trifluoromethyl)phenyl)benzyloxy)phenyl)-3-(isoxazol-5-yl)propanoate (62.4).** Compound 62.3 was alkylated according to the procedure of Example 2. LC-MS ESI (pos.) m/e: 496.1 (M+H). ^{1}H NMR (500MHz) ($CDCl_3$) δ 8.14 (s, 1H); 7.70 (s, 4H); 7.66 (s, 1H); 7.56 (d, J= 7.5 Hz, 1H); 7.50-7.45 (m, 2H); 7.22 (d, J=8.5 Hz, 2H); 6.96 (d, J=8.5, 2H); 5.99 (s, 1H); 5.12 (s, 2H); 4.67 (t, J= 7.7 Hz, 1H); 4.08 (m, 2H); 3.16 (dd, J=16, 7.5 Hz, 1H); 2.95 (dd, J=16, 8.0 Hz, 1H); 1.17 (t, J= 7.2 Hz, 3H).

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Scheme 62.5



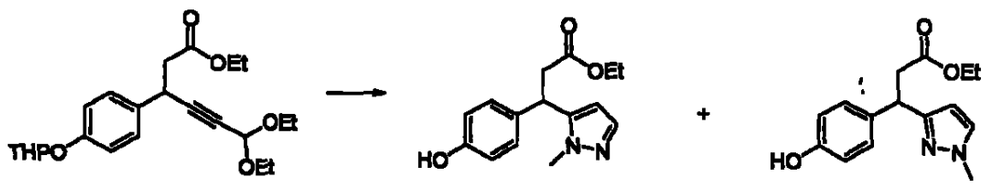
62.4 62

[0535] (+/-)-3-(4-(3-(4-(Trifluoromethyl)phenyl)benzyloxy)phenyl)-3-(isoxazol-5-yl)propanoic acid (62). Compound 62.4 was dissolved in glacial acetic acid (1 mL) and water (0.3 mL) and heated to 95 °C for 16 h. 1N HCl (0.1 mL) was added and the reaction mixture was heated for another 16 h. The reaction mixture was poured into deionized water (50 mL) and extracted twice with diethyl ether. The combined organic layers were washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 5% methanol in dichloromethane eluant). Compound 62 was obtained as a thick oil (26 mg). LC-MS ESI (pos.) m/e: 468.1 (M+H). ^{1}H NMR (500MHz) ($CDCl_3$) δ 8.14 (s, 1H); 7.70 (s, 4H); 7.66 (s, 1H); 7.56 (d, J= 7.5 Hz, 1H); 7.50-7.45 (m, 2H); 7.22 (d, J=8.5 Hz, 2H); 6.96 (d, J=8.5, 2H); 5.99 (s, 1H); 5.12 (s, 2H); 4.67 (t, J= 7.7 Hz, 1H); 4.08 (m, 2H); 3.16 (dd, J=16, 7.5 Hz, 1H); 2.95 (dd, J=16, 8.0 Hz, 1H); 1.17 (t, J= 7.2 Hz, 3H).

6.63 Example 63

[0536] This example illustrates the preparation 3-[4-(2'-butoxy-5'-methyl-biphenyl-4-ylmethoxy)-phenyl]-3-(1-methyl-1*H*-pyrazol-5-yl) propionic acid and 3-[4-(2'-butoxy-5'-methyl-biphenyl-4-ylmethoxy)-phenyl]-3-(1-methyl-1*H*-pyrazol-3-yl) propionic acid.

Scheme 63.1

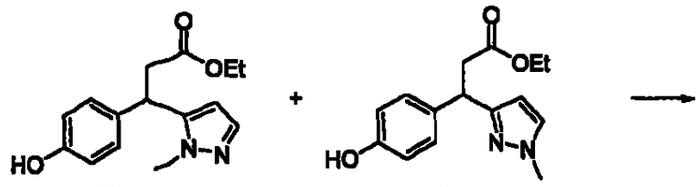


62.2 63.1 63.2

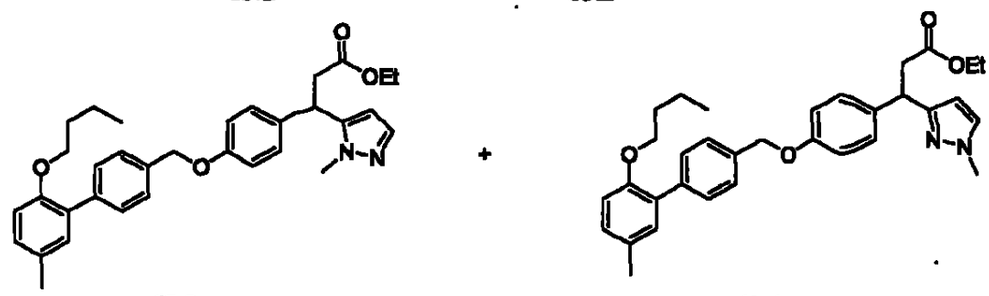
[0537] Ethyl 3-(4-hydroxyphenyl)-3-(1-methyl-1H-pyrazol-5-yl)propanoate (63.1) and ethyl 3-(4-hydroxyphenyl)-3-(1-methyl-1H-pyrazol-3-yl)propanoate (63.2). Compound 62.2 was dissolved in abs. Ethanol (6 mL). A solution of methylhydrazine (173 mg, 3.7 mmol) in 6N $HCl_{(aq)}$ (0.6 mL) was added and the reaction mixture heated to reflux. After 2 h, the reaction mixture was diluted with 200 mL of water, neutralized with saturated aqueous $NaHCO_3$, and extracted with diethyl ether (2 x 100 mL). The combined

organic layers were washed with saturated brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 5% methanol in dichloromethane). Compounds 63.1 and 63.2 were obtained as an inseparable mixture in a ~4:5 ratio by 1H-NMR. LC-MS ESI (pos.) m/e: 275.2 (M+H).

Scheme 63.2



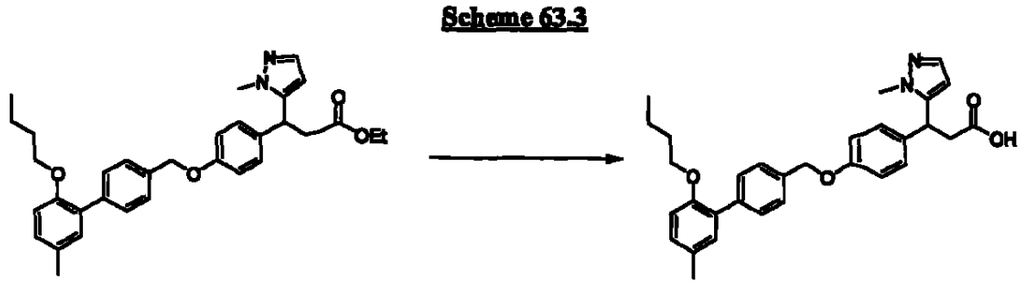
63.1 63.2



63.3 63.4

[0538] **Ethyl 3-[4-(2'-Butoxy-5'-methyl-biphenyl-4-ylmethoxy)-phenyl]-3-(1-methyl-1*H*-pyrazol-5-yl) propionic (63.3) and Ethyl 3-[4-(2'-butoxy-5'-methyl-biphenyl-4-ylmethoxy)-phenyl]-3-(1-methyl-1*H*-pyrazol-3-yl) propanoate (63.4).** The mixture of 63.1 and 63.2 was alkylated with 4-(2-butoxy-5-methyl)phenyl)benzyl bromide according to the method of Example 2. Separation of 63.3 and 63.4 could be accomplished by flash chromatography (silica gel, 3% acetone in dichloromethane).

Scheme 63.3

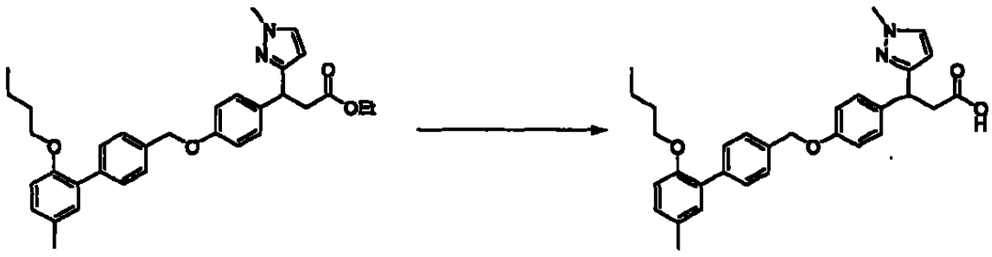


63.3 63.5

[0539] **(+/-)-3-[4-(2'-Butoxy-5'-methyl-biphenyl-4-ylmethoxy)-phenyl]-3-(1-methyl-1*H*-pyrazol-5-yl) propionic acid (63.5).** A 25 mL pear-shaped flask was charged with ethanol (1 mL), compound 63.3 (20 mg, 0.04 mmol), and 2N $NaOH_{(aq)}$ (2 mL, 4.0 mmol). The resulting mixture was stirred overnight at room temperature. The mixture was acidified to a pH of 3 with 1N HCl and extracted with ethyl acetate (2 x 10 mL). The

combined extracts were washed with brine and concentrated. The resulting residue was purified *via* preparatory TLC (30% Acetone in dichloromethane) to yield compound 63.5 (4.0 mg). ^{1}H NMR(400MHz)($CDCl_3$) δ 7.55 (d, 2H, *J*=2 Hz); 7.42 (d, 2H, *J*=2 Hz); 7.29 (m, 1H); 7.19-7.08 (m, 4H); 6.95-6.86 (m, 3H); 5.98 (s, 1H); 5.05 (s, 2H); 4.46 (m, 1H); 3.94 (s, 3H); 3.31 (m, 1H); 3.01 (m, 1H); 2.33 (s, 3H); 1.67 (m, 3H); 1.40 (m, 3H); 0.90 (t, 3H, *J*=6 Hz). MS ESI (neg.) m/e: 497.2 (M – H).

Scheme 63.4

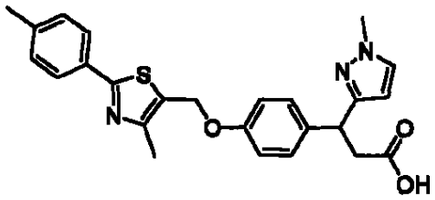


63.4 63.6

[0540] **(+/-)-3-[4-(2'-Butoxy-5'-methyl-biphenyl-4-ylmethoxy)-phenyl]-3-(1-methyl-1*H*-pyrazol-3-yl) propionic acid (63.6).** Hydrolysis of 63.4 was carried out as described above. MS ESI (neg.) m/e: 497.2 (M – H).

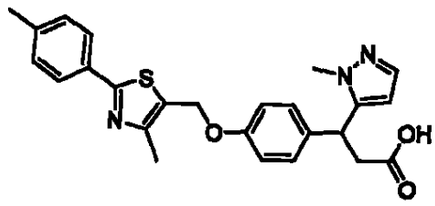
6.64 **Example 64**

[0541] The following compounds were prepared from compounds 63.1 and 63.2 according to the methods described in Example 63.



64.1

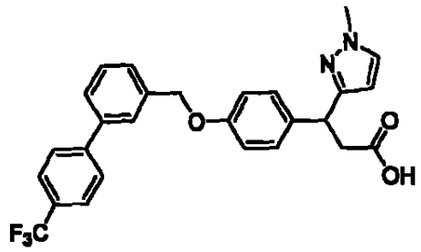
[0542] **(+/-)-3-(1-Methyl-1*H*-pyrazol-3-yl)-3-(4-((4-methyl-2-*p*-tolylthiazol-5-yl)methoxy)phenyl) propanoic acid (64.1).** ^{1}H NMR (400MHz) ($CDCl_3$) δ 7.84 (m, 2H); 7.12 (m, 5H); 6.89 (m, 2H); 5.92 (s, 1H); 5.13 (s, 2H); 4.46 (q, 1H, *J*=6 Hz); 3.88 (s, 3H); 3.23 (m, 1H); 2.98 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H). MS ESI (neg.) m/e: 446.2 (M – H).



64.2

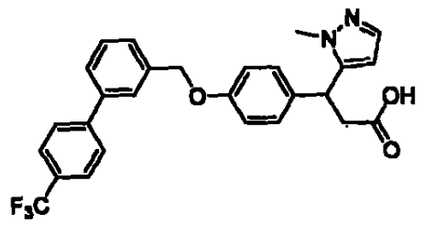
147
142

[0543] (+/-)-3-(1-Methyl-1*H*-pyrazol-5-yl)-3-(4-((4-methyl-2-*p*-tolylthiazol-5-yl)methoxy)phenyl) propanoic acid (64.2). MS ESI (neg.) m/e: 446.2 (M – H).



64.3

[0544] (+/-)-3-(1-Methyl-1*H*-pyrazol-3-yl)-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-propionic acid (64.3). ^{1}H NMR (400MHz) ($CDCl_3$) δ 7.69–7.46 (m, 8H); 7.26-6.92 (m, 5H); 5.96 (s, 1H); 5.01 (s, 2H); 4.47 (m, 1H); 3.91 (s, 3H); 3.25 (m, 1H); 2.99 (m, 1H). MS ESI (neg.) m/e: 479.2 (M – H).



64.4

[0545] (+/-)-3-(1-Methyl-1*H*-pyrazol-5-yl)-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-propionic acid (64.4). ^{1}H NMR (400MHz) ($CHCl_3$-d_3) δ 7.85–7.44 (m, 8H); 7.06 (d, 2H, *J*=6 Hz); 6.92 (s, 1H); 5.10 (s, 2H); 4.46 (m, 1H); 3.71 (s, 3H); 3.05 (m, 1H); 2.96 (m, 1H). MS ESI (neg.) m/e: 479.2 (M – H).

6.65 **Example 65 Cell-based Aequorin Assay**

[0546] A cell-based aequorin assay may be employed to characterize the modulatory activity of compounds on the GPR40 signaling pathway. In an exemplary assay, CHO cells are transfected in a 15 cm plated containing 14 million cells with 5 μg of GPR40 expression vector and 5 μg of Aequorin expression vector (Euroscreen) using Lipofectamine 2000 (Invitrogen). After 17-24 hours post-transfection, cells are washed with phosphate buffered saline (PBS) and detached from the tissue culture dish with 2 mL of trypsin (0.25%(w/v)). Trypsinization is halted with 28 mL of Hanks Buffered Salt Solution containing 20 mM Hepes (H/HBSS) and 0.01% fatty acid-free bovine serum albumin (BSA) or 0.625% fatty acid-free human serum albumin (HSA). Coelantrazine is added to 1 ug/mL and the cells are incubated for 2 hours at room temperature. Cells are gently mixed every 15 minutes. Compounds are dissolved in dimethyl sulfoxide for preparation of 10 mM stock solutions.

Compounds are diluted in H/HBSS containing either 0.01% BSA or 0.625% HSA. Serial dilutions of the test compounds are prepared to determine dose response.

[0547] Aequorin luminescence measurements are made using an EG&G Berthold 96-well luminometer and the response is measured over a 20 second interval after cells and compounds were mixed. The area-under-curve from 2-20 seconds is plotted to determine dose reponse. The EC_{50} (effective concentration to reach 50% maximal response) is determined from the dose response plot.

[0548] Table 21 presents representative data (EC_{50} values) obtained for exemplary compounds of the invention for the relative activation of human GPR40.

[0549] The stereoisomers in Table 21 are as specified, *i.e.*, *S*-enantiomers or *R*-enantiomers, and if not specified, are mixtures of *S*-enantiomers and *R*-enantiomers. In addition, the present invention provides the *S*-enantiomers, the *R*-enantiomers, and mixtures of both *S*-enantiomers and *R*-enantiomers including racemates of each compound prepared according to the synthetic methods described herein or adapted with the necessary minor modifications from these methods.

6.66 Example 66: Insulin Secretion Assay

[0550] C57/Bl6 mice are euthanized with carbon dioxide gas. The pancreatic bile duct is clamped proximal to the duodenum and then cannulated. H/HBSS containing 0.75 mg/ml collagenase XI (Sigma) is then infused into the pancreas through the cannula. The pancreas is excised and then incubated at 37°C for 13 minutes to complete enzymatic digestion. The collagenase digestion is quenched in H/HBSS containing 1% BSA and washed once in the same buffer. Islets can be purified using density gradient centrifugation using Histopaque (Sigma) and are hand-picked under a stereomicroscope.

[0551] Islets are cultured overnight in Roswell Park Memorial Institute (RMPI) media containing 10% fetal bovine serum and 50 uM beta-mercaptoethanol. Following overnight culture, islets are incubated in Dulbecco's Modifcation of Eagle's medium (DMEM) containing 2.8 mM glucose for one hour.

[0552] For determination of insulin secretion, islets are incubated in DMEM containing 12.5 mM glucose and test compounds for one hour. Insulin released into the culture medium from the islets is measured using an insulin ELISA.

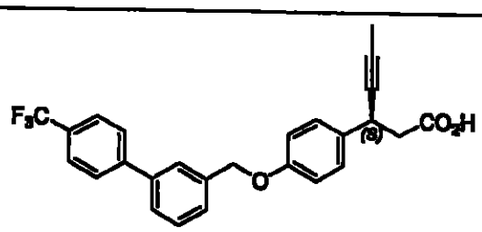
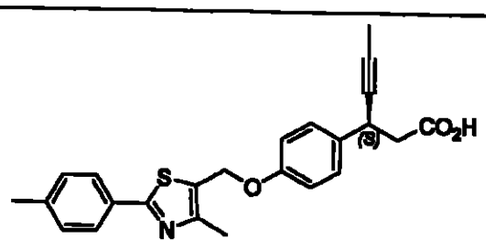
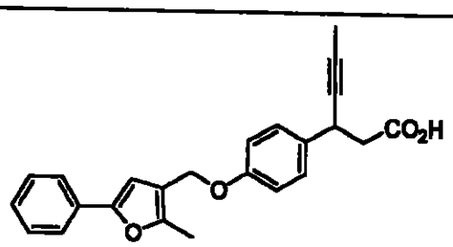
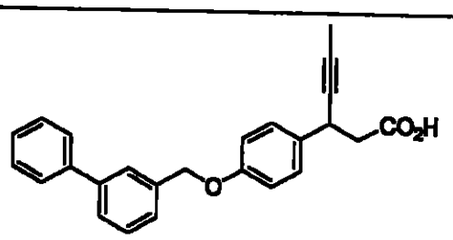
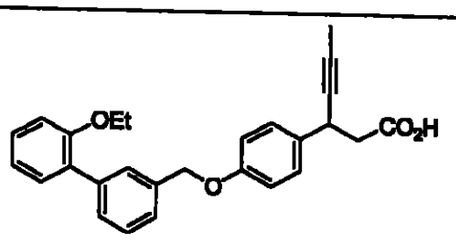
[0553] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill

in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

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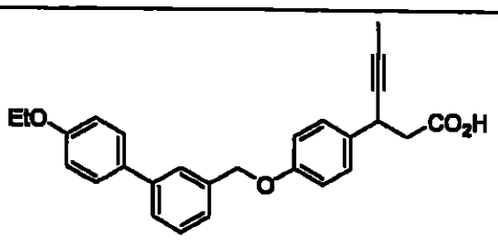
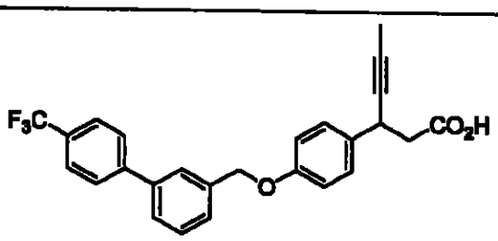
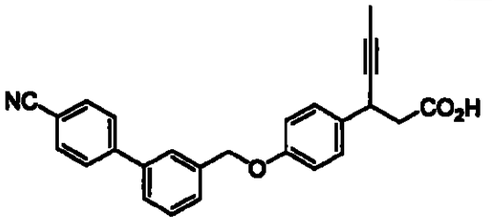
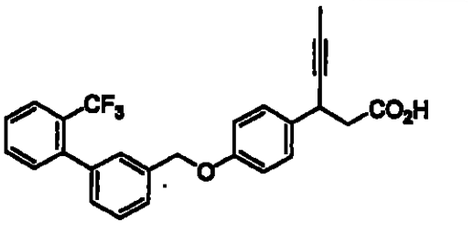
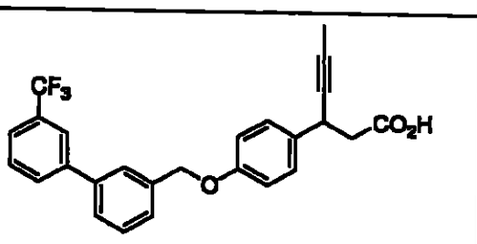
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TABLE 21
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC_{50}[a]
2		++++
3		+++++
5		++++
6.1		++++
6.2		++++

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TABLE 21
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC_{50}[a]
6.3		++++
6.5		++++
6.7		+++
6.8		++++
6.9		++++

[1]TABLE 21
Aequorin Assay Using Human GPR40

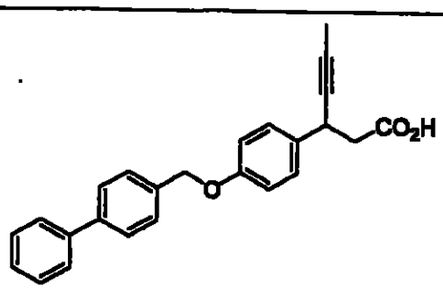
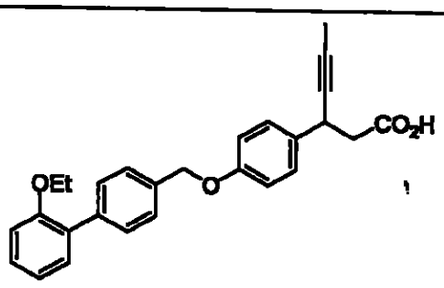
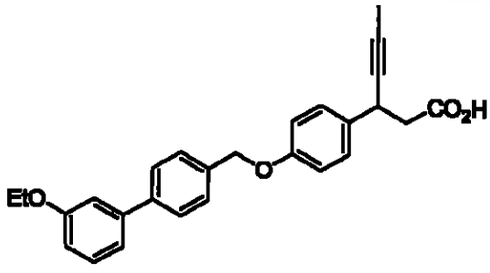
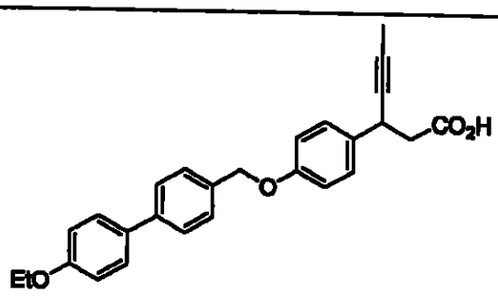
No.	Structure	Relative EC_{50}[a]
7.3		++
7.5		++++
7.8		+++
7.9		+++

TABLE 21
Aequorin Assay Using Human GPR40

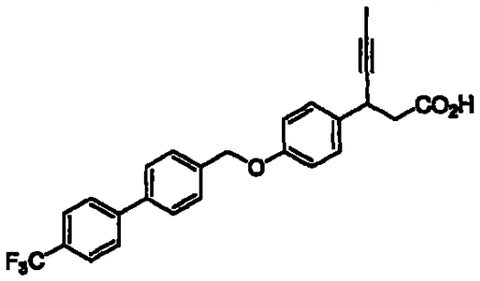
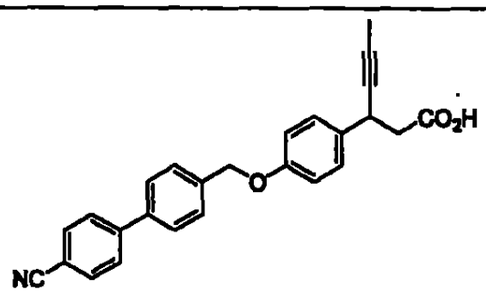
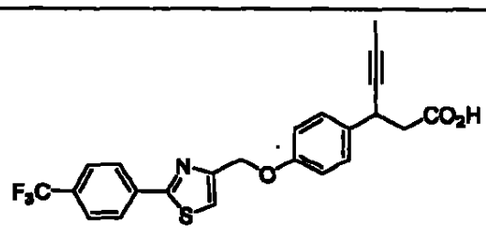
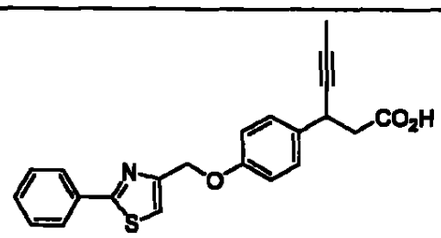
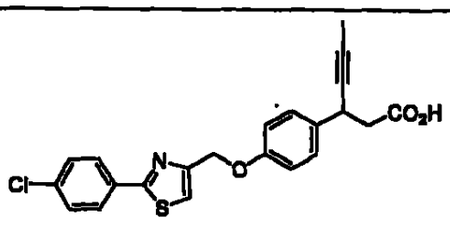
No.	Structure	Relative EC_{50}[a]
7.10		+++
7.15		++++
8.1		++++
8.2		++++
8.3		++++

TABLE 21
Aequorin Assay Using Human GPR40

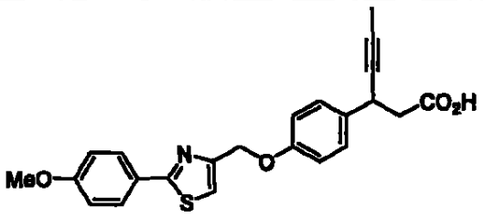
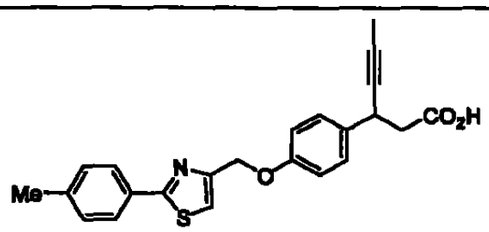
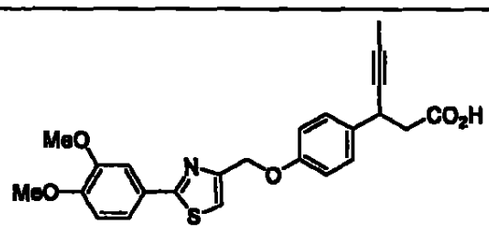
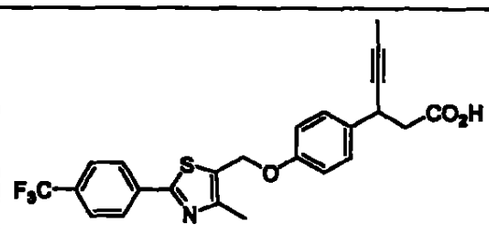
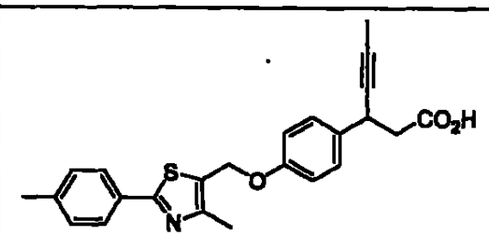
No.	Structure	Relative EC_{50}[a]
8.4		++++
8.5		++++
8.6		+++
9.1		++++
9.2		+++++

TABLE 21
Aequorin Assay Using Human GPR40

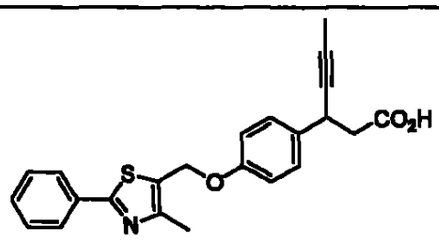
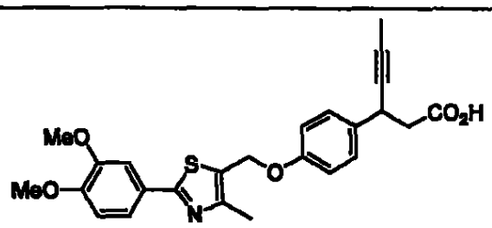
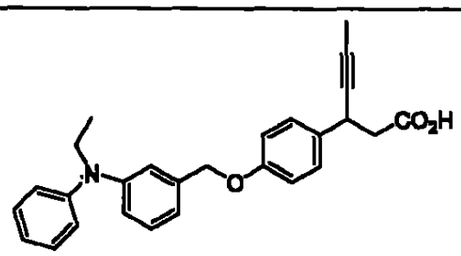
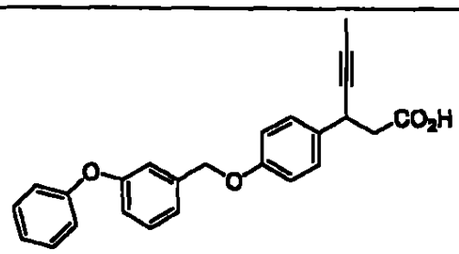
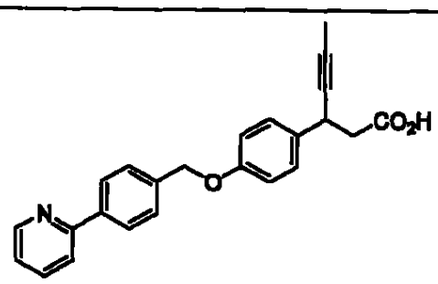
No.	Structure	Relative EC_{50}[a]
9.3		++++
9.4		++++
10.2		++++
10.3		++++
10.4		++++

TABLE 21
Aequorin Assay Using Human GPR40

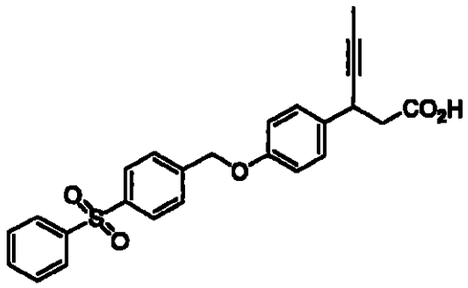
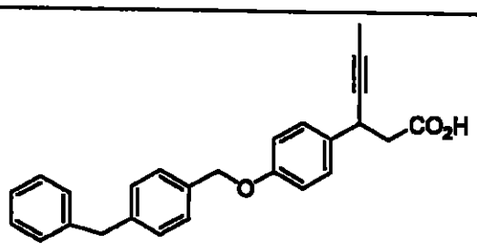
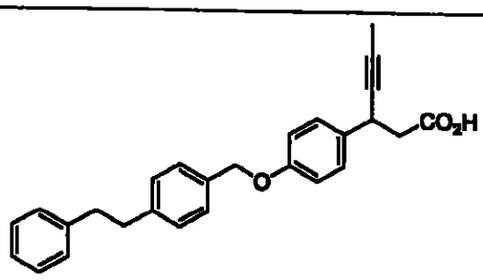
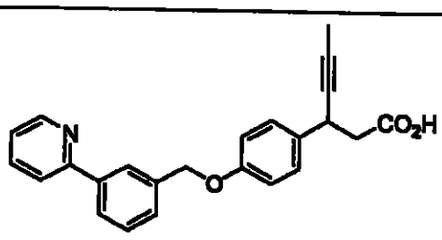
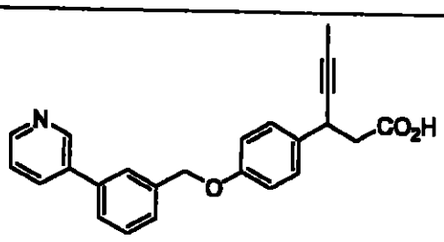
No.	Structure	Relative EC_{50}[a]
10.5		+++
10.6		++++
10.7		+++
10.8		+++
10.9		+++

TABLE 21
Aequorin Assay Using Human GPR40

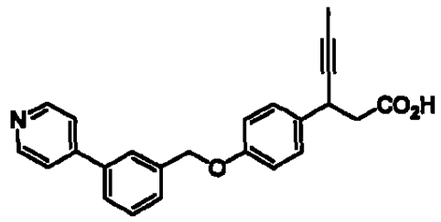
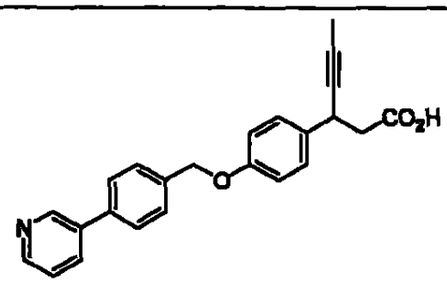
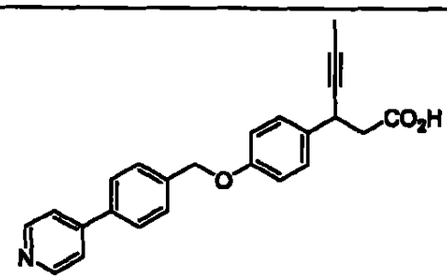
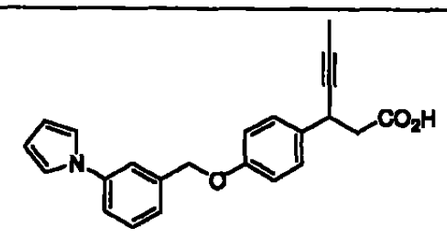
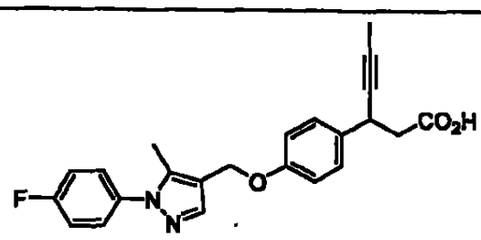
No.	Structure	Relative EC_{50}[a]
10.10		+++
10.12		++
10.13		+++
10.14		++++
11.1		+++

TABLE 21
Aequorin Assay Using Human GPR40

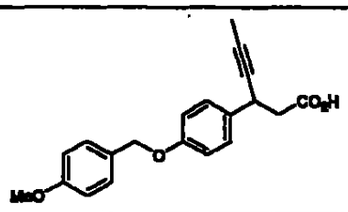
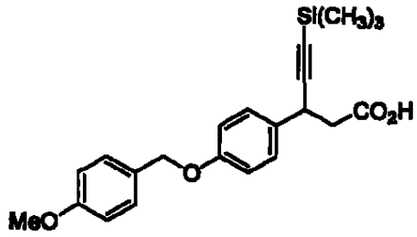
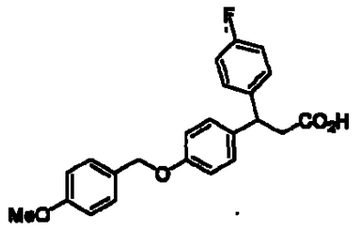
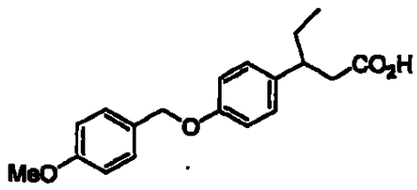
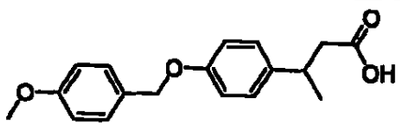
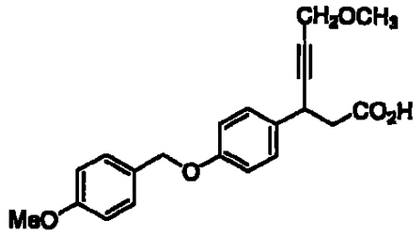
No.	Structure	Relative EC_{50}[a]
12		+++
14.1		++
14.2		+++
14.3		++
14.4		+
14.5		++

TABLE 21
Aequorin Assay Using Human GPR40

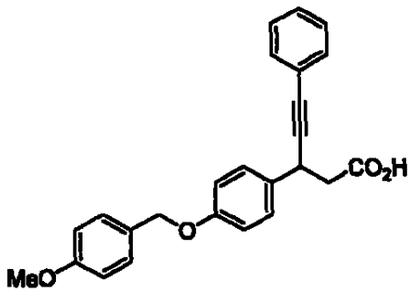
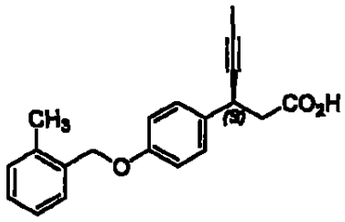
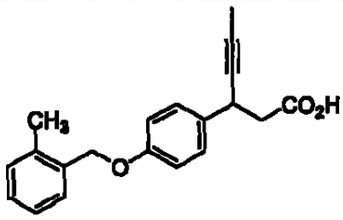
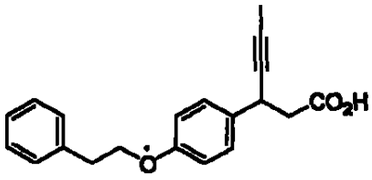
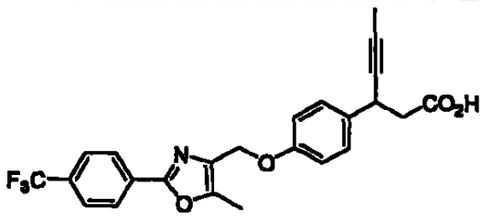
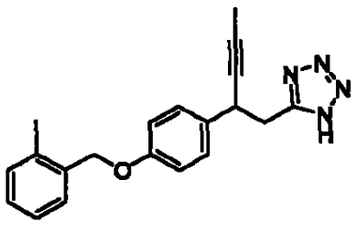
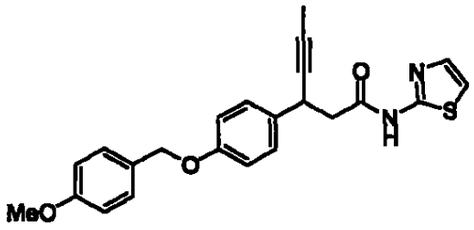
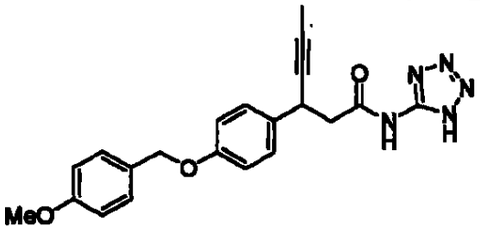
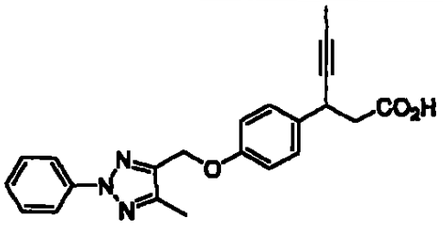
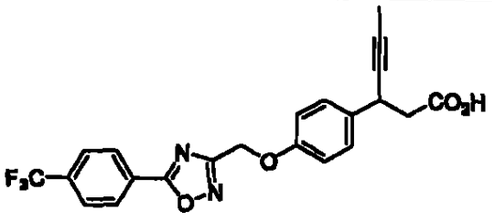
No.	Structure	Relative EC_{50}[a]
14.6		++
15		++++
17.6		+++
17.8		++
18		++++

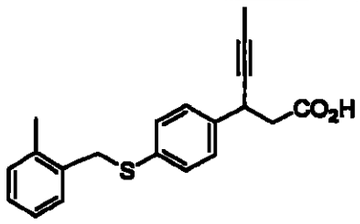
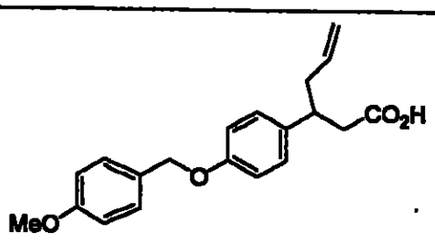
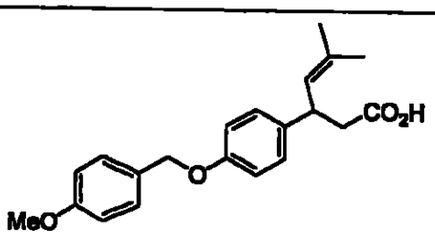
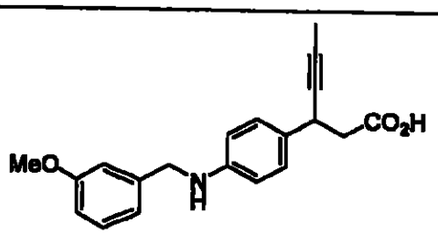
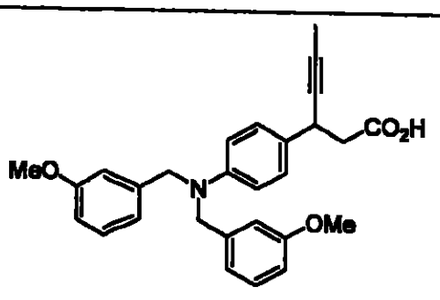
TABLE 21
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC_{50}[a]
23		++
24		+++
25.1		++
26		++++
27.1		+++

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TABLE 21
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC_{50}[a]
28		+++
34.4		++
34.5		+++
36.1		+++
36.2		+++

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TABLE 21
Aequorin Assay Using Human GPR40

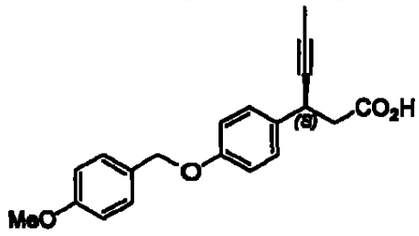
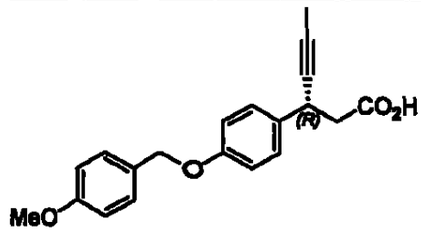
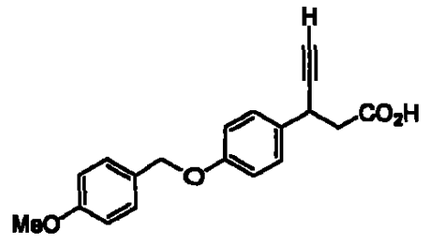
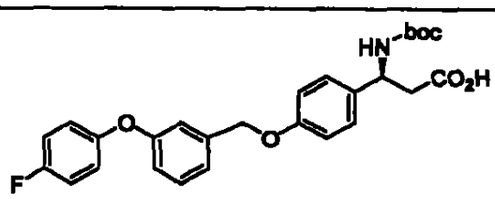
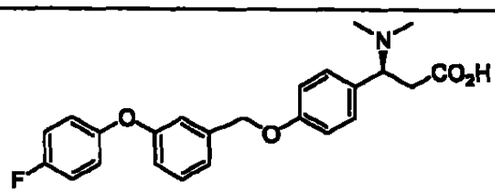
No.	Structure	Relative EC_{50}[a]
39.7		++++
40.5		++
41		+++
42.11		+++
42.14		+++

TABLE 21
Aequorin Assay Using Human GPR40

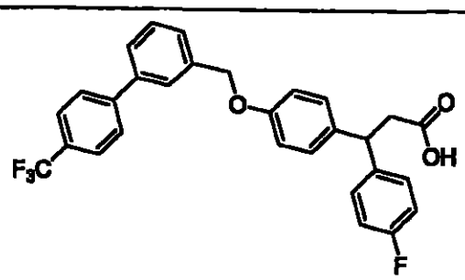
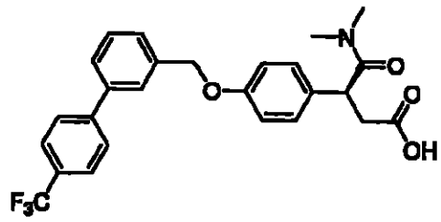
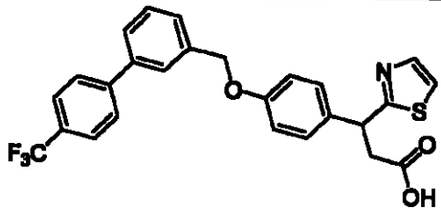
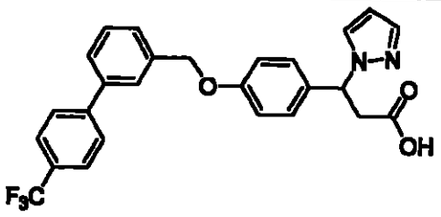
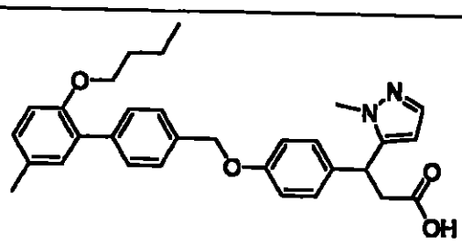
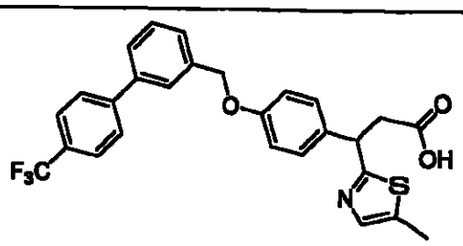
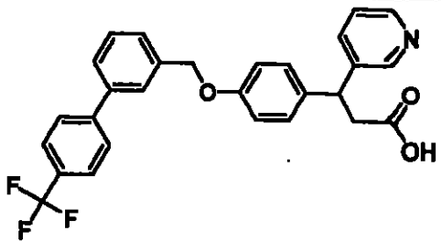
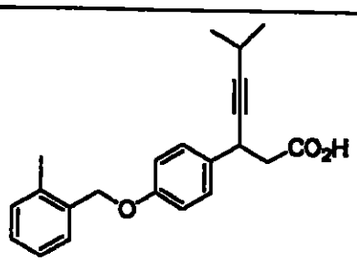
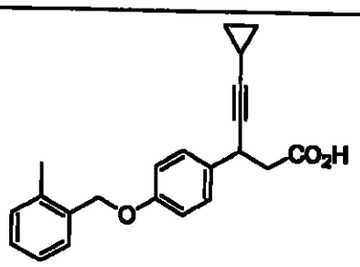
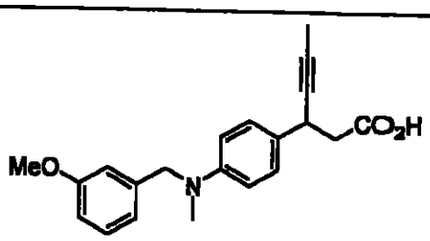
No.	Structure	Relative EC_{50}[a]
46.1		+++
53		++++
56		+++
62.3		++++
66.5		+++

TABLE 21
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC_{50}[a]
70.1		++
70.2		+++
71		+++
72		+++
73		++

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TABLE 21
Aequorin Assay Using Human GPR40

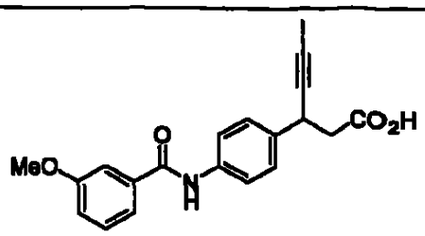
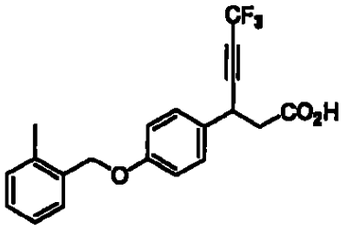
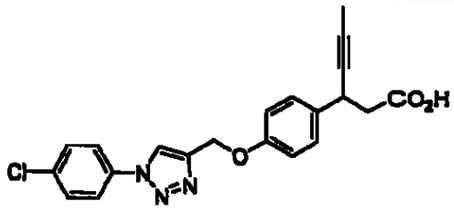
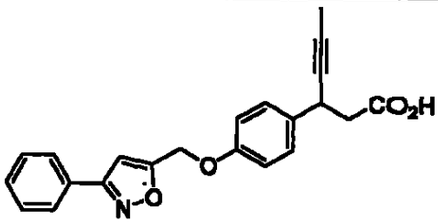
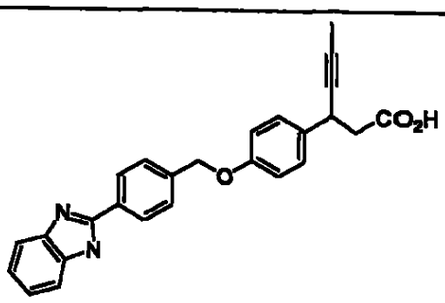
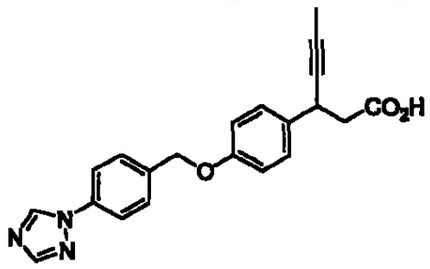
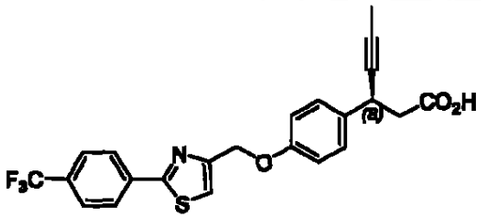
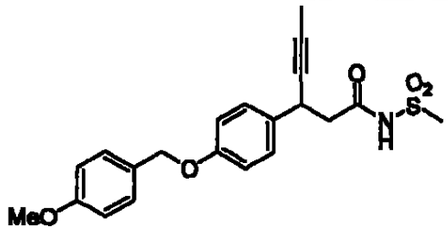
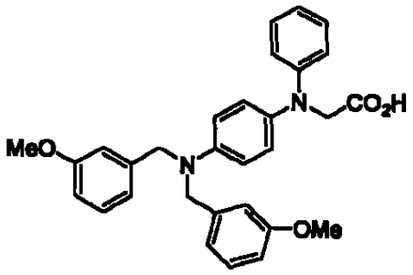
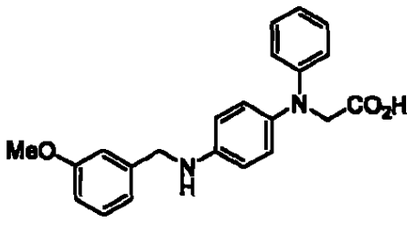
No.	Structure	Relative EC_{50}[a]
74		++
75		+
76		++
77		+++
78		++

TABLE 21
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC_{50}[a]
79		++
80		+++++
81		++
82.1[b]		++++
		+
82.2[b]		++++
		+

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TABLE 21
Aequorin Assay Using Human GPR40

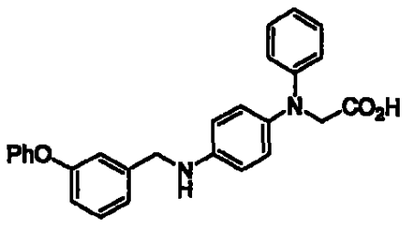
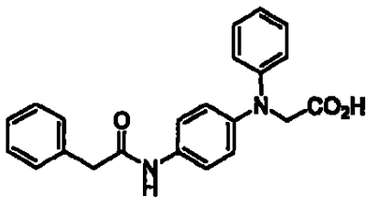
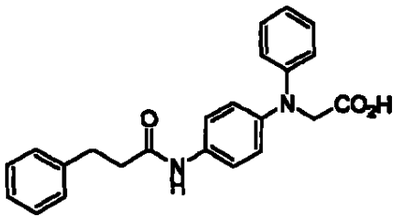
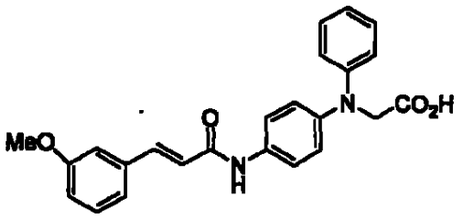
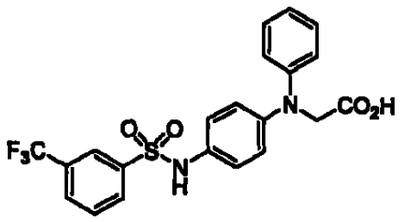
No.	Structure	Relative EC_{50} [a]
82.3 [b]		++++
		+
82.4 [b]		+++
		+
82.5 [b]		++++
		+
82.6 [b]		++++
		+
82.7 [b]		+++++
		+

TABLE 21
Aequorin Assay Using Human GPR40

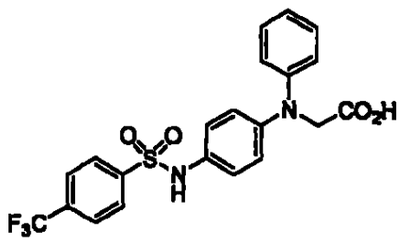
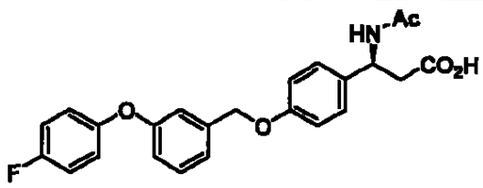
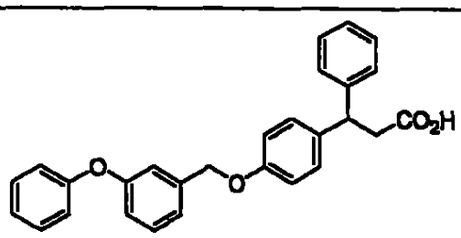
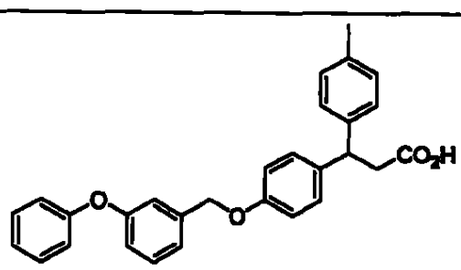
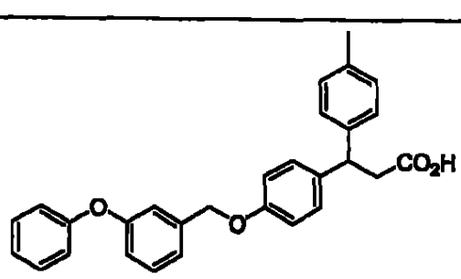
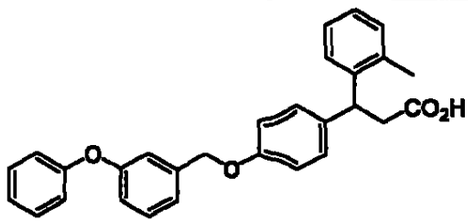
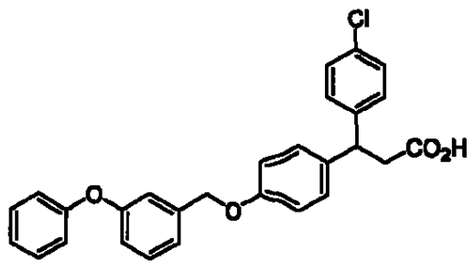
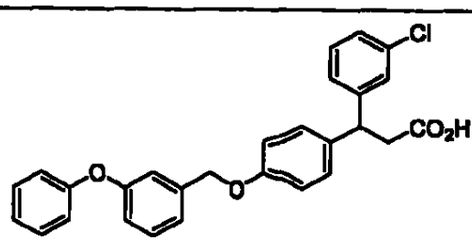
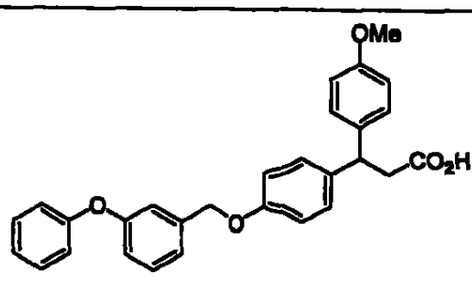
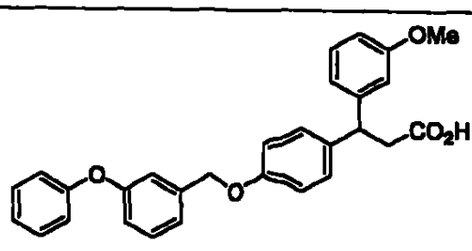
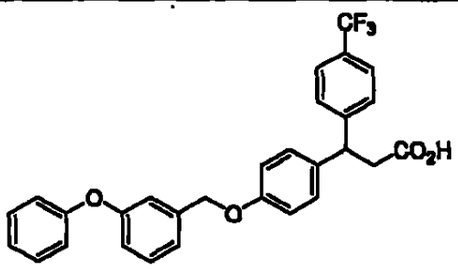
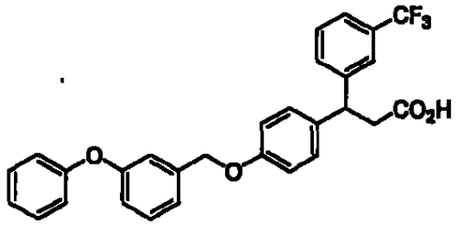
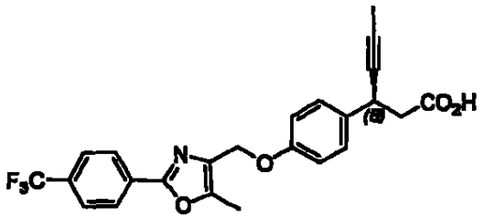
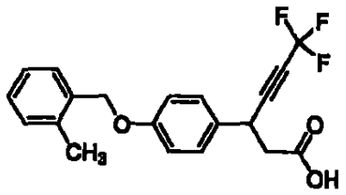
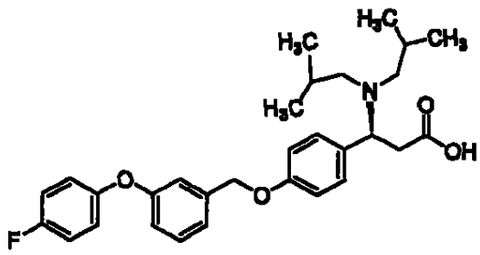
No.	Structure	Relative EC_{50}[a]
82.8[b]		+++++
		+
83		++
84.1		++++
84.2		++
84.3		+++

TABLE 21
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC_{50}[a]
84.4		+++
84.5		+++
84.6		+++
84.7		+++
84.8		+++

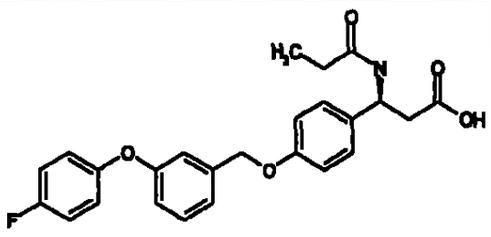
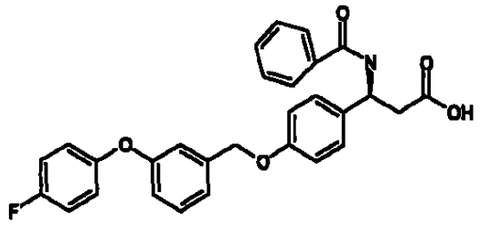
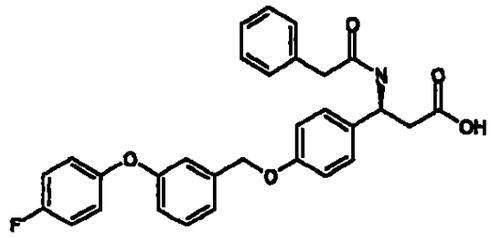
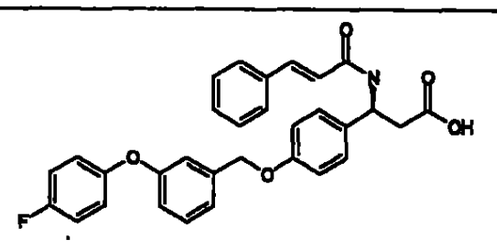
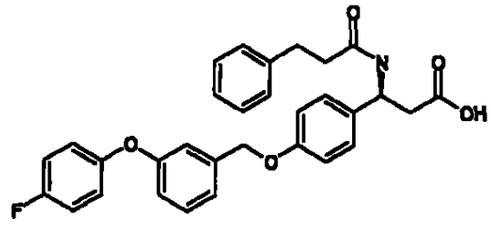
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TABLE 21
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC_{50}[a]
85.1		++
85.2		+++
86		+++++
87		+
88.1		+

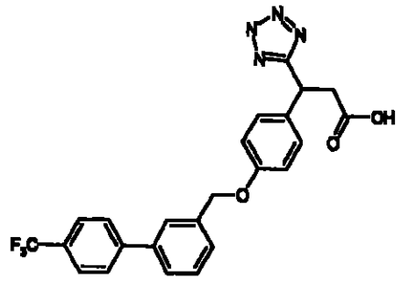
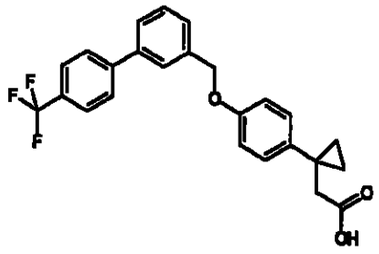
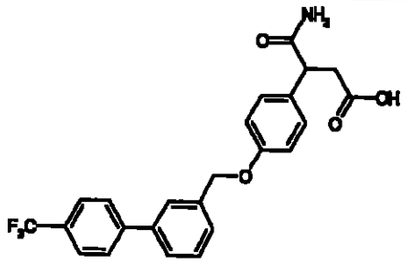
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TABLE 21
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC_{50}[a]
88.2		+
88.3		+
88.4		+
88.5		+
88.6		+

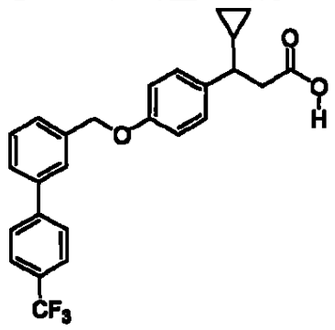
167

TABLE 21
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC_{50}[a]
88.7		++
89		++
90		++

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TABLE 21
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC_{50}[a]
91		++

[a] EC_{50} Ranges:
+ $EC_{50} > 10\ \mu M$
++ $1\ \mu M \leq EC_{50} \leq 10\ \mu M$
+++ $0.1\ \mu M \leq EC_{50} < 1\ \mu M$
++++ $0.01\ \mu M \leq EC_{50} < 0.1\ \mu M$
+++++ $EC_{50} < 0.01\ \mu M$

[b] Each relative EC_{50} range indicated for this compound reflects the range for an observed EC_{50} for the compound when determined in seperately performed assays.

WHAT IS CLAIMED:

1. A compound having the formula (I):

$$Q\text{–}L^1\text{–}P\text{–}L^2\text{–}M\text{–}X\text{–}L^3\text{–}A$$

I

or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein

Q is hydrogen, aryl, heteroaryl, $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$heteroalkyl;

L^1 is a bond, $(C_1\text{-}C_4)$alkylene, $(C_2\text{-}C_4)$heteroalkylene, O, $S(O)_m$, $N(R^1)$, $C(O)$-$(C_5\text{-}C_7)$heterocycloalkylene, $(C_1\text{-}C_4)$alkylene-$SO_2N(R^2)$, $(C_1\text{-}C_4)$alkylene–$N(R^2)SO_2$ or $C(O)N(R^2)$;

P is an aromatic ring, a heteroaromatic ring, $(C_3\text{-}C_8)$heterocycloalkylene or $(C_3\text{-}C_8)$cycloalkylene;

L^2 is a bond, $(C_1\text{-}C_6)$alkylene, $(C_2\text{-}C_6)$heteroalkylene, oxymethylene, O, $S(O)_m$, $N(R^1)$, $C(O)N(R^2)$, $SO_2N(R^2)$, $(C_1\text{-}C_4)$alkylene-$C(O)N(R^2)$, $(C_1\text{-}C_4)$alkylene-$N(R^2)C(O)$, $(C_2\text{-}C_4)$alkenylene-$C(O)N(R^2)$, $(C_2\text{-}C_4)$alkenylene-$N(R^2)C(O)$, $(C_1\text{-}C_4)$alkylene-$SO_2N(R^2)$, $(C_1\text{-}C_4)$alkylene-$N(R^2)SO_2$, $(C_2\text{-}C_4)$alkenylene-$SO_2N(R^2)$ or $(C_2\text{-}C_4)$alkenylene-$N(R^2)SO_2$;

M is an aromatic ring, a heteroaromatic ring, $(C_5\text{-}C_8)$cycloalkylene, aryl$(C_1\text{-}C_4)$alkylene or heteroaryl$(C_1\text{-}C_4)$alkylene;

X is CR^3R^4, $N(R^5)$, O or $S(O)_n$;

L^3 is a bond, $(C_1\text{-}C_5)$alkylene or $(C_2\text{-}C_5)$heteroalkylene, provided that L^3 is not a bond when L^2 is a bond;

A is $-CO_2H$, tetrazol-5-yl, $-SO_3H$, $-PO_3H_2$, $-SO_2NH_2$, $-C(O)NHSO_2CH_3$, $-CHO$, $-C(O)R^6$, $-C(O)NHR^6$, $-C(O)NHOR^7$, thiazolidinedion-yl, hydroxyphenyl or pyridyl;

R^1 is $(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_3)$ alkyl or $(C_2\text{-}C_6)$heteroalkyl;

R^2 is hydrogen, $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$heteroalkyl;

R^3 is cyano, aryl, heteroaryl, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_3\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_8)$alkynyl, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$, $-NR^{12}C(O)R^{13}$ or $-NR^{12}S(O)_pR^{13}$;

R^4 is hydrogen, cyano, aryl, heteroaryl, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl or $(C_2\text{-}C_8)$alkynyl;

optionally, R^3 and R^4 are combined to form a 3-, 4-, 5-, 6- or 7-membered ring containing from zero to three heteroatoms selected from N, O and S;

R^5 is hydrogen, aryl, heteroaryl, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl or $(C_3\text{-}C_8)$cycloalkyl;

R^6 is heteroaryl;

R^7 is hydrogen or (C_1-C_5)alkyl;

R^8 and R^9 are independently hydrogen, (C_1-C_5)alkyl, oxy(C_1-C_5)alkyl or carboxy(C_1-C_5)alkyl;

optionally, R^8 and R^9 are combined to form a 4-, 5-, 6- or 7-membered ring containing the nitrogen atom to which they are attached and from 0 to 2 additional heteroatoms selected from N, O and S;

R^{10}, R^{11} and R^{12} are independently selected from hydrogen, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_3-C_8)cycloalkyl and (C_3-C_8)heterocycloalkyl;

optionally, R^{10} and R^{11} are combined to form a 4-, 5-, 6- or 7-membered ring containing the nitrogen atom to which they are attached and from 0 to 2 additional heteroatoms selected from N, O and S;

R^{13} is aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_3-C_8)cycloalkyl or (C_3-C_8)heterocycloalkyl;

the subscripts m and n are independently 0, 1 or 2; and

the subscript p is 1 or 2; and

wherein the compound is other than 3-(4-(4-methoxybenzyloxy)phenyl)pent-4-ynoic acid; β-ethenyl-4-phenylmethoxy-benzenepropanoic acid; 4-(2-quinolinylmethoxy)-β-[4-(2-quinolinylmethoxy)phenyl]-benzenepropanoic acid; N-[4-(benzoylamino)phenyl]-N-phenyl-glycine; 3-(4-(isopentyloxy)benzamido)-3-phenylpropanoate; 3-(4-isobutoxybenzamido)-3-phenylpropanoate; (*R*)-2-((*1R,4R*)-4-isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid; (*R*)-3-(4-(benzyloxy)phenyl)-2-(tert-butoxycarbonyl)propanoic acid; 3-(4-chlorophenyl)-3-(furan-2-carboxamido)propanoic acid; 3-(3,4-dimethoxyphenyl)-3-(furan-2-carboxamido)propanoic acid; 3-(4-chlorobenzamido)-3-(4-(dimethylamino)phenyl)propanoic acid; 3-(2-(2-(3,4-dimethylphenoxy)ethylthio)-1*H*-benzo[d]imidazol-1-yl)propanoic acid; {2-Bromo-4-[(3,4-dichloro-phenyl)-hydrazonomethyl]-6-ethoxy-phenoxy}-acetic acid; 2-(4-(2-(2-(4-chlorophenyl)furan-5-carboxamido)ethyl)phenoxy)-2-methylpropanoic acid; 5-(3-(3,4-dimethoxyphenyl)-5-(2-fluorophenyl)-4,5-dihydropyrazol-1-yl)-5-oxopentanoic acid; 2-(2-(3-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-2-methyl-4-oxo-4*H*-chromen-7-yloxy)acetamido)acetic acid; 3-(4'-Bromo-biphenyl-4-yl)-4-phenyl-butyric acid; 3-(4'-Bromo-biphenyl-4-yl)-3-phenylsulfanyl-propionic acid; 3-(5-(2-chloro-6-fluoro-4-(trifluoromethyl)phenoxy)-2,4-dinitrophenyl)propanoic acid; 3-(3-(2-chloro-4-(trifluoromethyl)phenoxy)phenyl)propanoic acid; 3-(4-(4-methoxybenzyloxy)phenyl)pent-4-ynoic acid; 3-(4-(4-methoxybenzyloxy)phenyl)-5-(trimethylsilyl)pent-4-ynoic acid; β,β-dimethyl-4-[[[4-methyl-2-[4-(trifluoromethyl)phenyl]-5-thiazolyl]methyl]thio]-

benzenepropanoic acid; β-amino-4-[(4-bromo-2,5-dihydro-2-methyl-5-oxo-1-phenyl-1H-pyrazol-3-yl)methoxy]-3-methoxy-benzenepropanoic acid; or salt thereof.

2. The compound of Claim 1, wherein when P and M are benzene, at least two of L^2, X and L^3 are other than CH_2

3. The compound of Claim 1, wherein when Q is aryl or heteroaryl, L^1 is a bond, M is a monocyclic aromatic ring, X is $N(R^5)$, O or $S(O)_n$, and A contains a carbonyl group, then P is not a 1,2-azole ring.

4. The compound of Claim 1, wherein when Q is aryl, L^1 is a bond, M is an aromatic ring, X is CR^3R^4, O or $S(O)_n$ and A contains a carbonyl group, then P is other than furan or thiophene.

5. The compound of Claim 1, wherein P is selected from the group consisting of benzene, naphthalene, pyrrole, pyrazole, imidazole, pyrazine, oxazole, isoxazole, thiazole, furan, thiophene, pyridine, pyrimidine, pyridazine, benzothiazole, purine, benzimidazole, benzoxazole, triazole, oxadiazole, thiadiazole, benzooxadiazole, dibenzofuran, indole, indazole, carbazole, carboline, isoquinoline, quinoxaline and quinoline.

6. The compound of Claim 1, wherein P is selected from the group consisting of benzene, naphthalene, pyrrole, pyrazine, pyridine, pyrimidine, pyridazine, purine, indole, carboline, isoquinoline, quinoxaline and quinoline.

7. The compound of Claim 1.

8. The compound of Claim 1, wherein A is $-CO_2H$, tetrazol-5-yl, $-C(O)NHSO_2CH_3$ or $-C(O)NHR^6$.

9. The compound of Claim 1, wherein R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or $-NR^8R^9$.

10. The compound of Claim 9, wherein R^4 is hydrogen.

11. The compound of Claim 1, wherein M is an aromatic ring, a heteroaromatic ring or (C_5-C_8)cycloalkylene.

12. The compound of Claim 11, wherein R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or $-NR^8R^9$.

13. The compound of Claim 12, wherein A is $-CO_2H$ or tetrazol-5-yl.

14. The compound of Claim 12, wherein A is $-CO_2H$.

15. The compound of Claim 14, wherein X is CR^3R^4 or $N(R^5)$.

16. The compound of Claim 15, wherein L^3 is (C_1-C_5)alkylene or (C_2-C_5)heteroalkylene.

17. The compound of Claim 16, wherein P is an aromatic ring or a heteroaromatic ring.

18. The compound of Claim 1, wherein P is an aromatic ring or a heteroaromatic ring.

19. The compound of Claim 18, wherein X is CR^3R^4 or $N(R^5)$.

20. The compound of Claim 19, wherein L^3 is (C_1-C_5)alkylene.

21. The compound of Claim 20, wherein A is $-CO_2H$.

22. The compound of Claim 21, wherein R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or $-NR^8R^9$.

23. The compound of Claim 22, wherein M is benzene or a heteroaromatic ring.

24. The compound of Claim 23, wherein R^4 is hydrogen.

25. The compound of Claim 23, wherein L^1 is a bond, O or $N(R^1)$ and L^2 is (C_2-C_6)heteroalkylene.

26. The compound of Claim 24, wherein L^1 is a bond and L^2 is (C_2-C_6)heteroalkylene.

27. The compound of Claim 19, wherein M is benzene and X is *para* to L^2.

28. The compound of Claim 27, wherein L^3 is methylene.

29. The compound of Claim 28, wherein A is $-CO_2H$.

30. The compound of Claim 29, wherein R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or $-NR^8R^9$.

31. The compound of Claim 30, wherein L^1 is a bond and L^2 is oxymethylene or thiomethylene.

32. The compound of Claim 31, wherein R^4 is hydrogen.

33. The compound of Claim 1, wherein Q is aryl.

34. The compound of Claim 1, wherein L^1 is a bond and L^2 is oxymethylene or thiomethylene.

35. The compound of Claim 1, wherein P is an aromatic ring or a heteroaromatic ring and A is $-CO_2H$.

36. The compound of Claim 1, wherein P is an aromatic ring or a heteroaromatic ring and X is CR^3R^4 or $N(R^5)$.

37. The compound of Claim 1, wherein A is $-CO_2H$ and X is CR^3R^4 or $N(R^5)$.

38. The compound of Claim 36, wherein X is CR^3R^4 and R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or $-NR^8R^9$.

39. The compound of Claim 37, wherein X is CR^3R^4 and R^3 is cyano, aryl, heteroaryl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or $-NR^8R^9$.

40. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, diluent or excipient and the compound of Claim 1.

41. A method for treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, metabolic syndrome, syndrome X,

cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema comprising administering to a subject in need thereof a therapeutically effective amount of the compound of Claim 1.

42. The method of claim 41 wherein said disease or condition is type II diabetes.

43. A method for treating a disease or condition responsive to the modulation of GPR40 comprising administering to a subject in need thereof a therapeutically effective amount of the compound of Claim 1.

44. The method of Claim 43 wherein said disease or condition is selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

45. The method as in any one of Claims 41-44 wherein said compound is administered orally, parentally or topically.

46. The method of Claim 41 wherein said compound is administered in combination with a second therapeutic agent.

47. The method of Claim 46 wherein said second therapeutic agent is a metformin or a thiazolidinedione.

48. A method for modulating GPR40 function in a cell, comprising contacting a cell with the compound of Claim 1.

49. A method for modulating GPR40 function comprising contacting GPR40 with the compound of Claim 1.

50. A method for modulating circulating insulin concentration in a subject, comprising administering the compound of Claim 1 to the subject.

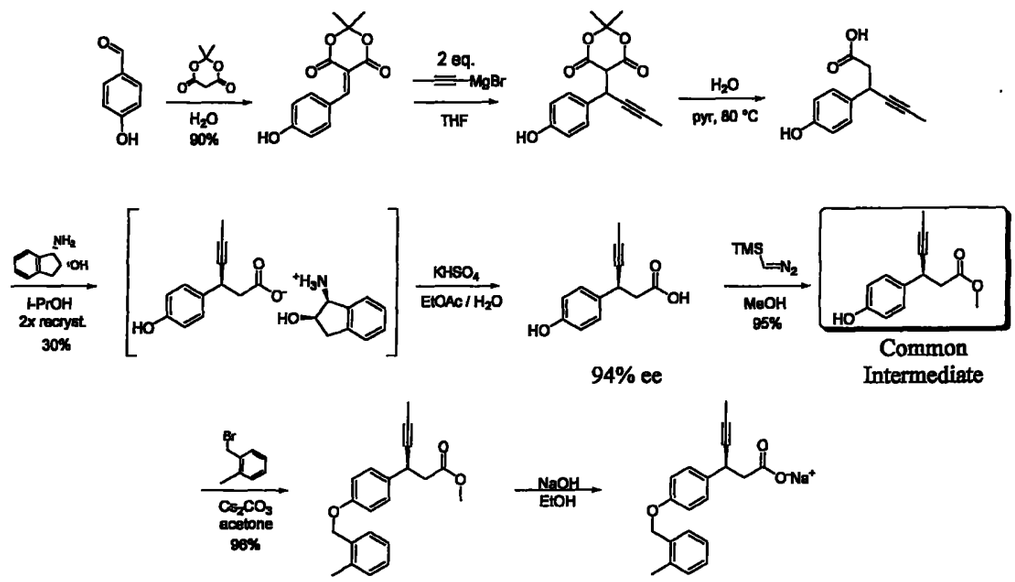
175

51. The method of Claim 50 where insulin concentration is increased.

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52. The method of Claim 50 where insulin concentration is decreased.

Figure 1



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PCT/US2005/005815

C MPUESTOS, COMPOSICIONES FARMACÉUTICAS Y MÉTODOS PARA EL USO EN EL TRATAMIENTO DE DESÓRDENES

[001] Esta solicitud reivindica el beneficio de la solicitud provisional de Estados Unidos no. 60/548,741, presentada el 27 de febrero de 2004, y la solicitud provisional de Estados Unidos no. 60/601,579, presentada el 12 de agosto de 2004, las que en su totalidad se incorporan aquí por referencia.

1. CAMPO DE LA INVENCIÓN

[002] La presente invención se relaciona con compuestos capaces de modular los receptores GPR40 acoplados a la proteína G, composiciones que comprenden dichos compuestos, y métodos para su uso en el control de niveles de insulina *in vivo* y para el tratamiento de condiciones tales como diabetes tipo II, hipertensión, cetoacidosis, obesidad, intolerancia a la glucosa, hipercolesterolemia y desórdenes relacionados con niveles anómalos, altos o bajos, de lipoproteína plasmática, triglicéridos o niveles de glucosa.

2. ANTECEDENTES DE LA INVENCIÓN

[003] La producción de insulina es medular para la regulación del metabolismo de carbohidratos y lípidos. Los desequilibrios de insulina llevan a condiciones tales como la diabetes mellitus tipo II, una enfermedad muy grave del metabolismo que aqueja a alrededor del 5% de la población en la sociedades occidentales y a 150 millones de personas en todo el mundo. La insulina es secretada por células pancreáticas ß en respuesta a la glucosa plásmica que aumenta ante la presencia de ácidos grasos. El reconocimiento reciente de la función de los receptores GPR40 acoplados a la proteína G en la modulación de la secreción de insulina ha permitido comprender la regulación del metabolismo de carbohidratos y lípidos en los vertebrados, y además, se ha podido enfocar el desarrollo en agentes terapéuticos para tratar desórdenes tales como la obesidad, diabetes, enfermedades cardiovasculares y dislipidemia.

[004] El GPR40 es un miembro de la súper familia de genes de receptores de la proteína G ("GPCRs"). Los GPCRs son proteínas de membrana caracterizadas por tener siete dominios transmembranales putativos que responden a una variedad de moléculas

por medio de la activación de vías de señalización intracelular críticas para una diversidad de funciones fisiológicas. Inicialmente el GPR40 fue identificado como un receptor huérfano (*i.e.*, un receptor que carece de un ligando conocido) de un fragmento de ADN genómico humano. *Sawzdargo et al.* (1997) *Biochem. Biophys. Re. Commun.* 239:543-54. El GPR40 se expresa de manera muy especial en la células pancreáticas ß y en células secretoras de insulina. El activador de GPR40 está relacionado con la modulación de la familia G_q de proteínas de señalización intracelular y la inducción concomitante de niveles elevados de calcio. Se ha reconocido que los ácidos grasos sirven como ligandos para GPR40, y que los ácidos grasos regulan la secreción de insulina a través de GPR40. Itoh *et al.* (2003) *Biochem. Biophys. Res. Commun.* 301: 406-410.

[005] El predominio de la diabetes tipo II, obesidad, hipertensión, enfermedades cardiovasculares y dislipidemia enfatizan la necesidad de nuevas terapias para tratar y prevenir esas condiciones de manera efectiva.

2. RESUMEN DE LA INVENCIÓN

[006] Por este medio se dan a conocer compuestos, composiciones y métodos útiles para el tratamiento o prevención de una condición o desorden tal como diabetes tipo II, obesidad, hiperglicemia, intolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, hipercolesterolemia, hipertensión, hiperliproteinemia, hiperlipidemia, hipertrigliceridemia, dislipidemia, síndrome metabólico, síndrome X, enfermedades cardiovasculares, aterosclerosis, enfermedades del riñón, cetoacidosis, desordenes trombóticos, nefropatía, neuropatía diabética, retinopatía diabética, disfunción sexual, dermatopatía, dispepsia, hipoglicemia, cáncer o edema.

[007] En un aspecto, los compuestos de la invención tienen la fórmula general (I):

$$Q\text{–}L^1\text{–}P\text{–}L^2\text{–}M\text{–}X\text{–}L^3\text{–}A$$

I

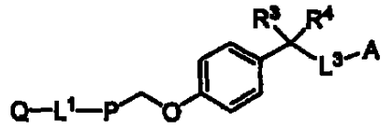
Donde Q es hidrógeno, arilo, heteroarilo, $(C_1\text{-}C_6)$alquilo o $(C_2\text{-}C_6)$heteroalquilo; L1 es un enlace, $(C_1\text{-}C_4)$alcalino, $(C_2\text{-}C_4)$heteroalquileno, O, $S(O)_m$, $N(R^1)$, C(O)-$(C_5\text{-}C_7)$heterocicloalquileno, $(C_1\text{-}C_4)$alquileno-$SO_2N(R^2)$, $(C_1\text{-}C_4)$alquileno-$N(R^2)SO_2$ o $C(O)N(R^2)$; P es un anillo aromático, un anillo heteroaromático, $(C_3\text{-}C_8)$heterocicloalquileno o $(C_3\text{-}C_8)$cicloalquileno; L^2 es un enlace, $(C_1\text{-}C_6)$alquileno, $(C_2\text{-}C_2)$heteroalquileno, O, $S(O)_m$, $N(R^1)$, $C(O)N(R^2)$, $SO_2N(R^2)$, $(C_1\text{-}C_4)$alquileno-$C(O)N(R^2)$, $(C_1\text{-}C_4)$alquileno-$N(R^2)C(O)$, $(C_2\text{-}C_4)$alquenileno-$C(O)N(R^2)$, $(C_2\text{-}C_4)$alquenileno-$N(R^2)C(O)$, $(C_1\text{-}C_4)$alquileno-$SO_2N(R^2)$, $(C_2\text{-}$

C_4)alquileno-$N(R^2)SO_2$, (C_2-C_4)alquenileno-$SO_2N(R^2)$ o (C_2-C_4)alquenileno-$N(R^2)SO_2$; M es un anillo aromático, un anillo heteroaromático, (C_5-C_8)cicloalquileno, aril(C_1-C_4)alquileno o heteroaril(C_1-C_4)alquileno; X es CR^3R^4, $N(R^5)$, O o $S(O)_n$; L^3 es un enlace, (C_1-C_5)alquileno o (C_2-C_5)heteroalquileno, siempre que L^3 no sea un enlace donde L^2 es un enlace; A es -CO_2H, tetrazol-5-il, -SO_3H, -PO_3H_2, -SO_2NH_2, -$C(O)NHSO_2CH_3$, -CHO, -$C(O)R^6$, -$C(O)NHR^6$, -$C(O)NHOR^7$, tiazolidinedion-il, hidroxifenol o piridil; R^1 es (C_1-C_6)alquilo o (C_2-C_6)heteroalquil; R^2 es hidrógeno, (C_1-C_6)alquilo o (C_2-C_5)heteroalquilo; R^3 es ciano, arilo, heteroaril, (C_1-C_8)alquil, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo, -NR^8R^9, -$C(O)NR^{10}R^{11}$, -$NR^{12}C(O)R^{13}$ o -$NR^{12}S(O)_pR^{13}$; R^4 es hidrógeno, ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo o (C_2-C_8)alquinilo, opcionalmente R^3 y R^4 se combinan para formar un anillo de 3-, 4-, 5-, 6- ó 7- miembros que contienen de cero a tres heteroátomos seleccionados de N, O y S; R^5 hidrógeno, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o (C_3-C_8)cicloalquilo; R^6 es heteroarilo; R^7 es hidrógeno o (C_1-C_5)alquilo; R^8 y R^9 son independientemente hidrógeno, (C_1-C_5)alquilo, oxi(C_1-C_5)alquilo o carboxi(C_1-C_5)alquilo, opcionalmente, R^8 y R^9 se combinan para formar un anillo de 4-, 5-, 6- ó 7- miembros que contiene el átomo de nitrógeno al que se adhieren y de 0 a 2 heteroátomos adicionales seleccionados de N, O y S; R^{10}, R^{11} y R^{12} se seleccionan independientemente de hidrógeno, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)heteroalquilo, (C_3-C_8)cicloalquilo y (C_3-C_8)heterocicloalquilo, opcionalmente, R^{10} y R^{11} se combinan para formar un anillo de 4-, 5-, 6- ó 7- miembros que contienen el átomo de nitrógeno al que se adhieren y de 0 a 2 heteroátomos adicionales seleccionados de N, O y S; R^{13} es arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)heteroalquilo, (C_3-C_8)cicloalquilo o (C_3-C_8)heterocicloalquilo; los subíndices m y n son independientemente 0, 1 ó 2; y el subíndice p es 1 ó 2; y donde el compuesto no sea igual al ácido 3-(4-(4-metoxibenciloxi)fenil)pent-4-inóico; ácido β-etenil-4-fenilmetoxi- bencenopropanóico; ácido 4-(2-quinolinilmetoxi)-β-[4-(2-quinolinilmetoxi)fenil]- bencenopropanóico; ácido N-[4-(benzoilamino)fenilo]-N-fenil-glicina; 3-(4- (isopentiloxi)benzamido)-3-fenilpropanoato; ácido 3-(4-isobutoxibenzamido)-3-fenilpropanoato; (R)-2-((1R,4R)-4-isopropilciclohexanocarboxamido)-3-fenilpropanóico; ácido (R)-3-(4-(benciloxi)fenilo)-2-(tert-butoxicarbonil)propanóico; ácido 3-(4-clorofenil)-3-(furan-2-carboxamido)propanóico; ácido 3-(3,4-dimetoxifenil)-3-(furan- 2-carboxamido)propanóico; ácido 3-(4-clorobenzamido)-3-(4- (dimetiamino)fenil)propanóico; ácido 3-(2-(2-(3,4-dimetilfenoxi)etiltio)-1H- benzo[d]imidazol-1-il)propanóico; ácido {2-Bromo-4-[(3,4-dicloro-fenil)- hidrazonometil]-6-etoxi-fenoxi}-acético; ácido 2-(4-(2-(2-(4-

clorofenil)furan-5- carboxamido)etil)fenoxi)-2-metilpropanóico; ácido 5-(3-(3,4-dimetoxifenil)-5-(2-fluorofenil)-4,5-dihidropirazol-1-il)-5-oxopentanóico; ácido 2-(2-(3-(3,4-dihidro-2H- benzo[b][1 ,4]dioxepin-7-il)-2-metil-4-oxo-4H-cromen-7-iloxi)acetamido)acético; ácido 3-(4'-Bromo-bifenil-4-il)-4-fenilo-butírico; ácido 3-(4'-Bromo-bifenil-4-il)-3- fenilsulfanil-propiónico; ácido 3-(5-(2-cloro-6-fluoro-4-(trifluorometil)fenoxi)-2,4- dinitrofenil)propanóico; ácido 3-(3-(2-cloro-4-(trifluorometil)fenoxi)fenilo)propanóico; ácido 3-(4-(4-metoxibenciloxi)fenil)pent-4-inóico; ácido 3-(4-(4- metoxibenciloxi)fenil)-5-(trimetilsilyl)pent-4-inóico; ácido β,β-dimetil-4-[[[4-metil-2-[4-(trifuorometil)fenil]-5-tiazolil]metil]tio]-bencenopropanóico; ácido β- amino-4-[(4-bromo-2,5-dihidro-2-metil-5-oxo-1-fenilo-1H-pirazol-3-il)metoxi]-3-metoxi-bencenopropanóico; o su sal.

[008] Los compuestos de la invención incluyen sales aceptables farmacéuticamente, solvatos o sus prodrogas.

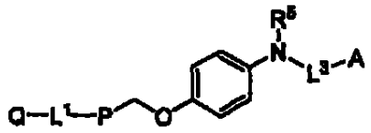
[009] En ciertas materializaciones la presente invención brinda un compuesto de la fórmula (**Ia**):



Ia

donde Q,L^1, P,L^3,A,R^3 y R^4 se definen como en la fórmula I anterior.

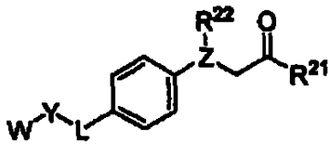
[010] En ciertas materializaciones, la presente invención brinda un compuesto de la fórmula (**Ib**):



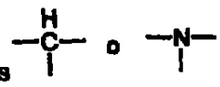
Ib

donde Q, L^1, P, L^3, A y R^5 se definen como en la fórmula I anterior.

[11] En otro aspecto, los compuestos de la invención tienen la fórmula general (**II**):



II

donde Z es  ; R^{21} es -H, -OH, $-NHS(O_2)CH_3$, heteroarilo, o -NH- heteroarilo; R^{22} es $-(C_2-C_8)$alquilo, $-(C_3-C_8)$alquenilo, $-NR^{23}R^{24}$, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, $-C\equiv N$ o $-C\equiv C-R^{25}$; u opcionalmente donde Z es un átomo de nitrógeno, R^{22} es -H; R^{23} y R^{24} son independientemente -H, $-(C_1-C_5)$alquilo, o $-(C_1-C_5)$oxialquilo; R^{25} es -H, $-(C_1-C_5)$alquilo, -hetero(C_1-C_5)alquilo, $-(C_1-C)$oxialquilo, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido; L es -O-, -S-, o $-N(R^{26})-$; R^{26} es -H , $-(C_1-C_5)$alquilo, arilo(C_1-C_{10})alquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido; Y no está presente o es $-CH_2-$, $-CH_2CH_2-$, -CH=CH- , $-C(O)CH_2-$, $-C(O)CH_2CH_2-$, -C(O)CH=CH- , $-S(O_2)-$, $-S(O_2)CH_2-$, $-S(O_2)CH_2CH_2$, $-S(O_2)CH=CH-$, o -C(O)-; W arilo sustituido o no sustituido o heteroarilo sustituido o no sustituido.

[012] En otro aspecto, la invención brinda composiciones farmacéuticas que comprenden un portador aceptable farmacéuticamente, diluyente o excipiente y un compuesto de la fórmula **I, Ia, Ib** o **II**.

[013] En otro aspecto, la invención brinda métodos para el tratamiento o la prevención de una enfermedad o condición seleccionada del grupo consistente en la diabetes tipo II, obesidad, hiperglicemia, glucosa, intolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, hipercolesterolemia, hipertensión, hiperliproteinemia, hiperlipidemia, hipertriglilceridemia, dislipidemia, síndrome metabólico, síndrome X, enfermedades cardiovasculares, aterosclerosis, enfermedades del riñón, cetoacidosis, nefropatía, neuropatía diabética, retinopatía diabética, disfunción sexual, desordenes trombóticos, dermatopatía, dispepsia, hipoglicemia, hipertensión, cáncer y edema que comprenden la administración de una cantidad efectiva desde un punto de vista terapéutico de un compuesto de la fórmula **I, Ia, Ib** o **II** a un sujeto que la necesite.

[014] En otro aspecto, la invención brinda métodos para el tratamiento o la prevención de una enfermedad o condición responsable de la modulación de GPR40 que

comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de la fórmula **I, Ia, Ib** o **II** a un sujeto que la necesite.

[015] En otro aspecto, la invención brinda métodos para el tratamiento o la prevención de una enfermedad o condición mediada, regulada o influenciada por células pancreáticas β que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de la fórmula **I, Ia, Ib** o **II** a un sujeto que la necesite.

[016] En otro aspecto, la invención brinda métodos para modular la función GPR40 en una célula, que comprende poner en contacto a una célula con los compuestos de la fórmula **I, Ia, Ib** o **II**.

[017] En otro aspecto, la invención brinda métodos para modular la función GPR40 que comprende que el GPR40 entre en contacto con un compuesto de la fórmula **I, Ia, Ib** o **II**.

[018] En otro aspecto, la invención brinda métodos para la modulación circular de la concentración de insulina en un sujeto, que comprende la administración al sujeto de un compuesto de la fórmula **I, Ia, Ib** o **II**.

[019] Otros objetivos, características y ventajas de la invención serán aparentes a los entendidos en la materia, según las siguientes descripciones y reivindicaciones.

4. BREVE DESCRIPCIÓN DE LAS FIGURAS

[020] La FIG. 1 brinda un esquema para síntesis de los compuestos ejemplares de la invención.

5. DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

5.1 Abreviaturas y Definiciones

[021] Los términos "tratar", "tratando" y "tratamiento", como se utilizan aquí, incluyen el alivio o cesación de una condición o enfermedad y/o el alivio de sus síntomas acompañantes. Los términos "prevenir", "previniendo" y "prevención", como se utilizan aquí, se refieren a un método para demorar o prevenir el comienzo de una condición o enfermedad y/o sus síntomas acompañantes, previniendo que un sujeto adquiera una condición o enfermedad o bajando el riego de que el sujeto adquiera una condición o enfermedad.

[022] El término "cantidad terapéuticamente efectiva " se refiere a una cantidad del compuesto que producirá en un tejido, sistema, o materia la respuesta médica o biológica que se busca. El término "cantidad terapéuticamente efectiva " incluye aquella cantidad del compuesto que, cuando se administra, es suficiente para prevenir el desarrollo de, o aliviar en alguna magnitud, uno o más de los síntomas de la condición o desorden por los que el sujeto se encuentra bajo tratamiento. La cantidad terapéuticamente efectiva en un sujeto variará dependiendo del compuesto, la enfermedad, su severidad, así como la edad, peso, etc., del sujeto bajo tratamiento.

[023] El "sujeto" se define aquí para incluir a animales tales como mamíferos, que incluyen, pero no se limitan a, primates (e.g. humanos), vacas, ovejas, cabras, caballos, perros, gatos, conejos, ratas, ratones y sus similares. En materializaciones preferidas, el sujeto es un humano.

[024] Los términos "modular", "modulación" y similares se refieren a la habilidad de un compuesto de incrementar o disminuir la función o actividad de GPR40, ya sea directa o indirectamente. Los inhibidores son compuestos que, por ejemplo, aglutinan, interrumpen parcial o totalmente la estimulación, disminuyen, previenen, demoran la activación, desactivan, desensibilizan, o regulan por disminución la señal de transducción, como por ejemplo, antagonistas. Los activadores son compuestos que, por ejemplo, aglutinan, estimulan, incrementan, activan, facilitan, mejoran la activación, sensibilizan o regulan por incremento la señal de transducción, como por ejemplo, agonistas. La modulación puede ocurrir *in vitro* o *in vivo*.

[025] Como se utiliza aquí, el término "condición o desorden por intermedio de GPR40" y similares se refiere a una condición o desorden tipificado como inapropiado, por ejemplo, por una actividad de GPR40 inferior o superior a la normal. Una condición o desorden intermediado-GPR40 puede ser completa o parcialmente intermediado por una actividad inapropiada de GPR40. Sin embargo, una condición o desorden por intermedio de GPR40 es una en la cual la modulación de GPR40 resulta en algún efecto en la condición o enfermedad subyacente (e.g., un modulador GPR40 resulta en alguna mejora del bienestar en al menos algunos pacientes). Ejemplos de condiciones o desordenes por intermedio de GPR40 incluyen cáncer y otros desordenes metabólicos, e.g. diabetes, diabetes tipo II, obesidad, hiperglicemia, intolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, hipercolesterolemia, hipertensión, hiperlipoproteinemia, hiperlipidemia, hipertriglilceridemia, dislepidemia, cetoacidosis, hipoglucemia, desordenes trombóticos,

síndrome metabólico, síndrome X y desordenes relacionados, e.g., enfermedades cardiovasculares, arteriosclerosis, enfermedades del riñón, neuropatía diabética, retinopatía diabética, disfunción sexual, dermatopía, dispepsia y edema.

[026] El término "alquilo", por sí mismo o como parte de otro sustituyente, significa, a menos que se indique lo contrario, una cadena recta o ramificada, o un radical libre de hidrocarbono cíclico, o una combinación de éstos, el cual está totalmente saturado, con el número de átomos de carbón designados (e.g., C_1-C_{10} significa de uno a diez carbonos). Ejemplos de grupos de alquilo incluyen el metilo, etilo, n-propilo, isopropilo, n-butilo, t-butilo, isobutilo, sec-butilo, ciclohexilo, (ciclohexilo)metilo, ciclopropilo, ciclopropilmetilo, homólogos e isómeros de, por ejemplo, n-pentilp, n-hexilp, n-heptilo, n-octilo y los similares.

[027] El término "alquenilo", por sí mismo o como parte de otro sustituyente, significa, a menos que se indique lo contrario, una cadena recta o ramificada, o un radical libre de hidrocarbono cíclico, o una combinación de éstos, el cual puede ser mono- o polisaturado, con el número de átomos de carbono designados (e.g., C_2-C_8 significa dos a ocho carbonos) y uno o más enlaces. Ejemplos de grupos de alquenilo incluyen vinilo, 2-propenilo, crotilo, 2-isopentenilo, 2-(butadienilo), 2,4-pentadienilo, 3-(1,4-pentadienilo) y sus homólogos e isómeros superiores.

[028] El término "alquinilo", por sí mismo o como parte de otro sustituyente, significa, a menos que se indique lo contrario, una cadena recta o ramificada, o un radical libre de hidrocarbono cíclico, o una combinación de éstos, el cual puede ser mono- o polisaturado, con el número de átomos de carbono designados (e.g., C_2-C_8 significa dos a ocho carbonos) y uno o más enlaces. Ejemplos de grupos de alquinilo son etinilo, 1- y 3-propinilo, 3-butinilo y sus homólogos e isómeros superiores.

[029] El término "alquileno" por sí mismo o como parte de otro sustituyente significa un radical libre divalente derivado de alquilo, como se ejemplifica por -$CH_2CH_2CH_2CH_2$-. Típicamente, un alquilo, un grupo (o alquileno) tendrá de 1 a 24 átomos de carbono, siendo los preferidos en la presente invención aquellos grupos que tengan 12 o menos átomos de carbono. Un "alquilo inferior" o "alquileno inferior" es una cadena más corta de un grupo de alquilo o alquileno, que generalmente contienen ocho átomos o menos de carbono.

[030] Los términos "Alcoxi," "alquiloamino" y "alquilotio" (o tioalcoxi) se utilizan en su sentido convencional, y se refieren a los grupos de alquilo adheridos al residuo de la

molécula por medio de un átomo de oxígeno, un grupo amino, o un átomo de azufre, respectivamente. De forma similar, el término dialquiloamino se refiere a un grupo de amino que tenga adheridos dos grupos de alquilo que puedan ser iguales o distintos.

[031] El término "heteroalquilo," por sí mismo o en combinación con otro término, significa, a menos que se indique lo contrario, una cadena recta o ramificada, o un radical libre de hidrocarbono cíclico, o sus combinaciones, que consisten en átomos de carbono y de uno a tres heteroátomos seleccionados de un grupo que consiste en O, N y S, y donde los átomos de nitrógeno y de azufre opcionalmente pueden ser oxidados y el heteroátomo de nitrógeno opcionalmente puede ser cuaternizado. El/los heteroátomo(s) O, N y S puede/n ser colocado/s en cualquier posición del grupo heteroalquilo. Los ejemplos incluyen $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, y $-CH_2-CH=N-OCH_3$. Hasta dos heteroátomoos pueden ser consecutivos, como por ejemplo, $-CH_2-NH-OCH_3$. Cuando se utiliza un prefijo como (C_2-C_8) para referirse a un grupo heteroalquilo, el numero de carbonos (2 a 8, en este ejemplo) incluye también los heteroátomos. Por ejemplo, un grupo C_2-heteroalquilo se entiende que incluye, por ejemplo, $-CH_2OH$ (un átomo de carbono y un heteroátomo que reemplaza un átomo de carbono) y $-CH_2SH$.

[032] Para ilustrar más la definición de un grupo de heteroalquilo, donde el heteroátomo es oxígeno, un grupo heteroalquilo es un grupo oxialquilo. Por ejemplo, (C_2-C_5)oxialquilo se entiende que incluye, por ejemplo $-CH_2-O-CH_3$ (un grupo C_3-oxialquilo con dos átomos de carbono y uno de oxígeno que reemplaza un átomo de carbono), $-CH_2CH_2CH_2CH_2OH$, y similares.

[033] El término "heteroalquileno" por sí mismo o como parte de otro sustituyente significa un radical libre divalente derivado de heteroalquilo, como se ejemplifica por $-CH_2-CH_2-S-CH_2CH_2-$ y $-CH_2-S-CH_2-CH_2-NH-CH_2-$. Para grupos de heteroalquileno, los heteroátomos además pueden ocupar una o ambas terminales de la cadena (e.g., alquilenoxi, alquilenodioxi, alquilenoamino, alquilenodiamino, y similares). Aún más, para los grupos de enlace de alquileno y heteroalquileno, no se implica una orientación del grupo de enlace.

[034] Los términos "cicloalquilo" y "heterocicloalquilo," por sí mismos o en combinación con otros términos, representan, a menos que se indique lo contrario, versiones cíclicas de "alquilo" y "heteroalquilo," respectivamente. Así, se entiende que los términos "cicloalquilo" y "heterocicloalquilo" están incluidos en los términos "alquilo" y

"heteroalquilo," respectivamente. Además, para heterocicloalquilo, un heteroátomo puede ocupar la posición en la cual el heterociclo se adhiere al remanente de la molécula. Ejemplos de cicloalquilo incluyen ciclopentil, ciclohexil, 1-ciclohexenil, 3-cyclohexenil, cicloheptil, y similares. Ejemplos de heterocicloalquilo incluyen 1-(1,2,5,6-tetrahidropiridil), 1-piperidinil, 2-piperidinil, 3-piperidinil, 4-morfolinil, 3-morfolinil, tetrahidrofuran-2-il, tetrahidrofuran-3-il, tetrahidrotien-2-il, tetrahidrotien-3-il, 1-piperacinil, 2-piperacinil, y similares.

[035] Los términos "cicloalquileno" y "heterocicloalquileno," por sí mismos o en combinación con otros términos, representan, a menos que se indique lo contrario, versiones cíclicas de "alquileno" y "heteroalquileno," respectivamente. Así, se entiende que los términos "cicloalquileno" y "heterocicloalquileno" están incluidos en los términos "alquileno" y "heteroalquileno," respectivamente. Además, para el heterocicloalquileno, uno o más heteroátomos pueden ocupar la posición en la cual el heterociclo se adhiere al remanente de la molécula. Típicamente, un cicloalquileno o un heterocicloalquileno tendrá de 3 a 9 átomos formando un anillo, más típicamente, 4 a 7 átomos formando el anillo, y aún más típicamente, de 5 a 6 átomos formarán el anillo de cicloalquileno o hetercicloalquileno.

[036] Los términos "halo" o "halógeno," por sí mismos o como parte de otro sustituyente, significan, a menos que se indique lo contrario, un átomo de flúor, cloro, bromo, o iodo. Además, términos como "haloalquilo", incluyen alquilo sustituido con átomos de halógeno los cuales pueden ser iguales o distintos, en un número de rango de uno a (2m' + 1), donde m' es el número total de átomos de carbono en el grupo alquilo. Por ejemplo, el término "halo(C_1-C_4)alquilo" incluye trifluorometil, 2,2,2-trifluoroetil, 4-clorobutil, 3-bromopropil, y similares. De esta manera, el término "haloalquilo" incluye monohaloalquilo (alquilo sustituido con un átomo de halógeno) y polihaloalquilo (alquilo sustituido con átomos de halógeno en un numero de rango de dos a (2m' + 1) átomos de halógeno). El término "perhaloalquilo" significa, a menos que se indique lo contrario, alquilo sustituido con (2m' + 1) átomos de halógeno, donde m' es el número total de átomos de carbono en el grupo alquilo. Por ejemplo, el término "perhalo(C_1-C_4)alquilo", incluye trifluorometil, pentacloroetil, 1,1,1-trifluoro-2-bromo-2-cloroetilo, y similares.

[037] El término "arilo" significa, a menos que se indique lo contrario, un poli-saturado, típicamente aromático, sustituyente de hidrocarbono en el cual pueden estar uno o múltiples anillos (más de tres anillos) los cuales están fusionados o enlazados

covalentemente. El término "heteroarilo" se refiere a grupos (o anillos) de arilo que contienen de uno a cuatro heteroátomos seleccionados del grupo que consiste en N, O y S, donde los átomos de nitrógeno y de azufre son opcionalmente oxidados, y el(los) átomo(s) de nitrógeno es/son opcionalmente cuaternizado/s. Un grupo heteroarilo puede ser adherido al remanente de la molécula a través de un heteroátomo. Ejemplos de grupos de arilo y heteroarilo incluyen pero no se limitan a fenilo, 1-naftilo, 2-naftilo, 4-bifenilo, 1-pirrolilo, 2-pirrolilo, 3-pirrolilo, 1-pirazolilo, 3-pirazolilo, 5-pirazoliol, 2-imidazolilo, 4-imidazolilo, pirazinilo, 2-oxazolilo, 4-oxazolilo, 2-fenil-4-oxazolilo, 5-oxazolilo, 3-isoxazolilo, 4-isoxazolilo, 5-isoxazolilo, 2-tiazolilo, 4-tiazolilo, 5-tiazolilo, 2-furilo, 3-furilo, dibenzofurilo, 2-tienilo, 3-tienilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-pirimidilo, 4-pirimidilo, 2-pirimidinilo, 4-pirimidinilo, 5-pirimidinilo, 3-piridazinilo, 4- piridazinilo, 5-benzotiazolilo, 2-benzoxazolilo, 5-benzoxazolilo, benzo[c][1,2,5]oxadiazolilo, purinilo, 2-benzimidazolilo, 5-indolilo, 1H-indazolilo, carbazolilo, α-carbolinilo, β-carbolinilo, γ- carbolinilo, 1 -isoquinolilo, 5-isoquinolilo, 2-quinoxalinilo, 5-quinoxalinilo, 2-quinolilo, 3- quinolilo, 4-quinolilo, 5-quinolilo, 6-quinolilo, 7-quinolilo y 8-quinolilo.

[038] Preferiblemente, el término "arilo" se refiere a un grupo fenilo o napftilo el cual es sustituido o no sustituido. Preferiblemente, el término "heteroarilo" se refiere a un grupo pirrolilo, pirazolilo, imidazolilo, pirazinilo, oxazolilo, isoxazolilo, tiazolilo, furilo, tienilo, piridilo, pirimidilo, benzotiazolilo, purinilo, benzimidazolilo, indolilo, isoquinolilo, quinoxalinilo o quinolilo, sustituido o no sustituido.

[039] Para brevedad, el término "arilo" cuando se utiliza en combinación con otros términos (e.g., ariloxi, arilotioxi, arilоalquilo) incluye anillos de arilo y heteroarilo en la forma descrita anteriormente. Así, el término "arilоalquilo" incluye a aquellos radicales libres en los que un grupo de arilo se adhiere a un grupo alquilo (e.g., , bencilo, fenetilo, piridilmetilo y similares) incluyendo a aquellos grupos de alquilo en los cuales un átomo de carbono (e.g., un grupo metileno) se ha reemplazado, por ejemplo, por un átomo de oxígeno (e.g., fenoximetil, 2-piridiloximetil, 3-(1-naftiloxi)propil, y similares).

[040] Cada uno de los términos anteriores (e.g. , "alquilo," "heteroalquilo", "arilo" y "heteroarilo") incluye ambas formas sustituidas y no sustituidas de los radicales libres indicados, a menos que se indique lo contrario. Más adelante se especifican los sustituyentes preferidos para cada tipo de radical.

[041] Los sustituyentes para los radicales de alquilo y heteroalquilo (como también para aquellos grupos denominados alquileno, alquenilo, heteroalquileno, heteroalquenilo,

alquinilo, cicloalquilo, heterocicloalquilo, cicloalquenilo y heterocicloalquenilo) pueden ser una variedad de grupos seleccionados de: -OR', =0, =NR', =N-OR', -NR'R", -SR', halógeno, -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(0)NR'R", -NR"C(O)R', -NR'-C(0)NR"R"', -NR'-$S0_2$NR"R"', -NR"CO_2R', -NH-C(NH_2)=NH, -NR'C(NH_2)=NH, -NH-C(NH_2)=NR', -SiR'R"R"', -S(O)R', -SO_2R', -SO_2NR'R", -NR"SO_2R, -CN y -NO_2, en una rango de entre cero a tres, particularmente se prefieren los grupos que contengan cero, uno o dos sustituyentes. R', R" y R"' en forma independiente se refieren a hidrógeno, (C_1-C_8)alquilo no sustituido y heteroalquilo, arilo no sustituido, arilo sustituido con uno a tres halógenos, alquilo no sustituido, grupos de alcoxi o tioalcoxi, halo(C_1-C_4)alquilo, o grupos de arilo-(C_1-C_4)alquilo. Cuando R' y R" están adheridos al mismo átomo de nitrógeno, se pueden combinar con el átomo de nitrógeno para formar un anillo de 5, 6 ó 7 miembros. Por ejemplo, -NR1R" se entiende que incluye 1-pirrolidinilo y 4-morfolinilo.

[042] Típicamente, un grupo de alquilo o heteroalquilo tendrá de cero a tres sustituyentes, en la presente invención se prefieren los grupos que contengan dos o menos sustituyentes. Más preferiblemente, un radical de alquilo o heteroalquilo será no sustituible o mono sustituible. Más preferiblemente, un radical de alquilo o heteroalquilo será no sustituible. De la discusión anterior de sustituyentes, alguien entendido en la materia comprenderá que el término "alquilo" incluye grupos como trihalalquilo (e.g., -CF_3 y -CH_2CF_3).

[043] Los sustituyentes preferidos para los radicales de alquilo y heteroalquilo se seleccionan de: -OR', =0, -NR'R", -SR', halógeno, -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(0)NR'R", -NR"C(O)R', -NR"$C0_2$R', -NR'-$S0_2$NR"R"', -S(O)R', -SO_2R', -$S0_2$NR'R", -NR"SO_2R, -CN y -NO_2, donde R' y R" son como se definieron anteriormente. Los sustituyentes aún más preferidos se seleccionan de: -OR', =0, -NR'R", halógeno, -OC(O)R', -CO_2R, -CONR'R", -OC(O)NRTR.", -NR"C(0)R', -NR"CO_2R', -NR'-$S0_2$NR"R", -SO_2R', -SO_2NR'R", -NR"SO_2R, -CN y -NO_2.

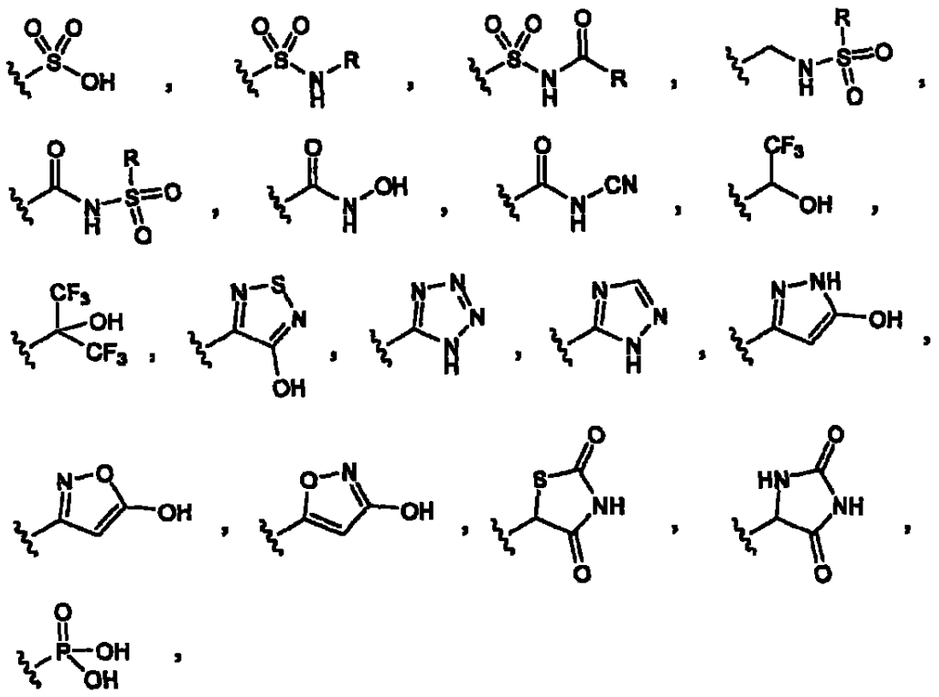
[044] De forma similar, los sustituyentes para los grupos de arilo y heteroarilo son variados y son seleccionados de: -halógeno, -OR, -OC(O)R', -NR'R", -SR', -R', -CN, -NO_2, -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(0)R, -NR"$C(O)_2$R', -NR'-C(0)NR"R"', -NH-C(NH_2)=NH, -NR'C(NH_2)=NH, -NH-C(NH_2)=NR', -S(O)R', -S(O)2R', -$S(O)_2$NR'R", -N_3, -$CH(Ph)_2$, perfluoro(C_1-C_4)alcoxi, y perfluoro(C_1-C4)alquilo, en un rango de cero al número total de valencias abiertas en el sistema aromático del anillo; y donde R', R" y R"' se seleccionan

independientemente de hidrógeno, (C_1-C_8)alquilo y heteroalquilo, arilo no sustituido y heteroarilo, (arilo no sustituido)-(C_1-C_4)alquilo, y (arilo no sustituido)oxi-(C_1-C_4)alquilo.

[045] Dos de los sustituyentes de los átomos adyacentes del anillo de arilo o heteroarilo se pueden reemplazar opcionalmente con un sustituyente de la fórmula -T-C(0)-$(CH_2)_q$-U-, donde T y U son independientemente -NH-, -0-, -CH_2- en un enlace simple, y q es un entero de 0 a 2. De manera alterna, dos de los sustituyentes en los átomos adyacentes del anillo de arilo o heteroarilo opcionalmente se pueden reemplazar por un sustituyente de la fórmula -A-$(CH_2)_r$-B-, donde A y B son independientemente -CH_2-, -0-, -NH-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- o un enlace simple, y r es un entero de 1 a 3. Uno de los enlaces simples del nuevo anillo formado de esta manera opcionalmente se puede reemplazar con un enlace doble. De manera alterna, dos de los sustituyentes de los átomos adyacentes del anillo de arilo o heteroarilo opcionalmente se pueden reemplazar con un sustituyente de la fórmula -$(CH_2)_s$-X-$(CH_2)_t$, donde s y t son enteros independientes de 0 a 3, y X es -O-NR-, -S-, -$S(O)_2$-, o –$S(O)_2$NR'-. El sustituyente R' en -NR'- y -$S(O)_2$NR'- se selecciona de hidrógeno o (C_1-C_6)alquilo no sustituido. De otra forma, R' es como se definió anteriormente.

[046] El término "heteroátomo" se utiliza para incluir oxígeno (O), nitrógeno (N), y azufre (S).

[047] La frase "bioisóstero de -CO2H" se utiliza para indicar que el sustituyente -CO_2H opcionalmente se puede reemplazar con sustitutos bioisostéricos como:



y similares. véase, e.g., *The Practice of Medicinal Chemistry, Wermuth*, C. G., Ed., Academic Press: New York, 1996, p. 203.

[048] El término "sal aceptable farmacéuticamente" se utiliza para indicar una sal del compuesto activo que se prepara con ácidos o bases relativamente no tóxicos, dependiendo de los sustituyentes en particular que se encuentran en los compuestos que aquí se describen. Cuando un compuesto de la invención contiene funcionalidades relativamente ácidas, se puede obtener una sal básica de adición al poner en contacto la forma neutral de dicho compuesto con una cantidad suficiente de la base deseada, ya sea limpia o en un solvente inerte apropiado. Ejemplos de sales básicas de adición aceptables farmacéuticamente incluyen sodio, potasio, calcio, amonio, amino orgánico, o sal de magnesio, o una sal similar. Cuando un compuesto de la invención contiene funcionalidades relativamente básicas, se puede obtener una sal de adición ácida al poner en contacto con la forma neutral de dichos compuestos con una cantidad suficiente del ácido deseado, ya sea limpia o en un solvente inerte apropiado. Ejemplos de sales de adición ácidas aceptables farmacéuticamente incluyen a las derivas de ácidos orgánicos como hidroclórico, hidrobrómico, nítrico, carbónico, monohidrógenocarbónico, fosfórico, monohidrogenofosfórico, dihidrogenofosfórico, sulfúrico, monohidrogenosulfúrico,

hidriódico, o ácidos fosfóricos y similares, así como las sales derivadas de ácidos orgánicos relativamente no tóxicos tales como acético, propiónico, isobutírico, maleico, malónico, benzoico, succínico, subérico, fumárico, mandélico, ftálico, bencenosulfúrico, p-tolilsulfónico, cítrico, tartárico, metanesulfónico, y similares. También están incluidas las sales de amino ácidos tales como arginina y similares, y sales de ácidos orgánicos como ácidos glucurónico o galacturónico y similares (véase, por ejemplo, Berge et al. (1977) *J Pharm. Sci* 66:1- 19). Algunos compuestos específicos de la invención contienen ambas funcionalidades básicas y acídicas que permiten que los compuestos se conviertan en sales de adición básicas o acídicas.

[049] Las formas neutrales de los compuestos se pueden regenerar al poner en contacto la sal con una base o ácido y aislar el compuesto madre de la manera tradicional. La forma madre del compuesto se diferencia de las varias formas de sales por ciertas propiedades físicas tales como solubilidad en compuestos polares, pero de otra forma, para los fines de la invención, las sales son equivalentes a la forma madre de los compuestos.

[050] Además de las sales, la invención brinda compuestos en forma de prodroga. Las prodrogas de los compuestos aquí descritos son aquellos compuestos que fácilmente experimentan cambios químicos bajo condiciones fisiológicas para brindar los compuestos de la invención. Además, las prodrogas se pueden convertir en los compuestos de la invención por métodos químicos o bioquímicos en un ambiente *ex vivo*. Por ejemplo, las prodrogas se pueden convertir lentamente en los compuestos de la invención cuando se colocan en un parche de contención transdermal con una encima o reactivo químico adecuado. Las prodrogas comúnmente son útiles porque, en algunas situaciones, pueden ser más fáciles de administrar que la droga madre. Pueden, por ejemplo, ser biodisponibles para administración de forma oral cuando las drogas madres no puedan serlo. La prodroga también tiene una mejor solubilidad en composiciones farmacéuticas que la droga madre. En la ciencia se conocen una amplia variedad de derivados de prodrogas, tales como los que dependen del desdoblamiento de hidrolíticos o la activación de oxígeno de la prodroga. Un ejemplo de prodroga, sin ser limitante, puede ser un compuesto de la invención que se administre como un éster (la "prodroga"), que luego es hidrolizado metabolicamente para formar ácido carboxílico, el componente activo. Otros ejemplos incluyen derivados de peptidilo de un compuesto.

[051] Como se utiliza aquí, el término "solvato" se refiere a un compuesto de la invención o su sal, que además incluye una cantidad estequiométrica o no estequiométrica

de solvente enlazada por fuerzas intramoleculares no covalentes. Cuando el solvente es agua, el solvato es un hidrato.

[052] Ciertos compuestos de la invención pueden existir en varias formas cristalinas o amorfas. En general, todas las formas físicas son equivalentes para los usos contemplados por la invención y se encuentran dentro del ámbito de la invención.

[053] Algunos componentes de la invención poseen átomos de carbón asimétricos (centros ópticos) o enlaces dobles; los racemates, enantiómeros, diastereómeros, isómeros geométricos e isómeros individuales se incluyen dentro del alcance de la invención.

[054] Como se utiliza aquí, y a menos que se indique lo contrario, el término "estereoisómero" o "estereoméricamente puro" significa un estereoisómero de un compuesto que está sustancialmente libre de otros estereoisómeros del compuesto. Por ejemplo, un compuesto estereomericamente puro que contenga un centro quiral estará sustancialmente libre del enantiómero opuesto del compuesto. Un compuesto estereomericamente puro que contenga dos centros quirales estará sustancialmente libre de otros diastereómeros del compuesto. Un compuesto típico estereomericamente puro comprende más de aproximadamente 80% por peso de los estereoisómeros del compuesto y menos de aproximadamente 20% por peso de otros estereoisómeros del compuesto, más preferiblemente aproximadamente más del 90% por peso de un estereoisómero del compuesto y menos de aproximadamente 10% por peso de otros estereoisómeros del compuesto, aún más preferiblemente aproximadamente más del 95% por peso de un estereoisómero del compuesto y menos de aproximadamente 5% por peso de otros estereoisómeros del compuesto, y todavía aún más preferiblemente aproximadamente más del 97% por peso de un estereoisómero y menos de aproximadamente 3% por peso de otros estereoisómeros del compuesto. Se debe notar que si la estereoquímica de una estructura o una porción de una estructura no está indicada, por ejemplo, con líneas marcadas o quebradas, se debe interpretar que la estructura o la porción de la estructura abarca todos los estereoisómeros de ésta.

[055] Varios de los compuestos de la invención contienen uno o más centros quirales, y pueden existir como mezclas racémicas de enantiómeros, mezclas de diastereómeros o compuestos enatiomericamente u ópticamente puros. Esta invención engloba el uso de formas puras estereomericamente de dichos compuestos, como también el uso de mezclas de estas formas. Por ejemplo, mezclas que comprenden cantidades iguales o no de los enantiómeros de un compuesto en particular de la invención pueden

utilizarse en métodos y composiciones de la invención. Estos isómeros pueden ser sintetizados de forma asimétrica o resueltos utilizando técnicas estándares como columnas quirales o agentes de resolución quiral. Véase e.g., Jacques, J., *et ah, Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., (1997) *Tetrahedron* 33:2725; Eliel, E. L., *Stereochemistry of carbon Compounds* (McGraw-Hill, NY, 1962), y Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (EX. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[056] Los compuestos de la invención pueden también contener proporciones no naturales de isótopos atómicos en uno o más de los átomos que constituyen dichos compuestos. Por ejemplo, los compuestos pueden ser radio-etiquetados con isótopos radioactivos, como por ejemplo tritio (^{3}H), iodo-125 (^{125}I) o carbono-14 (^{14}C). Los compuestos radio-etiquetados son útiles como agentes terapéuticos o profilácticos, reactivos de investigación, e.g., reactivos de ensayo GPR40, y agentes de diagnósticos, e.g., agentes de imagenología *in vivo*. Todas las variaciones isotópicas de los compuestos de la invención, ya sean radioactivos o no, están destinados a ser incluidos dentro del ámbito de la invención.

5.2 Materializaciones de la Invención

[057] En un aspecto, se describe una clase de compuestos que modulan el GPR40. Dependiendo de la materialización biológica (e.g., tipo de célula, condición patológica del sujeto, etc.), estos compuestos pueden modular, e.g., activar o inhibir, las acciones de GPR40. Por medio de la modulación del GPR40, los compuestos encuentran su uso como agentes terapéuticos capaces de regular los niveles de insulina en un sujeto. Los compuestos encuentran su uso como agentes terapéuticos para enfermedades de modulación o condiciones que responden a la modulación del GPR40 y/o intermediadas por GPR40 y/o intermediadas por células β pancreáticas. Como se mencionó anteriormente, los ejemplos de estas enfermedades y condiciones incluyen diabetes, obesidad, hiperglicemia, intolerancia a la glucosa, resistencia a la insulina, cáncer, hiperinsulinemia, hipercolesterolemia, hipertensión, hiperlipoproteinemia, hiperlipidemia, hipertriglilceridemia, dislepidemia, cetoacidosis, hipoglicemia, síndrome metabólico, syndrome X, enfermedades cardiovasculares, arteriosclerosis, enfermedades renales, nefropatía, desordenes trombóticos, neuropatía diabética, retinopatía diabética, dermatopatía, dispepsia y edema. Además, los compuestos son útiles para el tratamiento

y/o prevención de complicaciones de estas enfermedades y desordenes (e.g., diabetes de tipo II, disfunción sexual, dispepsia y más).

[058] Aunque se cree que los compuestos de la invención ejercen sus efectos al interactuar con el GPR40, el mecanismo de acción por el cual los compuestos actúan no están limitados a las materializaciones de la invención.

[059] Los compuestos contemplados en la invención incluyen, pero no se limitan, a los compuestos ejemplares brindados aquí.

[060] En un aspecto, la presente invención brinda un compuesto que tiene la fórmula (I):

$$Q\text{-}L^1\text{-}P\text{-}L^2\text{-}M\text{-}X\text{-}L^3\text{-}A$$

I

donde Q, L^1, P, L^2, M, X, L^3 y A son como se definen a continuación.

[061] Q es hidrógeno, arilo, heteroarilo, $(C_1\text{-}C_6)$alquilo o $(C_2\text{-}C_6)$heteroalquilo.

[062] En materializaciones preferidas, Q es arilo.

[063] En materializaciones aún más preferidas, Q es 4-(trifluorometil)fenil o *p*-tolil.

[064] L^1 es un enlace, $(C_1\text{-}C_4)$alquileno, $(C_2\text{-}C_4)$heteroalquileno, O, $S(O)_m$, $N(R^1)$, $C(O)$-$(C_5\text{-}C_7)$heterocicloalquileno, $(C_1\text{-}C_4)$alquileno-$SO_2N(R^2)$, $(C_1\text{-}C_4)$alquileno-$N(R^2)SO_2$ o $C(O)N(R^2)$.

[065] En ciertas materializaciones, L^1 es un enlace, $(C_1\text{-}C_4)$alquileno, $(C_2\text{-}C_4)$heteroalquileno, O, $S(O)_m$, $N(R^1)$ o $C(O)N(R^2)$.

[066] En ciertas materializaciones, L^1 es un enlace, O o $N(R^1)$.

[067] En materializaciones preferidas, L^1 es un enlace.

[068] P es un anillo aromático, un anillo heteroaromático, $(C_3\text{-}C_8)$heterocicloalquileno o $(C_3\text{-}C_8)$cicloalquileno. En ciertas materializaciones donde P es un anillo aromático, el término aromático incluye arilo. En otras materializaciones P es un anillo heteroaromático, el término heteroaromático incluye heteroarilo.

[069] En algunas materializaciones, P es un anillo aromático o un anillo heteroaromático.

[070] En ciertas materializaciones, P es un anillo aromático monocíclico o un anillo heteroatomático monocíclico.

[071] En algunas materializaciones, P se selecciona de un grupo que consiste en benceno, naftaleno, pirrol, pirazol, imidazol, piracina, oxazol, isoxazol, tiazol, furano, tiofeno, piridina, pirimidina, piridazina, benzotiazol, purino, benzimidazola, benzoxazol,

triazol, oxadiazol, tiadiazol, benzooxadiazol, dibenzofurano, indol, indazol, carbazol, carbolina, isoquinolina, quinoxalina y quinolina. Por ejemplo, P puede ser benceno, naftaleno, pirrol, pirazina, piridina, pirimidina, piridazina, purino, indol, carbolina, isoquinolina, quinoxalina o quinolina. En algunas materializaciones, P es un anillo de benceno, tiazol, o oxazol.

[072] En materializaciones preferidas, L^1 es un enlace, O o $N(R^1)$ y P es un anillo aromático o heteroaromático.

[073] L^2 es un enlace, (C_1-C_6)alquileno, (C_2-C_6)heteroalquileno, oximetileno, O, $S(O)_m$, $N(R^1)$, $C(O)N(R^2)$, $SO_2N(R^2)$, (C_1-C_4)alquileno-$C(O)N(R^2)$, (C_1-C_4)alquileno-$N(R^2)C(O)$, (C_2-C_4)alquileno-$C(O)N(R^2)$, (C_2-C_4)alquileno-$N(R^2)C(O)$, (C_1-C_4)alquileno-$SO_2N(R^2)$, (C_1-C_4)alquileno-$N(R^2)SO_2$, (C_2-C_4)alquenileno-$SO_2N(R^2)$ o (C_2-C_4)alquenileno- $N(R^2)SO_2$.

[074] En ciertas materializaciones, L^2 es un enlace, (C_1-C_6)alquileno, (C_2-C_6)heteroalquileno, oximetileno, O, $S(0)_m$, $N(R^1)$, $C(O)N(R^2)$, $SO_2N(R^2)$, (C_1-C_4)alquileno-$C(O)N(R^2)$, (C_2-C_4)alquenileno-$C(O)N(R^2)$, (C_1-C_4)alquileno-$SO_2N(R^2)$ o (C_2-C_4)alqueniloeno-$SO_2N(R^2)$.

[075] En ciertas materializaciones, L^2 es (C_2-C_6)heteroalquileno.

[076] En algunas materializaciones, L^2 es (C_2-C_4)heteroalquileno.

[077] En ciertas materializaciones, L^1 es un enlace, O o $N(R^1)$ y L^2 es (C_2-C_6)heteroalquileno.

[078] En ciertas materializaciones, L^2 es oximetileno o tiometileno.

[079] En materializaciones preferidas, L^1 es un enlace y L^2 es oximetileno o tiometileno.

[080] M es un anillo aromático, un anillo heteroaromático, (C_5-C_8)cicloalquileno, arilo(C_1-C_4)alquileno o heteroarilo(C_1-C_4)alquileno. En ciertas materializaciones donde M es un anillo aromático, el término aromático incluye arilo. En otras materializaciones donde M es un anillo heteroaromático, el término heteroaromático incluye heteroarilo.

[081] En algunas materializaciones, M es un anillo aromático o un anillo heteroaromático.

[082] En algunas materializaciones, M es un (C_5-C_8)cicloalquileno.

[083] En algunas materializaciones, M es un anillo aromático monocíclico o heteroaromático monocíclico o (C_5-C_8)cicloalquileno.

[084] En algunas materializaciones, M es un anillo aromático monocíclico no sustituido o un anillo heteroaromático monocíclico no sustituido.

[085] En ciertas materializaciones, M es un anillo de benceno o un anillo heteroaromático.

[086] En materializaciones preferidas, M es un anillo de benceno.

[087] En materializaciones preferidas, M es un anillo aromático o un anillo heteroaromático y M es un anillo aromático, un anillo heteroaromático o (C_5-C_8)cicloalquileno.

[088] X es CR^3R^4, $N(R^5)$, O o $S(O)_n$.

[089] En materializaciones preferidas, X es CR^3R^4 o $N(R^5)$.

[090] En materializaciones aún más preferidas, X es CHR^3.

[091] En ciertas materializaciones, M es un anillo de benceno sustituido o no sustituido y X es *para* a L^2.

[092] En algunas materializaciones preferidas, M es un anillo aromático, un anillo heteroaromático o (C_5-C_8)cicloalquileno y X es CR^3R^4 o $N(R^5)$.

[093] En materializaciones preferidas, P es un anillo aromático o un anillo heteroaromático y X es CR^3R^4 o $N(R^5)$.

[094] L^3 es un enlace, (C_1-C_5)alquileno o (C_2-C_5)heteroalquileno, con la condición de que L^3 no sea un enlace cuando L^2 sea un enlace.

[095] En algunas materializaciones, L3 es (C_1-C_5)alquileno o (C_2-C_5)heteroalquileno.

[096] En ciertas materializaciones, L^3 es (C_1-C_3)alquileno.

[097] En algunas materializaciones, L^3 es metileno.

[098] En ciertas materializaciones, L^3 es un metileno sustituido con un arilo monocíclico o heteroarilo monocíclico.

[099] En ciertas materializaciones, X es CR^3R^4 o $N(R^5)$, y L^3 es un metileno sustituido o no sustituido.

[0100] En materializaciones preferidas, L^2 es (C_2-C_4)heteroalquileno y L^3 es (C_1-C_3)alquileno.

[0101] En ciertas materializaciones preferidas, L^1 es un enlace, O o $N(R^1)$, L^2 es (C_2-C_4)heteroalquileno y L^3 es (C_1-C_3)alquileno.

[0102] A es $-CO_2H$, tetrazol-5-il, $-SO_3H$, $-PO_3H_2$, $-SO_2NH_2$, $-C(O)NHSO_2CH_3$, -CHO, $-C(O)R^6$, $-C(O)NHR^6$, $-C(O)NHOR^7$, tiazolidinedión-il, hidroxifenilo o piridil.

[0103] En ciertas materializaciones, A es un bioisóstero de $-CO_2H$.

[0104] En ciertas materializaciones, A es $-CO_2H$ o tetrazol-5-il, $-C(O)NHSO_2CH_3$ o $-C(O)NHR^6$.

[0105] En algunas materializaciones, A es $-CO_2H$ o tetrazol-5-il.

[0106] En materializaciones preferidas, A es $-CO_2H$ o su sal.

[0107] En algunas materializaciones, P es un anillo aromático o un anillo heteroaromático y A es $-CO_2H$.

[0108] En ciertas materializaciones, X es CR^3R^4 o $N(R^5)$ y A es $-CO_2H$.

[0109] En materializaciones preferidas, M es un anillo aromático, un anillo heteroaromático o (C_5-C_8)cicloalquileno y A es $-CO_2H$ o tetrazol-5-il.

[0110] En ciertas materializaciones preferidas, M es un anillo aromático, un anillo heteroaromático o (C_5-C_8)cicloalquileno, X es CR^3R^4 o $N(R^5)$, L^3 es (C_1-C_5)alquileno o (C_2-C_5)heteroalquileno y A es $-CO_2H$.

[0111] R^1 es (C_1-C_6)alquilo, arilo(C_1-C_3) alquilo o (C_2-C_6)heteroalquilo.

[0112] En ciertas materializaciones, R^1 es (C_1-C_6)alquilo o (C_2-C_6)heteroalquilo.

[0113] R^2 es hidrógeno, (C_1-C_6)alquilo o (C_2-C_6)heteroalquilo.

[0114] R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquilo, (C_2-C_8)alquenilo, (C_3-C_8)alquenilo, (C_2-C_8)alquinilo, (C_3-C_8)alquinilo, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$, $-NR^{12}C(O)R^{13}$ o $-NR^{12}S(O)_pR^{13}$.

[0115] En ciertas materializaciones, R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$, $-NR^{12}C(O)R^{13}$ o $-NR^{12}S(O)_pR^{13}$.

[0116] En algunas materializaciones, R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_9)alquenilo, (C_2-C_8)alquinilo o $-NR^8R^9$.

[0117] En ciertas materializaciones, R^3 es ciano, heteroarilo, (C_2-C_6) alquenilo o (C_2-C_6)alquinilo.

[0118] En ciertas materializaciones, R^3 es (C_2-C_8)alquilo, (C_3-C_8)alquenilo o (C_3-C_8)alquinilo.

[0119] En algunas materializaciones, R^3 es arilo o heteroarilo.

[0120] En ciertas materializaciones preferidas, R^3 es etrazolil, tiazolil, pirazolil, isoxazolil, oxazolil, pirrolil, tienil o prop-1-inil.

[0121] En ciertas materializaciones, R^3 es tetrazolil, tiazolil, o prop-1-inil.

[0122] R^4 es hidrógeno, ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo o (C_2-C_8)alquinilo.

[0123] Opcionalmente, R^3 y R^4 se combinan para formar un anillo de 3-, A-, 5-, 6- ó 7- miembros que contiene de cero a tres heteroátomos seleccionados de N, O y S. El anillo formado por la combinación de R^3 o R^4 puede ser saturado o no saturado.

[0124] En algunas materializaciones, R^4 es hidrógeno o metilo.

[0125] En materializaciones preferidas, R^4 es hidrógeno.

[0126] En otras materializaciones preferidas, R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquilo, (C_2-C_8)alquenilo, (C_3-C_8)alquenilo, (C_2-C_8)alquinilo, (C_3-C_8)alquinilo o -NR^8R^9 y R^4 es hidrógeno.

[0127] R^5 es hidrógeno, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o (C_3-C_8)cicloalquilo.

[0128] R^6 es heteroarilo.

[0129] R^7 es hidrógeno o (C_1-C_5)alquilo.

[0130] R^8 y R^9 son independientemente hidrógeno, (C_1-C_5)alquilo, Oxi(C_1 -C_5)alquilo o carboxi(C_1-C_5)alquilo.

[0131] Opcionalmente, R^8 y R^9 se combinan para formar un anillo de A-, 5-, 6- ó 7-miembros que contiene el átomo de nitrógeno al cual se acoplan y de 0 a 2 heteroátomos adicionales seleccionados de N, O y S. El anillo formado por la combinación de R^8 y R^9 puede ser un anillo saturado, no saturado o aromático.

[0132] R^{10}, R y R^{12} son seleccionados de forma independiente de hidrógeno, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)heteroalquilo, (C_3-C_8)cicloalquilo y (C_3-C_8)heterocicloalquilo.

[0133] Opcionalmente, R^{10} y R11 se combinan para formar un anillo de 4-, 5-, 6- ó 7- miembros que contienen el átomo de nitrógeno al cual se acoplan y de 0 a 2 heteroátomos adicionales seleccionados de N, O y S. El anillo formado por la combinación de R^{10} y R^{11} puede ser un anillo saturado, no saturado o aromático.

[0134] R^{13} es arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)heteroalquilo, (C_3-C_8)cicloalquilo o (C_3-C_8)heterocicloalquilo.

[0135] Los subíndices m y n son independientemente 0, 1 ó 2.

[0136] El superíndice p es 1 ó 2.

[0137] En algunas materializaciones, P es un anillo aromático o un anillo heteroaromático, X es CR^3R^4 y R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o -NR^8R^9.

[0138] En algunas materializaciones A es -CO_2H, X es CR^3R y R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o -NR^8R^9.

[0139] En algunas materializaciones, cuando P y M son benceno, al menos dos de L^2, X y L^3 no son CH_2.

[0140] En algunas materializaciones, los compuestos de la fórmula I no incluyen ácido 3-(4-(4-metoxibenciloxi)fenil)pent-4-inóico; ácido β-etenil-4-fenilmetoxi-bencenopropanóico; ácido 4-(2-quinolinilmetoxi)-β-[4-(2-quinolinilmetoxi)fenil]-bencenopropanóico; N-[4-(benzoilamino)fenilo]-N-fenil-glicino; 3-(4-(isopentiloxi)benzamido)-3-fenilpropanoato; 3-(4-isobutoxibenzamido)-3-fenilpropanoato; ácido (R)-2-((1R-4R)-4-isopropilciclohexanocarboxamido)-3-fenilpropanóico; ácido (R)-3-(4-(benciloxi)fenilo)-2-(tert-butoxicarbonil)propanóico; ácido 3-(4-clorofenil)-3-(furan-2-carboxamido)propanóico; ácido 3-(3,4-dimetlioxifenil)-3-(furan-2-carboxamido)propanóico; ácido 3-(4-clorobenzamido)-3-(4- (dimetiamino)fenilo)propanóico; ácido 3-(2-(2-(3,4-dimetilfenoxi)etitio)-1H- benzo[d]imidazol-1-il)propanóico; ácido {2-Bromo-4-[(3,4-dicloro-fenilo)- hidrazonometil]-6-etoxi-fenoxi} -acético; ácido 2-(4-(2-(2-(4-clorofenil)furan-5-carboxamido)etil)fenoxi)-2-metilpropanóico; ácido 5-(3-(3,4-dimetoxifenil)-5-(2- fluorofenil)-4,5-dihidropirazol-1-il)-5-oxopentanóico; ácido 2-(2-(3-(3,4-dihidro-2H-benzo[b][1,4]dioxepin-7-il)-2-metil-4-oxo-4H-cromen-7-iloxi)acetamido)acético; ácido 3-(4'-Bromo-bifenil-4-il)-4-fenilo-butírico; ácido 3-(4'-Bromo-bifenil-4-il)-3-fenilsulfanil-propiónico; ácido 3-(5-(2-cloro-6-fluoro-4-(trifluorometil)fenoxi)-2,4- dinitrofenil)propanóico; ácido 3-(3-(2-cloro-4-(trifluorometil)fenoxi)fenilo)propanóico; ácido 3-(4-(4-metoxibeciloxi)fenilo)pent-4-inoico; o ácido 3-(4-(4- metoxibenciloxi)fenilo)-5-(trimetilsilil)pent-4-inóico, sus sales o ésteres.

[0141] En algunas materializaciones, se entiende que los compuestos de la fórmula I no incluyen compuestos donde P es un anillo 1,2-azol donde Q es arilo o heteroarilo, L^1 es un enlace, M es un anillo aromático monocíclico, X es $N(R^5)$, O o $S(O)_n$, y A contiene un grupo carbonilo.

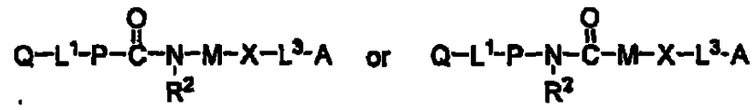
[0142] En algunas materializaciones, se entiende que los compuestos de la fórmula I no incluyen compuestos donde P es furano o tiofeno donde Q es arilo, L^1 es un enlace, M es un anillo aromático, X es CR^3R^4, O o $S(O)_n$ y A contiene un grupo carbonilo.

[0143] Los compuestos de la invención incluyen sales aceptables farmacéuticamente, solvatos o sus prodrogas.

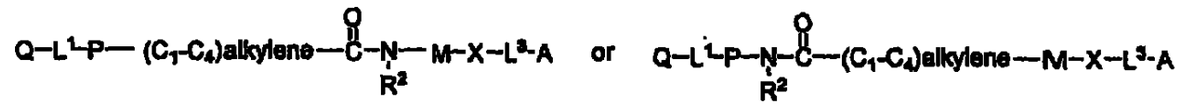
[0144] En algunas materializaciones, se prefieren las prodrogas ésteres.

[0145] Aquellos entendidos en la materia comprenderán que, a menos que se indique lo contrario, en los grupos divalentes tales como $C(O)N(R^2)$, SO_2-$N(R^2)$,(C_1-C_4)alquileno-$C(O)N(R^2)$ y similares, se permiten ambas orientaciones posibles de los grupos. Por ejemplo,

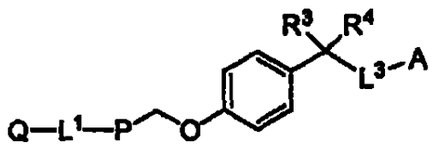
en la fórmula I donde L^2 es $C(O)N(R^2)$, el átomo de carbón puede ser adherido a P o a M, como se muestra:



Como otro ejemplo, en la fórmula I donde L^2 es $(C_1\text{-}C_4)$alquileno-$C(O)N(R^2)$ en la fórmula **Ia**, el grupo alquileno puede ser adherido a P o a M, como se muestra:



[0146] En algunas materializaciones, la presente invención brinda un compuesto de la fórmula (**Ia**):



Ia

donde Q, L^1, P, L^3, A R^3 y R^4 son como se definen en relación con la fórmula I anterior.

[0147] En algunas materializaciones de la fórmula **Ia**, Q es un benceno sustituido o no sustituido, y L^1 es a enlace, $(C_1\text{-}C_4)$alquileno, O o $S(O)_m$.

[0148] En algunas materializaciones, P es seleccionado de un grupo consistente de benceno, naftaleno, pirrol, imidazol, piracina, oxazol, tiazol, piridina, pirimidina, piridídacina, benzotiazol, purina, benzimidazol, indol, indazol, carbazol, carbolino, isoquinolino, quinoxalino y quinolino.

[0149] En algunas materializaciones donde P es benceno, Q es hidrógeno, arilo, heteroarilo o $(C_1\text{-}C_6)$alquilo, y L^1 es un enlace, $(C_1\text{-}C_4)$alquileno, O o $S(O)_m$.

[0150] En algunas materializaciones, L^3 es $(C_1\text{-}C_5)$alquileno. En algunas materializaciones, L^3 es metileno.

[0151] En algunas materializaciones, R^3 es ciano, arilo, heteroarilo, $(C_2\text{-}C_8)$alquilo, $(C_3\text{-}C_8)$alquenilo, $(C_3\text{-}C_8)$alquinilo, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$, $-NR^{12}C(O)R^{13}$ o $-R^{12}S(O)_pR^{13}$ y R^4 es hidrógeno, ciano, arilo, heteroarilo, $(C_1\text{-}C_8)$alquilo, $(C_2\text{-}C_8)$alquenilo o $(C_2\text{-}C_8)$alquinilo.

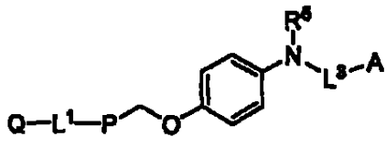
[0152] En algunas materializaciones, R^3 es ciano, un arilo no sustituido o un anillo heteroarilo monocíclico, $(C_2\text{-}C_8)$alquilo, $(C_3\text{-}C_8)$alquenilo, $(C_3\text{-}C_8)$alquinilo, o $-C(O)NR^{10}R^{11}$, R^4 es hidrógeno, y P se selecciona de un grupo consistente en benceno, naftaleno, pirrol,

imidazol, piracino, oxazol, tiazol, piridina, pirimidina, piridacina, benzotiazol, purina, benzimidazol, indol, indazol, carbazol, carbolina, isoquinolina, quinoxalina y quinolina.

[0153] En algunas materializaciones, R^3 es ciano, un arilo no sustituido o un anillo heteroarilo monocíclico, $(C_3\text{-}C_8)$alquenilo, $(C_3\text{-}C_8)$alquinilo, $-C(O)NR^{10}R^{11}$, R^4 es hidrógeno, y L^3 es metileno.

[0154] En algunas materializaciones, Q es arilo, heteroarilo, $(C_1\text{-}C_6)$alquilo o $(C_2\text{-}C_6)$heteroalquilo, L^1 es un enlace, $(C_1\text{-}C_4)$alquileno, $(C_2\text{-}C_4)$heteroalquileno, $S(O)_m$, $N(R^1)$, $(C_1\text{-}C_4)$alquileno-$SO_2N(R^2)$, $(C_1\text{-}C_4)$alquileno-$N(R^2)SO_2$ o $C(O)N(R^2)$, P es seleccionado de un grupo consistente en benceno, naftaleno, pirrol, imidazol, piracina, oxazol, tiazol, piridina, pirimidina, piridacina, benzotiazol, purina, bencimidazol, indol, indazol, carbazol, carbolina, isoquinolina, quinoxalina y quinolina, R^3 es ciano, un anillo aromático no sustituido o un anillo heteroaromático monocíclico, $(C_2\text{-}C_8)$alquilo, $(C_3\text{-}C_8)$alquenilo, $(C_3\text{-}C_8)$alquinilo, o $-C(O)NR^{10}R^{11}$, R^4 es hidrógeno, y L^3 es metileno.

[0155] En algunas materializaciones, la presente invención brinda un compuesto de la fórmula (**Ib**):



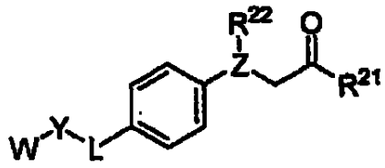
Ib

donde Q, L^1, P, L^3, A y R^5 son como se definieron en relación con la fórmula **I** anterior.

[0156] En algunas materializaciones de la fórmula **Ib**, P se selecciona de un grupo consistente en benceno, naftaleno, pirrol, imidazol, pirazina, oxazol, tiazol, furano, tiofeno, piridina, pirimidina, piridacina, bezotiazol, purina, bencimidazol, indol, indazol, carbazol, carbolina, isoquinolina, quinoxalina y quinolina.

[0157] En algunas materializaciones, R^5 es un benceno sustituido o no sustituido.

[0158] En otro aspecto, la presente invención brinda un compuesto de la fórmula (**II**):



II

donde R^{21}, R^{22}, Z, L, Y y W son como se definen a continuación.

[0159] R21 es -H, -OH, $-NHS(O_2)CH_3$, heteroarilo, o -NH-heteroarilo.

[0160] En algunas materializaciones, R^{21} es -OH, $-NHS(O_2)CH_3$, -NH-tetrazolil, o tetrazolil.

[0161] En algunas materializaciones, R^{21} es tetrazolil, pirimidinil, o piridinil.

[0162] En materializaciones preferidas, R^{21} es -OH, o su sal.

[0163] R^{22} es -H, $-(C_2-C_8)$alquilo, $-(C_3-C_8)$alquenilo, $-NR^{23}R^{24}$, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, $-C\equiv N$, o $-C\equiv N$.

[0164] En algunas materializaciones, R^{22} es $-(C_2-C_8)$alquilo, $-(C_3-C_8)$alquenilo, $-NR^{23}R^{24}$, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, $-C\equiv N$ o $-C\equiv C-R^{25}$.

[0165] En ciertas materializaciones, R^{22} es $-(C_2-C_3)$alquilo, $-NR^{23}R^{24}$, fenilo sustituido o no sustituido, $-CH=C(CH_3)_2$, $-CH_2CH=CH_2$, o $-C\equiv C-R^{25}$.

[0166] En otras materializaciones, R^{22} es arilo sustituido o no sustituido o heteroarilo no sustituido. En otras materializaciones, R^{22} es arilo sustituido y la sustitución sobre el arilo es $-(C_1-C_5)$alquilo, $-(C_1-C_5)$oxialquilo, o -halo(C_1-C_5)alquilo.

[0167] En ciertas materializaciones, R^{22} es $-C\equiv C-R^{25}$ y R^{25} es $-(C_1-C_5)$alquilo con 0 ó 1 heteroátomos.

[0168] En materializaciones preferidas, R^{22} es $-C\equiv CCH_3$.

[0169] En algunas materializaciones, R^{22} es $-CH=C(CH_3)_2$, o $-CH_2CH=CH_2$.

[0170] R^{23} y R^{24} son independientemente -H, $-(C_1-C_5)$alquilo, o $-(C_1-C_5)$oxialquilo.

[0171] R^{25} es -H, $-(C_1-C_5)$alquilo, -hetero(C_1-C_5)alquilo, $-(C_1-C_5)$oxialquilo, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido.

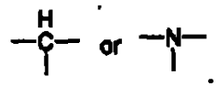
[0172] En algunas materializaciones, R^{25} es $-(C_1-C_5)$alquilo, $-(C_1-C_5)$oxialquilo, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido.

[0173] En algunas materializaciones, R^{25} es -hetero(C_1-C_5)alquilo que no contiene Si.

[0174] En algunas materializaciones, R^{25} es fenilo no sustituido.

[0175] En otras materializaciones, R^{25} es un fenilo sustituido.

[0176] En materializaciones preferidas, R^{25} es metilo

[0177] Z es  . En algunas materializaciones, Z es nitrógeno. En otras materializaciones, Z es carbono.

[0178] L es -O-, -S-, o -N(R^{26})-. En algunas materializaciones, L es -O-. En otras materializaciones, L es -S-. En otras materializaciones, L es -N(R^{26})-.

[0179] En otras materializaciones, Z es nitrógeno y L es -N(R^{26})-.

[0180] R^{26} es -H , -(C_1-C_5)alquilo, arilo(C_1-C_{10})alquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido.

[0181] En ciertas materializaciones, R^{26} es -H , arilo(C_1-C_{10})alquilo sustituido o no sustituido o arilo no sustituido.

[0182] En algunas materializaciones, R^{26} es -H.

[0183] En otras materializaciones , R^{26} es fenilo sustituido o no sustituido.

[0184] Y no está presente o es -CH_2- , -CH_2CH_2- , -CH=CH- , -C(O)CH_2- , -C(O)CH_2CH_2- , -C(O)CH=CH- , -S(O_2)-, -S(O_2)CH_2- , -S(O_2)CH_2CH_2- , -S(O_2)CH=CH-, o -C(O)-.

[0185] En un número de materializaciones, Y es -CH_2- , -CH_2CH_2- , -CH=CH- , -C(O)CH_2- , -C(O)CH_2CH_2- , -C(O)CH=CH- , -S(O_2)-, -S(O_2)CH_2- , -S(O_2)CH_2CH_2- , -S(O_2)CH=CH-.

[0186] En algunas materializaciones Y es -CH2-.

[0187] En algunas materializaciones L es -O- o -S-, y Y es -CH_2-, -CH_2CH_2-.

[0188] W es arilo sustituido o no sustituido o heteroarilo sustituido o no sustituido.

[0189] Por ejemplo y sin limitación, W puede ser un anillo tal como benceno, naftaleno, pirrol, pirazol, imidazol, piracina, oxazol, isoxazol, tiazol, furano, tiofeno, piridina, pirimidina, piridacina, benzotiazol, purina, benzimidazol, benzoxazol, triazol, oxadiazol, tiadiazol, benzooxadiazol, dibenzofurano, indol, indazol, carbazol, carbolina, isoquinolino, quinoxalino o quinolino, y así sucesivamente.

[0190] En algunas materializaciones, W es un anillo arilo monocíclico sustituido o no sustituido o un anillo heteroarilo monocíclico no sustituido.

[0191] En algunas materializaciones, W es un anillo arilo bicíclico sustituido o no sustituido o un anillo arilo bicíclico fusionado no sustituido o un anillo heteroarilo bicíclico sustituido o no sustituido. En ciertas materializaciones, W es anillo arilo bicíclico

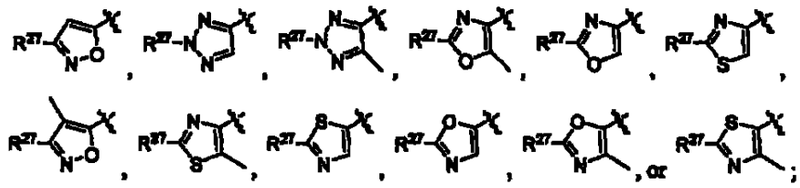
fusionado de 8- a 11- miembros o un anillo heteroarilo bicíclico fusionado de 8- a 11- miembros.

[0192] En otras materializaciones, W es un anillo arilo de 5- o 6- miembros o un anillo heteroarilo de 5- o 6- miembros.

[0193] En ciertas materializaciones donde W es un arilo sustituido o un anillo heteroarilo, el grupo de sustitución puede ser un halógeno, (C_1-C_{10})alquilo sustituido o no sustituido, hetero(C_1-C_{10})alquilo sustituido o no sustituido, halo(C_1-C_{10})alquilo sustituido o no sustituido, arilo(C_1-C_{10})alquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido.

[0194] En algunas materializaciones, W es un anillo de 5 miembros que tiene dos o más heteroátomos.

[0195] En ciertas materializaciones, W es un anillo de 5 miembros seleccionado del grupo que consiste en



y R^{27} es (C_1-C_{10})alquilo sustituido o no sustituido, hetero(C_1-C_{10})alquilo sustituido o no sustituido, halo(C_1-C_{10})alquilo sustituido o no sustituido, aril(C_1-C_{10})alquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido.

[0196] En algunas materializaciones donde Z es  , R^{21} es -OH, L es -O-, -S-, o -N(R^{26})-, y Y es $-CH_2-$, $-CH_2CH_2-$, -CH=CH- , $-C(O)CH_2-$, $-C(O)CH_2CH_2-$, -C(O)CH=CH- , o -C(O)-, W no es ni furano ni tiofeno.

[0197] En ciertas materializaciones, W es un fenilo sustituido o no sustituido.

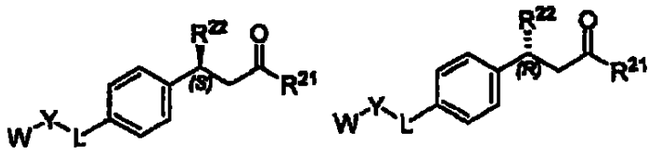
[0198] En algunas materializaciones, Z es carbono y R^{22} es -(C_2-C_8)alquilo, -(C_3-C_8)alquenilo, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, o $—C{\equiv}C\text{-}R^{25}$.

[0199] En algunas materializaciones donde Z es carbono, W es un anillo benceno, R^{22} es $—C{\equiv}C\text{-}R^{25}$, R^{25} es -hetero(C_1-C_5)alquilo, L es -O- o -S-, por lo que ningún heteroátomo en R^{25} es Si.

[0200] En algunas materializaciones, donde R^{21} es -OH, L es -O-, Y es -CH2-, y W es *para*-metoxifenilo, R^{22} es $—C{\equiv}C\text{-}R^{25}$, ningún R^{25} es –H.

[0201] En ciertas materializaciones, donde L es -N(R^{26})-, Z es nitrógeno, R^{22} es un fenilo, R^{26} es hidrógeno o un fenilo y W es un fenilo, Y no es -C(O)-.

[0202] Será aparente en las materializaciones de la fórmula II donde Z es  y R^{22} es -(C_2-C_8)alquilo, -(C_3-C_8)alquenilo, -$NR^{23}R^{24}$, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, —C≡N o —C≡C-R^{26}, que el carbono en Z es un carbono quiral como se muestra:



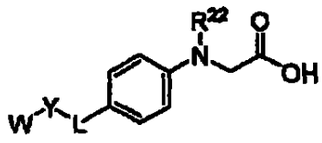
Así, un compuesto de la invención puede ser un enatiómero S, un enatiómero R, o una mezcla de un enatiómero S y un enatiómero R.

[0203] En materializaciones preferidas, un compuesto es un enatiómero S.

[0204] En ciertas materializaciones, R^{21} es -OH; L es -O-, o -S-; y Y es -CH_2- , o -CH_2CH_2-.

[0205] En algunas materializaciones donde Z es nitrógeno, W no es un anillo azol 1,2-azol.

[0206] En algunas otras materializaciones, la presente invención brinda un compuesto de la fórmula (III):



III

o una sal aceptable farmacéuticamente, hidrato o su prodroga, donde R^{22}, L, Y, y W son como se definieron en relación con la fórmula II anterior.

[0207] En algunas materializaciones, R^{22} es -H, -(C_2-C_3)alquilo, -$NR^{23}R^{24}$, o fenilo sustituido o no sustituido.

[0208] En ciertas materializaciones, L es -O-, -S-, o -N(R^{26})-.

[0209] En algunas materializaciones, R^{26} es -H , arilo(C_1-C_{10})alquilo sustituido o no sustituido o arilo sustituido o no sustituido.

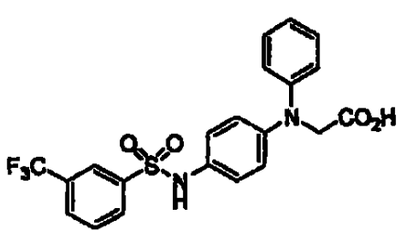
[0210] En algunas materializaciones, Y es -CH_2- , -CH_2CH_2- , -CH=CH- , -C(O)CH_2- , -C(O)CH_2CH_2- , -C(O)CH=CH- , -S(O_2)CH_2- , -S(O_2)CH_2CH_2- , -C(O)-, o -S(O_2)CH=CH- .

[0211] En algunas materializaciones, W es un anillo arilo de 5- ó 6- miembros sustituido o no sustituido o un anillo heteroarilo de 5- ó 6- miembros no sustituido con la condición de que si R^{22} es fenilo, L es -O-, -S-, o -N(R^{26})-, y W es un anillo benceno, Y no puede ser -C(O)-.

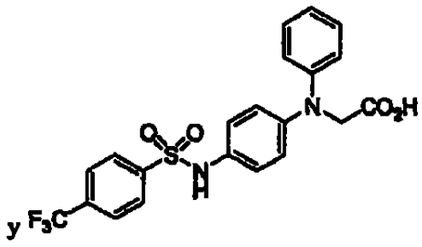
[0212] En algunas materializaciones, L es -N(R^{26})-, y R26 es hidrógeno.

[0213] En ciertas materializaciones, W no es un anillo 1,2-azol.

[0214] En otras materializaciones, el compuesto de la fórmula **III** se selecciona de un grupo consistente en



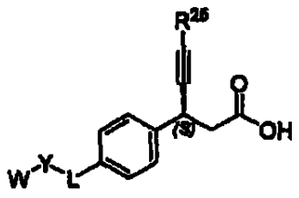
y



o su sal.

[0215] Aún en otras materializaciones, la presente invención brinda un compuesto de la fórmula **II** o una sal aceptable farmacéuticamente, solvato o su prodroga, donde R^{21} es -OH, -NHS(O_2)CH_3, -NH-tetazolilo, o tetrazolilo; R^{22} es -(C_2-C_8)alquilo, -$NR^{23}R^{24}$, fenilo sustituido o no sustituido, -CH=C(CH_3)$_2$, -CH_2CH=CH_2, o $-C\equiv C-R^{25}$; R^{23} y R^{24} son independientemente -H, -(C_1-C_5)alquilo, o -(C_1-C_5)oxialquilo; R^{25} es -H, -(C_1-C_5)alquilo, -(C_1-C_5)oxialquilo, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido; Z es $-\overset{H}{\underset{|}{C}}-$ or $-\underset{|}{N}-$; L es -0-, -S-, o -N(R^{26})-; R^{26} es -H , -(C_1-C_5)alquilo, arilo(C1-C10)alquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido; Y es -CH_2- , -CH_2CH_2- , -CH=CH- , -C(O)CH_2- , -C(O)CH_2CH_2- , -C(O)CH=CH- , -S(O_2)CH_2- , -S(O_2)CH_2CH_2-, o -S(O_2)CH=CH-; y W es un anillo arilo de 5- ó 6- miembros sustituido o no sustituido o un anillo heteroarilo de 5- ó 6- miembros sustituido o no sustituido.

[0216] En ciertas materializaciones, la presente invención brinda compuestos de acuerdo con la fórmula (**IV**):



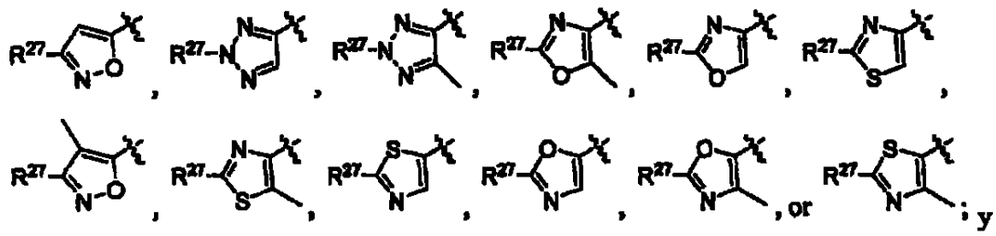
IV

o una sal aceptable farmacéuticamente, hidrato o su prodroga, donde R^{25}, W, Y, y L son como se definen en el párrafo **[0215]** anterior.

[0217] En algunas materializaciones, R^{25} es metilo.

[0218] En algunas materializaciones, L es -O- o -S- y Y es $-CH_2-$ o $-CH_2CH_2-$.

[0219] En algunas materializaciones, W es a un anillo de 5- miembros seleccionado de un grupo consistente en

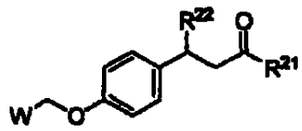


R^{27} es un (C_1-C_{10})alquilo sustituido o no sustituido, hetero(C_1-C_{10})alquilo sustituido o no sustituido, halo(C_1-C_{10})alquilo sustituido o no sustituido, aril(C_1-C_{10})alquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido.

[0220] En ciertas materializaciones, R^{27} es fenilo sustituido.

[0221] En otras materializaciones, R^{27} es fenilo no sustituido.

[0222] En algunas materializaciones, la presente invención brinda compuestos de acuerdo con la fórmula (V):



V

o una sal aceptable farmacéuticamente, hidrato o su prodroga, donde R^{21}, R^{22} y W son como se definieron en el párrafo **[0215]** anterior.

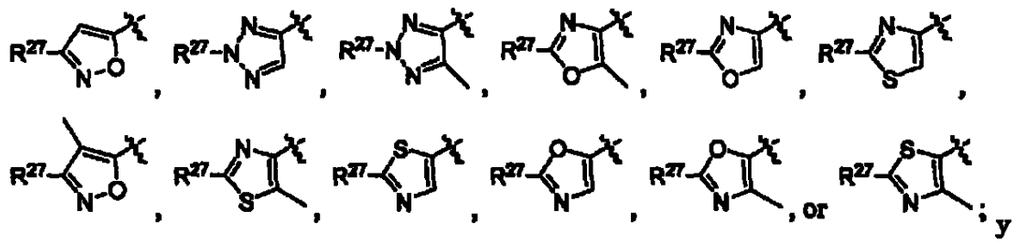
[0223] En algunas materializaciones, R^{21} es -OH, o una sal.

[0224] En algunas materializaciones, W es fenilo sustituido.

[0225] En ciertas materializaciones, W es sustituido con (C_1-C_{10})alquilo sustituido o no sustituido, hetero(C_1-C_{10})alquilo sustituido o no sustituido, halo(C_1-C_{10})alquilo

sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido.

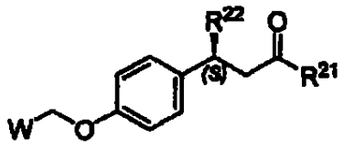
[0226] En otras materializaciones, W es un anillo de 5- membranas seleccionado del grupo consistente en



R^{27} es hidrógeno, (C_1-C_{10})alquilo sustituido o no sustituido, hetero(C_1-C_{10})alquilo sustituido o no sustituido, halo(C_1-C_{10})alquilo sustituido o no sustituido, arilo(C_1-C_{10})alquilo sustituido o no sustituido, arilo sustituido o no sustituido, o sustituido o no sustituido heteroarilo.

[0227] En ciertas materializaciones, un compuesto de la fórmula V es un racemato. En ciertas materializaciones, el compuesto de la fórmula V comprende un mezcla de enatiómeros (S) y (R).

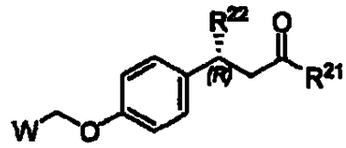
[0228] En ciertas materializaciones, la presente invención brinda compuestos que tienen la fórmula (**Va**):



Va

donde R^{21}, R^{22} y W son como se definieron en la fórmula **V** anterior.

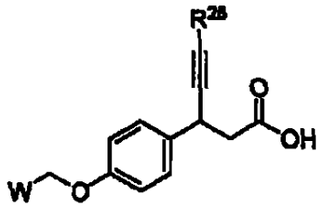
[0229] En otras materializaciones, el compuesto tiene la fórmula (Vb):



Vb

donde R^{21}, R^{22} y W son como se definieron en la fórmula **V** anterior.

[0230] En ciertas materializaciones, la presente invención brinda compuestos de acuerdo con la fórmula (**VI**):

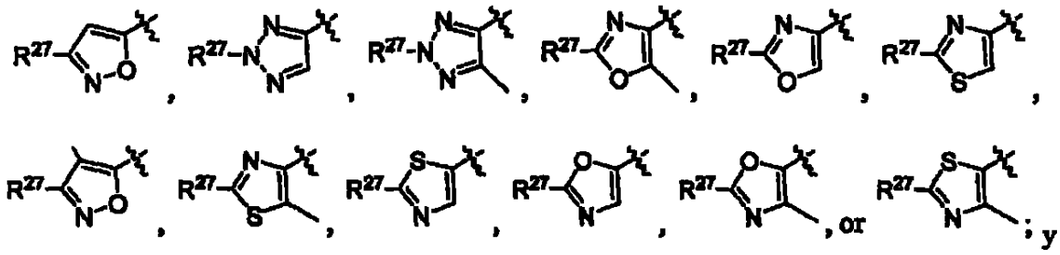


VI

o una sal aceptable farmacéuticamente, solvato o su prodroga, donde R^{25} y W se definieron en el párrafo **[0215]** anterior.

[0231] En algunas materializaciones, R25 es metilo.

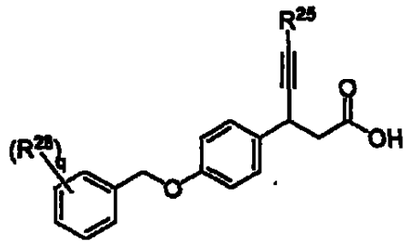
[0232] En algunas materializaciones, W es un anillo de 5- membranas seleccionado del grupo consistente en



R27 es hidrógeno, sustituido o no sustituido (C_1-C_{10})alquilo, hetero(C_1-C_{10})alquilo sustituido o no sustituido, halo(C_1-C_{10})alquilo sustituido o no sustituido, arilo(C_1-C_{10})alquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido.

[0233] En ciertas materializaciones, el compuesto de la fórmula **VI** comprende un enatiómero S- estereoméricamente puro. En otras materializaciones, el compuesto de la fórmula **VI** comprende un enatiómero R-estereoméricamente puro. Aún en otras materializaciones, el compuesto de la fórmula **VI** comprende una mezcla de enatiómeros S- y R-.

[0234] En ciertas materializaciones, brinda compuestos de acuerdo con la fórmula **(VII)**:



VII

o una sal aceptable farmacéuticamente, hidrato o su prodroga, donde cada R^{28} se selecciona de forma independiente de un grupo consistente en (C_1-C_{10})alquilo sustituido o no sustituido, hetero(C_1-C_{10})alquilo sustituido o no sustituido, halo(C_1-C_{10})alquilo sustituido o no sustituido, arilo(C1-C10)alquilo sustituido o no sustituido, arilo sustituido o no sustituido, y heteroarilo sustituido o no sustituido, el superíndice q es un entero de 0 a 5, y R^{25} es como se definió en el párrafo **[0215]**.

[0235] En algunas materializaciones, el superíndice q es 0, 1, ó 2.

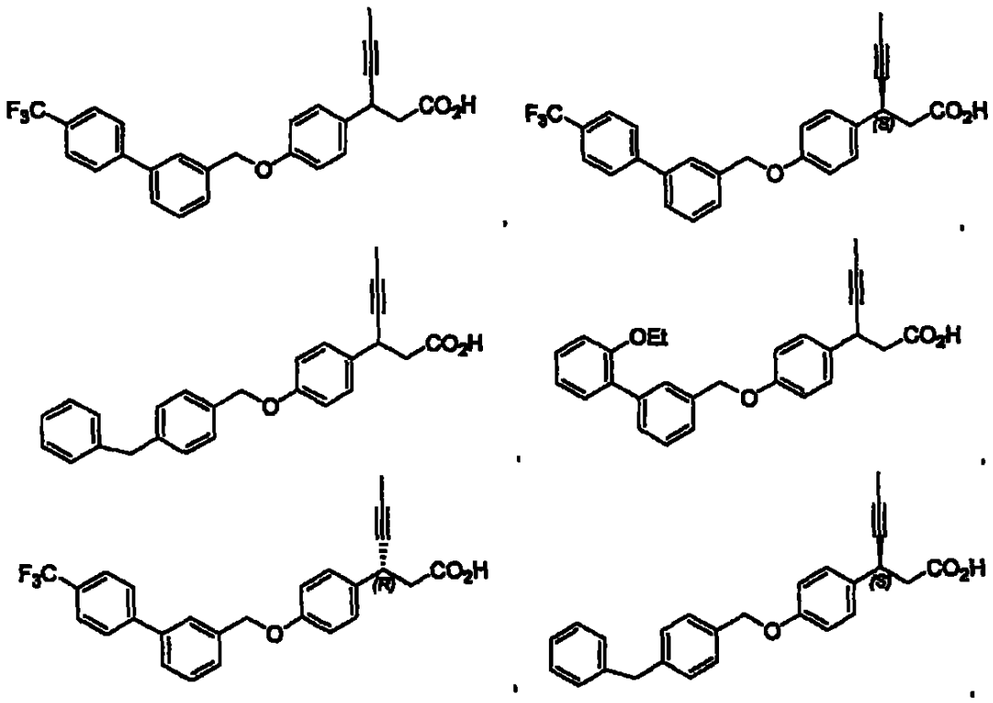
[0236] En otras materializaciones, R es un metoxi, etoxi, trihalometilo, metilo, halo, o grupo ciano y el subíndice q es 1 ó 2.

[0237] En otras manifestaciones, R es un fenilo, metoxifenilo, metilfenilo, trihalometilfenilo, bencilo, fenoxi, etoxifenilo, cianofenilo, halofenilo, halobencilo, piridilo, metoxibenilo, o grupo pirilo y el subíndice q es 1 ó 2.

[0238] En otras materializaciones, R^{25} es metilo.

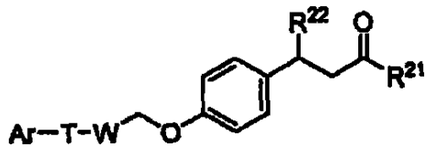
[0239] En ciertas materializaciones, el compuesto de la fórmula **VII** comprende un enatiómero S- estereomericamente puro. En otras materializaciones, el compuesto de la fórmula **VII** comprende un enatiómero R- esteomericamente puro. Aún en otras manifestaciones, el compuesto de la fórmula VII comprende una mezcla de enatiómeros S- y R-.

[0240] En otras manifestaciones, la fórmula se selecciona de un grupo consistente en



y sus sales.

[0241] En ciertas materializaciones, la presente invención brinda compuestos de acuerdo con la fórmula **(VIII)**:



VIII

o una sal aceptable farmacéuticamente, solvato o su prodroga, donde R^{21}, R^{22} y W son como se definieron en el párrafo **[0215]** anterior y Ar y T se definen a continuación.

[0242] T es un enlace directo, (C_1-C_5)alquileno, hetero(C_1-C_5)alquileno, O, C(O)-(C_5-C_7)heterocicloalquileno, (C_1-C_4)alquileno-SO_2NH, o (C_1-C_4)alquileno-$NHSO_2$.

[0243] En algunas materializaciones, T es un enlace directo, (C1-C5)alquilo sustituido o no sustituido o hetero(C_1-C_5)alquilo sustituido o no sustituido.

[0244] Ar es arilo sustituido o no sustituido o heteroarilo sustituido o no sustituido.

[0245] En ciertas materializaciones, Ar es a benceno, naftaleno, pirrol, pirazol, imidazol, piracina, oxazol, isoxazol, tiazol, furano, tiofeno, piridina, primidina, piridacina, benzotiazol, purina, benzimidazol, benzoxazol, triazol, oxadiazol, tiadiazol, benzooxadiazol,

dibenzofurano, indol, indazol, carbazol, carbolina, isoquinolina, quinoxalina o quinolina.

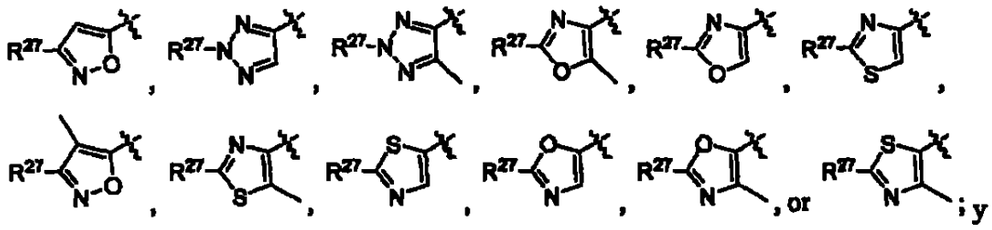
[0246] En algunas materializaciones, R^{22} es $-C\equiv C-CH_3$.

[0247] En algunas materializaciones, R^{21} es -OH.

[0248] En ciertas materializaciones, T es un enlace directo y Ar es anillo de benceno sustituido o no sustituido.

[0249] En algunas materializaciones, W es fenilo.

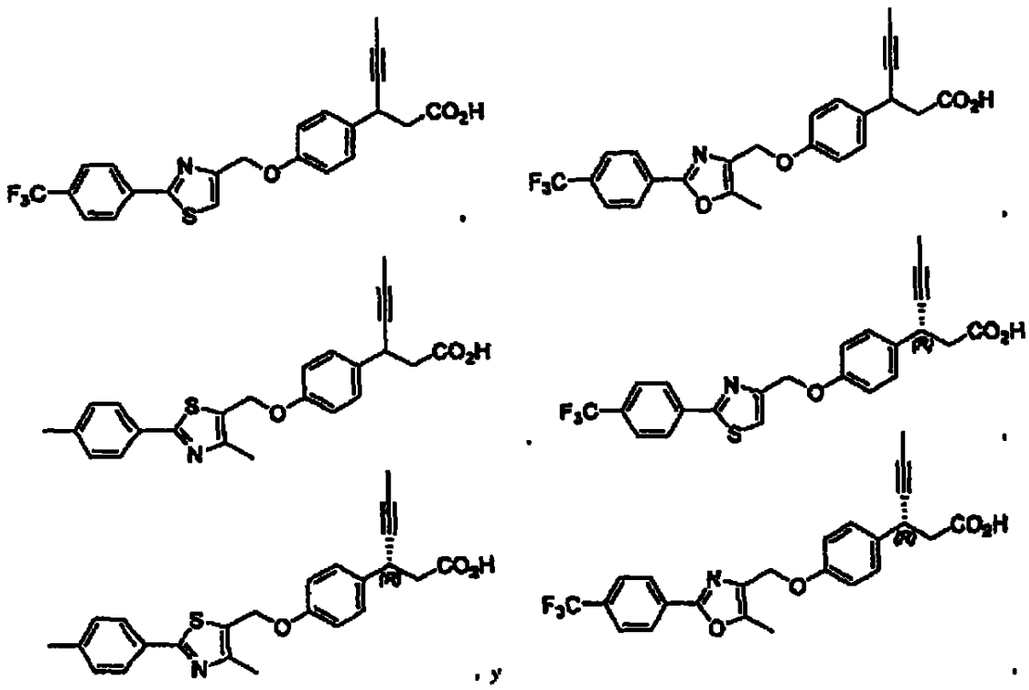
[0250] En otras materializaciones, W es un anillo de 5- miembros seleccionado del grupo consistente en



R^{27} es Ar-T.

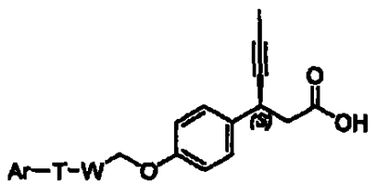
[0251] En ciertas materializaciones, el compuesto de la fórmula **VIII** comprende un enatiómero S-estereomericamente puro. En otras materializaciones, el compuesto de la fórmula **VIII** comprende un enatiómero R-esteomericamente puro. Aún en otras materializaciones, el compuesto de la fórmula **VIII** comprende una mezcla de enatiómeros S- y R-.

[0252] En ciertas materializaciones, el compuesto se selecciona de un grupo consistente en:



o su sal.

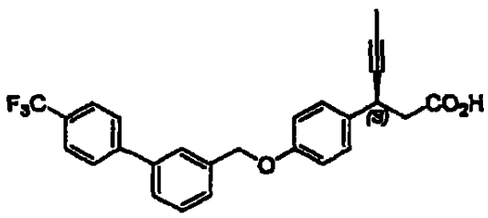
[0253] En ciertas materializaciones, la presente invención brinda compuestos de acuerdo con la fórmula (**IX**)



IX

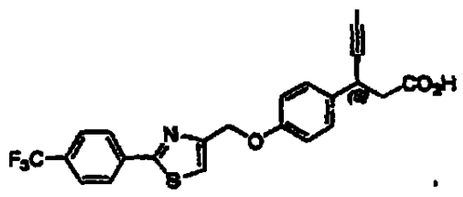
o una sal aceptable farmacéuticamente, hidrato o su prodroga, donde W, T y Ar son como se definieron en la fórmula **VIII** anterior.

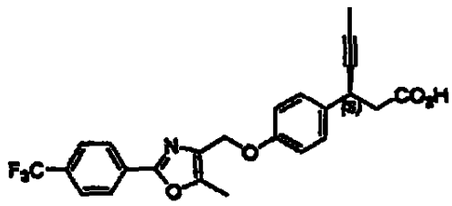
[0254] En algunas materializaciones, el compuesto tiene la fórmula:

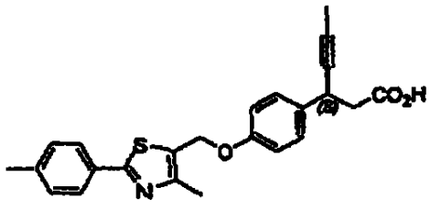


' o su sal.

[0255] En una materialización, el compuesto se selecciona de un grupo consistente en:

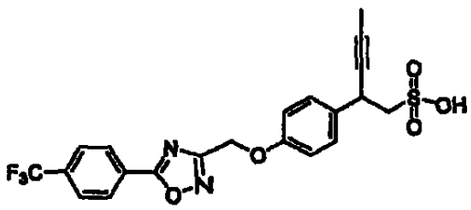

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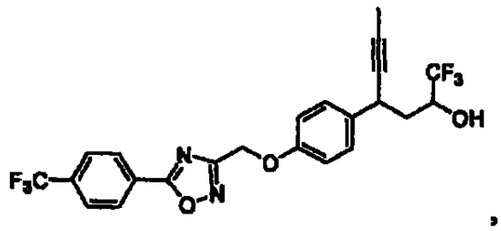

, y

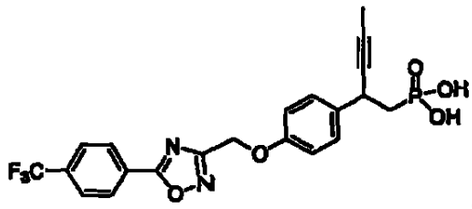

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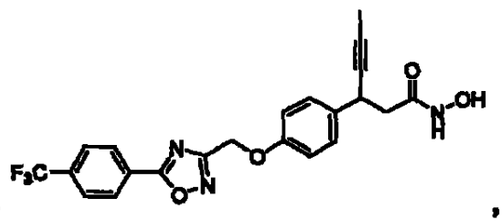
o una sal.

[0256] En ciertas materializaciones, la presente invención brinda compuestos, por ejemplo, de las fórmulas **III**, **IV**, **VI**, **VII**, o **IX**, que incluyen un bioisóstero de $-CO_2H$ en lugar de $-CO_2H$. A manera de ilustración, compuestos que incluyen un bioisóstero de $-CO_2H$ en lugar de $-CO_2H$ en el compuesto ejemplar **27.1**, descrito en los ejemplos posteriores, pueden incluir lo siguiente:


,


,


,


,

, y similares, sin limitación, como lo reconocen los entendidos en la materia. Véase, e.g., *The Practice of Medicinal Chemistry*, Wermuth, C. G., Ed., Academic Press: New York, 1996, que se incorpora en su totalidad por referencia.

[0257] En ciertas materializaciones, la invención brinda compuestos de acuerdo con las fórmulas anteriores siempre que el compuesto no sea alguno de los ácidos o sales siguientes, incluyendo:

ácido 3-(4-(4-metoxibenciloxi)fenil)pent-4-inóico;

ácido β-etenil-4-fenilmetoxi-bencenopropanóico;

ácido 4-(2-quinolinilmetoxi)-β-[4-(2-quinolinilmetoxi)fenil]-bencenopropanóico;

N-[4-(benzoilamino)fenil]-N-fenil-glicina;

3-(4-isopentiloxy)benzamido)-3-fenilpropanoato;

3-(4-isobutoxibenzamido)-3-fenilpropanoato;

ácido (R)-2-((1R,4R)-4-isopropilciclohexanocarboxamido)-3-fenilpropanóico;

ácido (R)-3-(4-(benciloxi)fenil)-2-(tert-butoxicarbonil)propanóico;

ácido 3-(4-clorofenil)-3-(furan-2-carboxamido)propanóico;

ácido 3-(3 ,4-dimetoxifenil)-3-(furan-2-carboxamido)propanóico;

ácido 3-(4-clorobenzamido)-3-(4-(dimetiamino)fenil)propanóico;

ácido 3-(2-(2-(3,4-dimetilfenoxi)etiltio)-1*H*-benzo[d]imidazol- 1-il)propanóico;

ácido {2-Bromo-4-[(3,4-dicloro-fenilo)-hidrazonometil]-6-etoxi-fenoxi}-acético;

ácido 2-(4-(2-(2-(4-clorofenil)furan-5-carboxamido)etil)fenoxi)-2-metilpropanóico;

ácido 5-(3-(3,4-dimetoxifenil)-5-(2-fluorofenil)-4,5-dihidropirazol-1-il)-5-oxopentanóico

ácido 2-(2-(3-(3,4-dihidro-2H-benzo[b][1,4]dioxepin-7-il)-2-metil-4-oxo-4*H*-cromen-7-iloxi)acetamido)acético;

ácido 3-(4'-Bromo-bifenil-4-il)-4-fenil-butírico;

ácido 3-(4'-Bromo-bifenil-4-il)-3-fenilsulfanil-propiónico;

ácido 3-(5-(2-cloro-6-fluoro-4-(trifluorometil)fenoxi)-2,4-dinitrofenil)propanóico;

3-(3-(2-cloro-4-(trifluorometil)fenoxi)fenilo)propanóico;

ácido 3-(4-(4-metoxibenciloxi)fenil)pent-4-inóico;

ácido 3-(4-(4-metoxibenciloxi)fenilo)-5-(trimetilsilil)pent-4-inóico;

ácido β,β-dimetil-4-[[[4-metil-2-[4-(trifluorometil)fenil]-5-tiazolil]metil]tio]-bencenopropanóico; o

ácido β-amino-4-[(4-bromo-2,5-dihidro-2-metil-5-oxo-1-fenil-1H-pirazol-3-il)metoxi]-3-metoxi-bencenopropanóico.

5.2.2 Preparación de los Compuestos

[0258] Los compuestos de la invención pueden prepararse por una variedad de técnicas sintéticas o semisintéticas. La FIG. 1 y los ejemplos en la Sección 6 posterior proveen una variedad de rutas para la síntesis de los compuestos que se brindan. Las materias primas se pueden preparar por técnicas conocidas o aparentes a los expertos en la materia, o pueden obtenerse de forma comercial. Un experto en la materia comprenderá que se pueden modificar las rutas sintéticas para emplear diferentes materias primas o reactivos alternos y que se pueden realizar los ajustes apropiados en las condiciones (e.g. temperaturas, solventes, etc.) para alcanzar las transformaciones deseadas. Además, un experto en la materia reconocerá que para la preparación de ciertos compuestos pueden ser necesarios grupos de protección y que se debe estar al tanto de las condiciones compatibles con el grupo de protección seleccionado. De tal manera, que, los métodos de ejemplo y los ejemplos aquí descritos son ilustrativos de la presente invención y no se debe entender que limitan su alcance.

5.2.3 Composiciones

[0259] En otro aspecto, la presente invención brinda composiciones farmacéuticas útiles para uso farmacéutico que comprenden uno o más compuestos de la invención y un portador farmacéuticamente aceptable, excipiente o diluyente.

[0260] El término "composición", como se usa aquí, abarca un producto que comprende los ingredientes especificados (en las cantidades especificadas, si se indica), así como cualquier producto que resulte, directa o indirectamente, de una combinación de los ingredientes especificados en las cantidades especificadas. Por "farmacéuticamente aceptable" se entiende que el portador o excipiente es compatible con otros ingredientes de la fórmula y no es perjudicial para el recipiente.

[0261] En ciertas materializaciones, la presente invención provee una composición farmacéutica que comprende un compuesto de la fórmula II, donde R^{22} comprende un alquinilo que contiene Si, y donde R^{21}, L, Y, y W son como se definieron en la fórmula II.

[0262] En algunas materializaciones, el átomo de Si es sustituido hasta con tres grupos de alquilo.

[0263] En algunas materializaciones, R^{22} es $-C\equiv C-Si(CH_3)_3$.

[0264] La composición de la formulación puede mejorar una o más propiedades farmacocinéticas (e.g., biodisponibilidad oral, permeabilidad membránica) de un compuesto de la invención (el que se designa como ingrediente activo).

[0265] Las composiciones farmacéuticas para la administración de los compuestos de la invención por conveniencia se pueden presentar en forma de unidad de dosis y se pueden preparar por lo métodos muy conocidos en la ciencia. Todos los métodos incluyen el paso de asociar el ingrediente activo con el portador que constituye uno o más ingredientes accesorios. En general, las composiciones farmacéuticas se preparan por medio de la asociación uniforme e íntima del ingrediente activo con un líquido portador, un sólido finamente dividido o ambos, y después, de ser necesario, se moldea el producto para alcanzar la fórmulación deseada. En la composición farmacéutica se incluye el componente activo en una cantidad suficiente para producir el efecto deseado en el proceso o condición de las enfermedades.

[0266] Las composiciones farmacéuticas que contienen el ingrediente activo pueden estar en un forma apropiada para la administración oral, por ejemplo, como tabletas, grageas, pastillas, suspensiones acuosas o aceitosas, polvos o gránulos dispersables, cápsulas suaves o rígidas, o jarabes o elíxires. Las composiciones destinadas al uso oral se pueden preparar de acuerdo con cualquier método conocido en la ciencia de fabricación de composiciones farmacéuticas. Dichas composiciones pueden contener uno o más agentes seleccionados de agentes edulcorantes, agentes saborizantes, agentes colorantes y agentes preservantes para llegar a preparaciones farmacéuticas elegantes y apetecibles. Las tabletas contienen el ingrediente activo en una mezcla con excipientes no tóxicos farmacéuticamente aceptables que sean apropiados para la fabricación de tabletas. Dichos excipientes pueden ser, por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio o fosfato de sodio; agentes granulantes y desintegrantes, por ejemplo, almidón de maíz, o ácido algínico; agentes aglutinantes, gelatina o acacia, y agentes lubricantes, por ejemplo estearato de magnesio, ácido esteárico o talco. Las tabletas pueden ser no recubiertas o recubiertas por medio de técnicas conocidas para demorar la desintegración o absorción en el tracto intestinal y de tal manera brindar una acción sostenida por un período mayor. Así, por ejemplo, se pueden emplear materiales de retardación tales como el gliceril monoestearato y el gliceril distearato. También se pueden recubrir con las técnicas descritas en las patentes de EE.UU. Nos. 4,256,108; 4,166,452 y 4,265,874 para formar tabletas osmóticas terapéuticas para liberación controlada.

[0267] Las formulaciones para uso oral también se pueden presentar como cápsulas duras de gelatina donde el ingrediente activo se mezcla con un diluyente sólido inerte, por

ejemplo, carbonato de calcio, fosfato de calcio o caolin, o como cápsulas suaves de gelatina donde el ingrediente activo se mezcla con agua o un medio aceitoso, por ejemplo, aceite de maní, parafina líquida o aceite de oliva.

[0268] Las suspensiones acuosas contienen los materiales activos de la mezcla con excipientes apropiados para la fabricación de suspensiones acuosas. Dichos excipientes son agentes de suspensión, por ejemplo, carboximetilcelulosa de sodio, metilcelulosa, hidroxi-propilmetilcelulosa, alginato de sodio, polivinil-pirrolidono, goma tragacant y goma arábica; los agentes dispersantes o humectantes pueden ser fosfátidos que ocurren de forma natural, por ejemplo lecitina, o productos de condensación de un óxido de alquileno con ácido grasos, por ejemplo estearato de polioxi-etileno, o productos de condensación de oxido de etileno con alcoholes alifáticos con cadenas largas, por ejemplo heptadecaetilenooxicetanol, o productos de condensación de óxido de etileno con esteres parciales derivados de ácido grasos y anhídridos de hexitol tales como monoleato de sorbitan polioxietilénico, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácido grasos y anhídrido de hexitol, derivados de ácidos grasos, por ejemplo monoleato de sorbitan polietilénico. La suspensión acuosa también puede contener uno o más preservantes, por ejemplo, etilo, o n-propilo, p-hidroxibesoato, o uno o más agentes de coloración, o uno o más agentes saborizantes, y uno o más agentes edulcorantes, tales como sucrosa o sacarina.

[0269] Las suspensiones aceitosas se pueden formular por la suspensión de un ingrediente activo en aceite vegetal, como por ejemplo aceite de arachis, aceite de oliva, aceite de sésamo o aceite de coco, o un aceite mineral como parafina líquida. La suspensión aceitosa puede contener un agente espesante, como por ejemplo cera de abejas, parafina sólida o alcohol cetílico. Los agentes edulcorantes como los mencionados anteriormente y los agentes saborizantes se pueden agregar para lograr un preparación oral apetecible.

[0270] Los polvos y gránulos dispersables apropiados para la preparación de una suspensión acuosa por la adición de agua en una mezcla con un agente dispersante o humectante, agente de suspensión o uno o más preservantes, dan como resultado el ingrediente activo. Con anterioridad se han dado ejemplos de agentes dispersantes o humectantes y agentes de suspensión apropiados. También pueden estar presentes otros excipientes, como por ejemplo edulcorantes, saborizantes y colorantes.

[0271] Las composiciones farmacéuticas de la invención también pueden ser en la forma de emulsiones de aceite en agua. La fase de aceite puede ser un aceite vegetal, como por ejemplo aceite de oliva o de arachis, o un aceite mineral, como por ejemplo, parafina en forma líquida o una mezcla de éstos. Los agentes emulsificantes apropiados pueden ser gomas que ocurren de forma natural, como por ejemplo, goma arábiga o tragacanth, fosfátidos que ocurren de forma natural, como por ejemplo, frijol de soya, lecitina y esteres o esteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monoleato de sorbitan, y productos de condensación de dichos ésteres parciales con óxido de etileno, por ejemplo, monoleato de sorbitan polioxietilénico. La emulsión también puede contener agentes edulcorantes y saborizantes.

[0272] Los jarabes y los elixires se pueden formular con agentes edulcorantes, por ejemplo glicerol, glicol propilénico, sorbitol o sucrosa. Dichas formulaciones también pueden contener demulcent, un agente preservante, saborizante y colorante.

[0273] Las composiciones farmacéuticas pueden ser en forma de suspensiones acuosas o aceitosas estériles inyectables. La suspensión puede ser formulada de acuerdo con la ciencia conocida con la utilización de los agentes dispersantes o humectantes y de suspensión que ya se han mencionado. La preparación estéril inyectable también puede ser una solución estéril inyectable o suspensión en un diluyente o solvente aceptable para administración parenteral, por ejemplo, una solución en 1,3-butano diol. Entre los vehículos o solventes aceptables que se pueden utilizar están el agua, solución de Ringer y cloruro de sodio isotónico. Además, los aceites fijos estériles se utilizan de forma convencional como solventes o medios de suspensión. Para este fin se puede utilizar cualquier aceite fijo suave, incluyendo mono o diglicéridos sintéticos. Además, en la preparación de las soluciones inyectables se pueden utilizar ácidos grasos como ácido oléico.

[0274] Las composiciones farmacéuticas también se pueden administrar en la forma de supositorios para la administración rectal de la droga. Estas composiciones se pueden preparar por la mezcla de la droga con excipiente apropiado que no produzca irritación con un sólido a temperaturas ordinarias pero líquido a la temperatura del recto y que por tanto se disuelva en el recto para liberar la droga.

[0275] Para uso tópico se emplean cremas, ungüentos, jaleas, soluciones o suspensiones, etc., que contengan los compuestos de la invención. Como se emplean aquí, en las aplicaciones tópicas se incluyen los lavados bucales y las gárgaras.

[0276] Las composiciones farmacéuticas y métodos de la invención también pueden comprender otros compuestos activos terapéuticos, como se nota aquí, útiles en el tratamiento de la diabetes tipo II, obesidad, hiperglicemia, intolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, hipercolesterolemia, hipertensión, hiperliproteinemia, hiperlipidemia, hipertrigliceridemia, dislipidemia, síndrome metabólico, síndrome X, enfermedades cardiovasculares, aterosclerosis, enfermedades del riñón, cetoacidosis, desordenes trombóticos, nefropatía, neuropatía diabética, retinopatía diabética, disfunción sexual, dermatopatía, dispepsia, hipoglicemia, cáncer o edema.

5.2.4 Métodos de Uso

[0277] En otro aspecto, la invención brinda métodos para el tratamiento o la prevención de enfermedades o condiciones seleccionadas de un grupo consistente en diabetes tipo II, obesidad, hiperglicemia, intolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, hipercolesterolemia, hipertensión, hiperliproteinemia, hiperlipidemia, hipertrigliceridemia, dislipidemia, síndrome metabólico, síndrome X, enfermedades cardiovasculares, aterosclerosis, enfermedades del riñón, cetoacidosis, desordenes trombóticos, nefropatía, neuropatía diabética, retinopatía diabética, disfunción sexual, dermatopatía, dispepsia, hipoglicemia, cáncer y edema, que comprenden la administración de una cantidad terapéuticamente efectiva del compuesto o composición de la invención al sujeto que la necesite.

[0278] En otra materialización, la enfermedad o condición es diabetes tipo II.

[0279] En otro aspecto, la presente invención brinda un método para el tratamiento de una enfermedad o condición que responde a la modulación de GPR40. que comprende la administración de una cantidad terapéuticamente efectiva del compuesto o composición de la invención a un sujeto que la necesite.

[0280] En algunas materializaciones, la enfermedad o condición se selecciona de un grupo consistente en diabetes tipo II, obesidad, hiperglicemia, intolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, hipercolesterolemia, hipertensión, hiperliproteinemia, hiperlipidemia, hipertrigliceridemia, dislipidemia, síndrome metabólico, síndrome X, enfermedades cardiovasculares, aterosclerosis, enfermedades del riñón, cetoacidosis, desordenes trombóticos, nefropatía, neuropatía diabética, retinopatía diabética, disfunción sexual, dermatopatía, dispepsia, hipoglicemia, cáncer y edema.

[0281] En ciertas materializaciones, la enfermedad o condición es diabetes tipo II.

[0282] En algunas materializaciones, la enfermedad o condición es obesidad.

[0283] En algunas materializaciones, la enfermedad o condición es hipertensión.

[0284] En algunas materializaciones, la administración de los compuestos o composiciones de la invención se efectúa por vía oral.

[0285] En otras materializaciones, el compuesto o composiciones se administran por vía parenteral.

[0286] En otras materializaciones, el compuesto o composición se administra en combinación con un segundo agente terapéutico.

[0287] En otras materializaciones, el segundo agente terapéutico es un agente sensibilizante de la insulina, como por ejemplo, metformina o un tiazolidinedionas.

[0288] En otro aspecto, la invención brinda métodos para el tratamiento o prevención de enfermedades o desórdenes que responden a la modulación de GPR40 que comprenden la administración de una cantidad terapéuticamente efectiva de uno de los compuestos o composiciones objeto de la invención a un sujeto aquejado con dicha enfermedad o desorden.

[0289] Aún en otro aspecto, la invención brinda métodos de tratamiento o prevención de una condición, enfermedad o desorden mediado por GPR40 que comprende la administración de una cantidad efectiva terapéuticamente de una cantidad de uno o más compuestos o composiciones objeto de la invención a un sujeto aquejado con dicha condición, enfermedad o desorden.

[0290] Aún en otro aspecto, la invención brinda métodos de modulación de GPR40 que comprenden el poner en contacto una célula con uno o más de los compuestos o composiciones objeto de la invención.

[0292] En ciertas materializaciones, se puede hacer que una célula en contacto exprese o sobre exprese GPR40, por ejemplo, al expresar GPR40 a partir de ácido nucleico heterólogo introducido en una célula, o como otro ejemplo, por sobre regulación de la expresión de GPR40 a partir de ácido nucleico endógeno de una célula.

[0293] Dependiendo de la enfermedad objeto del tratamiento y de la condición del sujeto, los compuestos de la invención se pueden administrar por vía oral o parenteral (e.g., intramuscular, intraperitonal, intravenosa, ICV (intracerebroventricular), inyección o infusión intracisternal, Inyección subcutánea o implante), inhalación, nasal, vaginal, rectal, sublingual, o tópica (e.g., transdermal, local) y se pueden formular, por sí mismos o en conjunto, en formulaciones de unidades de dosis que contienen portadores no tóxicos

farmaceuticamente aceptables, auxiliares y vehículos apropiados para cada vía de administración. La invención también contempla la administración de compuestos en un formulación depot en la que el ingrediente activo es liberado sobre un período definido de tiempo.

[0294] En el tratamiento o la prevención de diabetes tipo II, obesidad, hiperglicemia, intolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, hipercolesterolemia, hipertensión, hiperliproteinemia, hiperlipidemia, hipertrigliceridemia, dislipidemia, síndrome metabólico, síndrome X, enfermedades cardiovasculares, aterosclerosis, enfermedades del riñón, cetoacidosis, desordenes trombóticos, nefropatía, neuropatía diabética, retinopatía diabética, disfunción sexual, dermatopatía, dispepsia, hipoglicemia, cáncer y edema u otros desórdenes asociados con el GPR40, un nivel de dosis apropiado generalmente será de entre 0.001 y 100 mg al día por kg de peso del paciente que puede ser administrado dosis únicas o múltiples. Preferentemente el nivel de dosis será de entre 0.01 y 25 mg/kg al día; de manera más preferente de entre 0.05 a 10 mg/kg al día. Un nivel apropiado puede ser de entre 0.01 y 25 mg/kg al día, aproximadamente 0.05 a 10 mg/kg al día, o aproximadamente 0.1 a 5 mg/kg al día. Para administración oral, las composiciones preferiblemente deben ser en forma de tabletas que contengan de 1.0 a 1000 miligramos de ingrediente activo, particularmente 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, y 1000.0 miligramos de ingrediente activo para el ajuste sintomático de las dosis dada al paciente bajo tratamiento. Los compuestos pueden ser administrados en un régimen de 1 a 4 veces por día, preferiblemente una o dos veces por día.

[0295] Se entenderá, sin embargo, que la dosis específica y su frecuencia de administración para un paciente en particular se puede variar y dependerá de diversos factores incluyendo la actividad específica del compuesto utilizado, la estabilidad metabólica y duración de la acción del compuesto, la edad, peso corporal, salud en general, sexo, dieta, modo y tiempo de administración, tasa de excreción, combinación de drogas, la severidad de una condición en particular, y el que el receptor se encuentre bajo terapia.

[0296] Los compuestos de la invención se pueden combinar o usarse en combinación con otros agentes útiles en el tratamiento, prevención, supresión o mejoría de las enfermedades o condiciones para las que los compuestos son útiles, incluyendo diabetes tipo II, obesidad, hiperglicemia, intolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, hipercolesterolemia, hipertensión, hiperliproteinemia, hiperlipidemia,

hipertrigliceridemia, dislipidemia, síndrome metabólico, síndrome X, enfermedades cardiovasculares, aterosclerosis, enfermedades del riñón, cetoacidosis, desordenes trombóticos, nefropatía, neuropatía diabética, retinopatía diabética, disfunción sexual, dermatopatía, dispepsia, hipoglicemia, cáncer y edema. Dichos agentes, o drogas, se pueden administrar por la vía y en la cantidad normalmente usadas, ya sea de forma simultánea o secuencial con los compuestos de la invención. Cuando un compuesto de la invención es usado al mismo tiempo que una o más drogas, se prefiere una composición farmacéutica que contenga dichas otras drogas además del compuesto de la invención. De tal manera que las composiciones farmacéuticas de la invención incluyen aquellas que también contienen uno o más ingredientes activos o agentes terapéuticos, además de un compuesto de la invención.

[0297] Algunos ejemplos de otros agentes terapéuticos que se pueden combinar con un compuesto de la invención, ya sea para su administración por separado o en las mismas composiciones farmacéuticas, incluyen, sin estar limitados a: (a) agentes para reducir el colesterol tales como inhibidores de la reductasa HMG- CoA (e.g., lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin y otras estatinas), agentes secuestrantes del ácido bílico (e.g., colestiramina y colestipol), vitamina B3 también conocida como ácido nicotínico, o niacina), vitamina B6 (piridoxina), vitamina B12 (cianocobalamina), derivados del ácido fíbrico (e.g., gemfibrocil, clofibrato, fenofibrato y benzafibrato), probucol, nitroglicerina, e inhibidores de la absorción del colesterol (e.g., beta- sitosterol e inhibidores de acylCoA-colesterol aciltransferasa (ACAT) tales como melinamida), inhibidores de HMG-CoA sintasa, inhibidores de la escualeno-epoxidasa e inhibidores de la escualeno-sintasa; (b) agentes antitrombóticos, tales como agentes trombolíticos (e.g., estreptoquinasa, alteplasa, anistreplasa y reteplasa), heparina, hirudina y derivados de warfarina, bloqueadores β- (e.g., atenolol), antagonistas β-adrenérgica (e.g., isoproterenol), inhibidores ACE y vasodilatores (e.g., nitroprusiato sódico, hidrocloruro de nicardipina, nitroglicerina y enalaprilat); y (c) agentes anti-diabéticos tales como insulina y miméticos de insulina, sulfonilureas (e.g., glíburida, meglinatida), biguanides, e.g., metformina (Glucophage®), inhibidores de α-glucosidasa (acarbosa), sensibilizantes de la insulina, e.g., compuestos de tiazolidinona, rosiglitazona (Avandia®), troglitazona (Rezulin®), ciglitazona, pioglitazona (Actos®) y englitazona.

[0298] La razón entre el peso del compuesto de la invención y el segundo ingrediente puede variarse y dependerá de la dosis efectiva de cada ingrediente. Generalmente se

empleará una dosis efectiva de cada uno. La combinación de un compuesto de la invención y otros ingredientes activos generalmente estará en el rango antes mencionado, pero en cada caso, se deberá usar la dosis efectiva de cada ingrediente activo.

[0299] En otro aspecto, la presente invención brinda un método para la modulación de la insulina circulante en un sujeto, que comprende la administración de un compuesto o de una composición de la invención.

[0300] En algunas materializaciones se incrementa la concentración de insulina.

[0301] En algunas materializaciones se disminuye la concentración de insulina.

[0302] En ciertas materializaciones un compuesto, o composición comprende un compuesto de acuerdo con la fórmula II donde R^{22} contiene un alquiloilo que contiene Si, y donde R^{21}, L, Y, y W pueden ser utilizados de la forma en que se definieron anteriormente en la fórmula II.

[0303] En algunas materializaciones el átomo de Si es sustituido con más de tres grupos de alquilo.

[0304] En algunas materializaciones, R^{22} es $-C{\equiv}C-Si(CH_3)_3$.

[0305] Los ejemplos siguientes se ofrecen a manera de ilustración y no debe entenderse que limitan el ámbito de la invención. Los expertos en la materia fácilmente reconocerán una variedad de parámetros no cruciales que se pueden modificar para producir resultados esencialmente similares.

6. EJEMPLOS

6.1 Ejemplo 1

[0306] Este ejemplo ilustra la preparación de éster metílico de ácido *(3S)*-3-(4-Hidroxi-fenil)-hex- 4-inóico.

Esquema 1.1

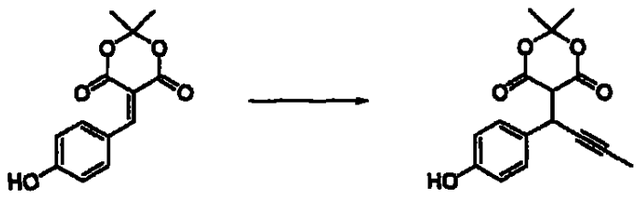


1.1

[0307] **5-(4-Hidroxi-benzolideno)-2,2-dimetilo-[1,3]dioxan-4,6-diono (1.1).**

La condensación con el ácido de Meldrum se lleva a cabo de acuerdo con el método de Bigi *et. al.* (2001) *Tetr. Lett.* 42: 5203-5205. Un matraz en forma de pera 2L se llenó con 4-hidroxibenzaldehido (50 g, 409 mmol) y agua (400 mL). El frasco se colocó en un baño de agua a 75 °C y se agregó el ácido de Meldrum (62 g, 430 mmol) como mezcla en 400 mL de agua. La mezcla de la reacción se agitó por 2h y luego se enfrió en un baño de hielo por 2 horas. El producto se recogió por métodos de filtración y luego se enjuagó con agua fría. Después de secarse exhaustivamente, se obtuvieron 95 g (94%) de aducto **1.1** como un fino polvo amarillo. ^{1}H NMR(500MHz)(DMSO- d_6) δ 9.75 (br s, ^{1}H); 8.27 (s, 1H); 8.24 (d, 2H, J=10 Hz); 6.98 (d, 2H, J=10 Hz);.1.76 (s, 6H). MS ESI (pos.) m/e: 519.0 (2M + Na).

Esquema 1.2



1.1 **1.2**

[0308] (+/-)-5-[1-(4-Hidroxi-fenil)-but-2-inil]-2,2-dimetil-[1,3]dioxan-4,6-diono (1.2). Un matraz de cuello-3 3L secado al horno se equipó con un agitador mecánico, entrada de nitrógeno, salida de nitrógeno y se colocó en agua a temperatura ambiente. Luego de purgarse con nitrógeno por 20 minutos, se agregó una solución de bromuro de 1-propinilomagnesio en THF (0.5 N, 600 mL) por medio de una cánula. En otro matraz RB de 500 ml secado al horno y enjuagado con nitrógeno, se disolvieron (35 g, 142 mmol) del compuesto 1.1 en THF anhidro (350 mL) con calentamiento suave. Luego, la solución de 1.1 se agregó en un lapso de 15 minutos. Durante el transcurso de la adición, la mezcla de la reacción cambió a una suspensión espesa de color amarillo. Luego de que la adición se completara, la mezcla de la reacción se agitó por 15 minutos y luego se aplacó con NH_4Cl acuoso (0.6N, 750 mL) y se diluyó con hexanos (800 mL). Las capas se separaron y se descartó la capa orgánica. La capa acuosa se acidificó a un pH ~2 con $KHSO_4$ acuoso saturado y se extrajo con acetato de etilo (2 x 400 mL). Los extractos combinados se lavaron con salmuera saturada, se secaron sobre $MgSO_4$, se filtraron y se concentraron hasta lograr sólido amarillo claro (37 g, 91%). ^{1}H NMR(500MHz)(acetona-d_6) δ 8.26 (s, 1H);

7.39 (d, 2H, *J*=8.5 Hz); 6.76 (d, 2H, *J*=8.4 Hz); 4.73 (br s, 1H); 4.46 (d, 1H, *J*=2.4 Hz); 1.82 (s, 3H); 1.81 (s, 3H); 1.64 (s, 3H). MS ESI (pos.) m/e: 599.0 (2M + Na).

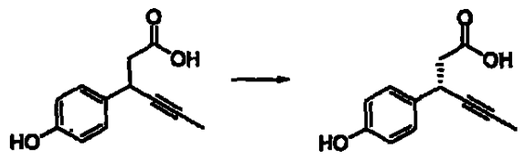
Esquema 1.3



1.2 1.3

[0309] **Ácido (+/-)-3-(4-Hidroxi-fenil)-hex-4-inóico (1.3).** Se cargó un matraz 1L RB con el compuesto **1.2** (37 g), cetona dietílica (160 mL), y agua (80 mL). La suspensión se calentó al reflujo por 48h. Después de enfriarse, se saturó y se separó la capa acuosa con $NaCl_{(s)}$. Se secó la capa orgánica sobre $MgSO_4$, se filtró, y se concentró hasta lograr un aceite de color marrón claro que fue cristalizado a partir de acetato de etilo:hexanos caliente (1:2). Luego de recoger y secar, se obtuvo el producto como un polvo blanco opaco (20.3 g, 77%).^{1}H NMR(SOOMHZ)(DMSO-d_6) δ 12.2 (s, 1H); 9.27 (s, 1H); 7.12 (d, 2H, *J*=8.5 Hz); 6.67 (d, 2H, *J*=8.6 Hz); 3.87 (m, 1H); 2.54 (m, 2H); 1.82 (d, 3H, *J*=2.4 Hz). MS ESI (pos.) m/e: 205.1 (M + H); 227.1 (M + Na).

Esquema 1.4

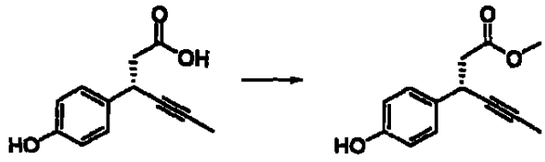


1.3 1.4

[0310] **Ácido (3S)-3-(4-Hidroxi-fenilo)-hex-4-inóico (1.4).** Se cargó un matraz 5L RB con el compuesto 1.3 (66.4 g, 325 mmol) y 2-propanol (1 L) y luego se calentó a 70°C. Se disolvió (*1S, 2R*)- 1-amino-2-indanol (46.1 g, 309 mmol) en 2-propanol (1 L) por medio de un calentamiento leve. La solución de amino se agregó al ácido carboxílico disuelto y se dejó la solución resultante a temperatura ambiente. Luego de 16h, los cristales se filtraron y se secaron. La sal fue se suspendió nuevamente en 2 L de 2-propanol y se disolvió por

medio de calentamiento al reflujo. Tras dejar que se secara a temperatura ambiente, la sal se recogió luego de 16h. Una pequeña muestra de la sal se descompuso con ácido acuoso y el ácido carboxílico libre se analizó con HPLC quiral (columna Daicel ChiralPAK AD-H, eluyente: 0.1% TFA en 90:10 hexanos:2-propanol) y se encontró que contenía 75% ee. La sal se suspendió nuevamente en 1.5 L de 2-propanol y se disolvió por medio del calentamiento al reflujo. Luego de dejar que se enfriara a temperatura ambiente, la sal se recogió después de 16h. Se encontró que este material contenía 96% ee de HPLC quiral. Dicho material se suspendió en acetato de etilo (300 mL) y agua (100 mL). El $KHSO_4$ acuoso saturado (100 mL) se agregó mezclándose vigorosamente. Luego se obtuvieron dos capas claras, las capas se separaron y la capa acuosa se extrajo con acetato de etilo (100 mL). Los extractos combinados se lavaron con salmuera saturada, se secaron sobre $MgSO_4$, se filtraron, y se concentraron hasta lograr un aceite de color amarillo claro que se cristalizó y se secó *in vacuo*. El compuesto **1.4** se obtuvo como un sólido blanco opaco (23.5 g, 35%).

Esquema 1.5



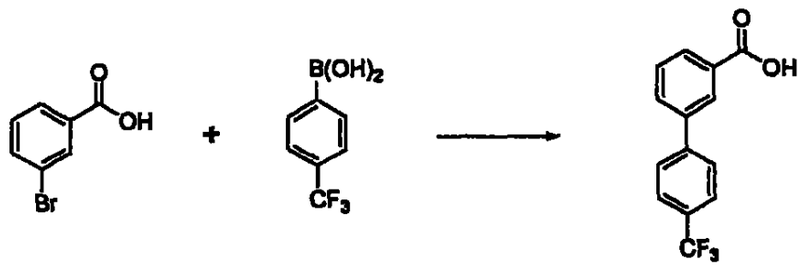
1.4 1

[0311] Éster metílico de ácido (3S)-3-(4-Hidroxi-fenil)-hex-4-inóico (1). El fenol **1.4** (23.5 g, 115 mmol) se disolvió en acetona (230 niL) y se trató con $KHCO_3$ (11.5 g, 115 mmol). Luego de 15 minutos, se agregó yoduro de metilo (5 mL, 80 mmol), y se agitó la reacción a 40 °C por 14h. Se agregó una porción adicional de yoduro de metilo (3 mL, 48 mmol) y se siguió calentando por 24h. Se removieron las sales de potasio por medio de filtración y se lavó con abundante acetona. El resultado de la filtración se concentró hasta conseguir un aceite que se purificó por filtración a través de un tapón de 1 cm de gel de sílice. La elución con 2.5% MeOH en diclorometano seguida de concentración brindó fenol 1 (21.5 g, 85%) como un aceite de color amarillo claro. ^{1}H NMR(500MHz)(acetona-d_6) δ 8.2 (br s, 1H); 7.20 (d, 2H, J=9.5 Hz); 6.77 (d, 2H, J=9.0 Hz); 3.98 (m, 1H); 3.60 (s, 3H); 2.65 (m, 2H); 1.78 (d, 3H, J=2.5 Hz). MS ESI (pos.) m/e: 219.1 (M + H); 241.1 (M + Na).

6.2 Ejemplo 2

[0312] Este ejemplo ilustra la preparación de sal sódica de ácido *(3S)*-3-[4-(4'-Trifluorometil-bifenil-3-ilmetoxi)-fenil]-hex-4-inóico.

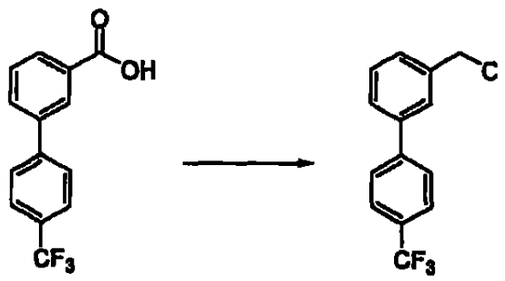
Esquema 2.1



2.1

[0313] **Ácido 3-(4-Trifluorometilfenil)-benzoico (2.1).** El acoplamiento Suzuki se llevó a cabo de acuerdo con el método de Dyer *et al.* (2001) *Tetrahedron Letters* 42: 1765-1767. El ácido 4-(Trifluorometil)fenilborónico (15g, 78.7 mmol) disponible comercialmente y el ácido 3-bromobenzoico (15. Ig, 75 mmol) se suspendieron en 2-propanol:agua (1:4, 72 mL). 10% Pd/C (1.5g) seguida de Na_2CO_3 acuoso (39 mL, 20% por peso). La mezcla resultante se calentó a 70°C por 4 horas. El precipitado se filtró y se lavó con 20% de solución acuosa Na_2CO_3. El filtrado se diluyó con agua y se acidificó a un pH=2. El sólido blanco se filtró y se secó *in vacuo*. El material crudo **(2.1)** (19.69g) se utilizó en el siguiente paso sin ninguna purificación posterior.

Esquema 2.2

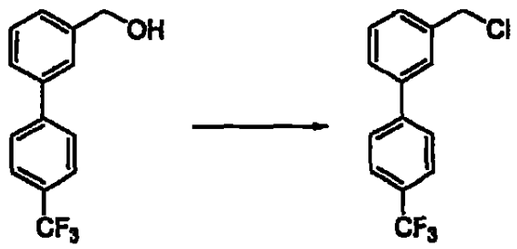


2.1 **2.2**

[0314] **Alcohol 3-(4-Trifluorometilfenilo)-bencílico (2.2).** El ácido carboxílico **2.1** (13.3g, 50mmol) en THF anhidro (10OmL) se agregó gota a gota a $LiAlH_4$ (2.9g, 75 mmol) en

THF anhidro (150mL) a 0°C por más de 30 minutos. La mezcla resultante se calentó lentamente a temperatura ambiente y se agitó por 4 horas. La reacción se aplacó lentamente con agua (2.9mL) a 0°C, 15% NaOH de solución acuosa (2.9mL) y otra porción de agua (8.7mL). La mezcla se secó sobre $Na2SO_4$ y se concentró para dar un sólido blanco (11.9g). El producto crudo **(2.2)** se uso en el siguiente paso sin ninguna purificación posterior.

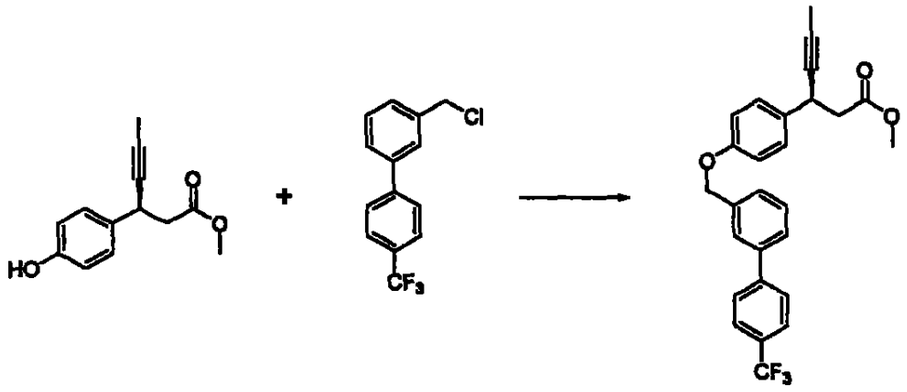
Esquema 2.3



2.2 **2.3**

[0315] **Cloruro de 3-(4-Trifluorometilfenil)-bencilo (2.3).** El alcohol 2.2 (15g, 59.5mmol) se disolvió en diclorometano anhidro (100mL). El cloruro de tionil (10mL) se agregó lentamente gota a gota a la solución anterior. La mezcla resultante se agitó a temperatura ambiente por 24 horas. El solvente orgánico se removió bajo *vacuo*. Luego el residuo se purificó por medio de cromatografía flash (SiO_2 gel 60, eluído con 20% DCM en hexanos). Las fracciones que contienen el producto 2.3 deseado se combinaron y se concentraron hasta llegar a un sólido blanco (14.0 g). ^1H NMR(400MHz) ($CDCl_3$) δ 7.73 (4H5 s); 7.65 (1H, s); 7.58 (1H, s); 7.52-7.28 (2H, m); 4.69 (2H, s).

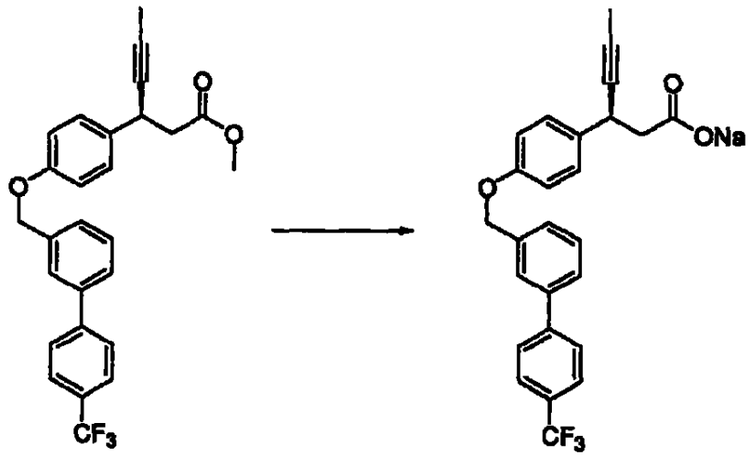
Esquema 2.4



1 2.3 2.4

[0316] **Éster metílico de ácido *(3S)*-3-[4-(4'-Trifluorometil-bifenil-3-ilmetoxi)-fenilo]-hex-4-inóico (2.4).** Se disolvieron cloruro de bencilo 2.3 (28.0 g, 103 mmol) y fenol 1 (21.5 g, 98 mmol) en acetona (150 mL) y se trataron con Cs_2CO_3 (39.9 g, 122 mmol). La reacción se agitó a 50°C por 16 h y luego se filtró y se concentró hasta lograr un aceite amarillo pálido, que se purificó por columna cromatográfica (gel de sílice, 33% a 66% diclorometano en hexanos). El eluyente que contiene el compuesto 2.4 se concentró hasta lograr un aceite incoloro (40.0 g, 92%).

Esquema 2.4

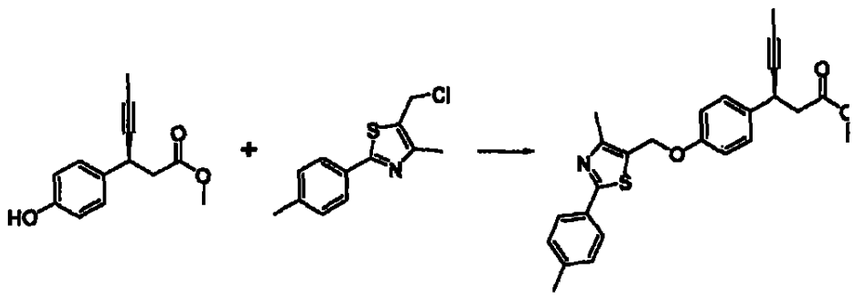


2.4 2

[0317] Sal sódica de ácido *(3S)*-3-[4-(4'-Trifluorometil-bifenil-3-ilmetoxi)-fenilo]-hex-4- inóico (2). Se disolvió éster metílico **2.4** en éter dietílico (50 mL). Se agregó sodio trimetilsilanolato en una porción y la mezcla de la reacción se agitó por 48h. El precipitado se recogió por filtración y se re-cristalizó a partir de acetato de etilo:hexanos. Luego de secarse en *vacuo*, la sal de sodio deseada se obtuvo como un polvo blanco (1.3 g). ^{1}H NMR (500MHz) (CD_3OD) δ 7.82 (d, 2H, *J*=8.5 Hz); 7.75-7.73 (m, 3H); 7.62 (m, 1H); 7.32 (d, 2H, *J*=8.5 Hz); 6.94 (d, 2H, *J*=8.5 Hz); 5.15 (s, 2H); 4.03 (m, 1H); 2.52 (dd, 1H, *J*=8.2, 14.5 Hz); 2.45 (dd, 1H, *J*-7.0, 14.0 Hz); 1.79 (d, 3H, *J*=2.5 Hz).

6.3 Ejemplo 3

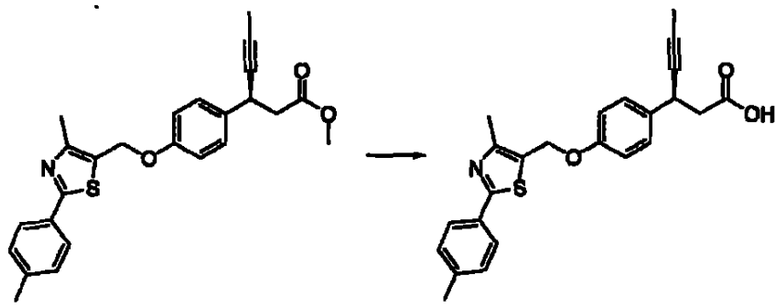
Esquema 3.1



1 3.1 3.2

[0318] Éster metílico de ácido *(3S)*-3-[4-(4-Metil-2-p-tolil-tiazol-5-ilmetoxi)-fenil]-hex-4-inóico (3.2). El compuesto **3.1** se preparó de acuerdo con el método descrito en el Ejemplo 2 a partir de ácido 4-metil-2-(4-metilfenil)-1,3- tiazol-5-carboxílico disponible comercialmente. El cloruro **3.1** (250 mg, 1.1 mmol) y el fenol **1** (230 mg, 1.1 mmol) se disolvieron en DMF anhidro (5 mL). Luego se agregó Cs_2CO_3 (650 mg, 2.2 mmol) finamente pulverizado y la mezcla de la reacción se agitó a temperatura ambiente por 14 h. La reacción se vertió en agua y se extrajo con acetato de etilo (15mL x 3). Las fases orgánicas se combinaron, se secaron sobre Na_2SO_4, y se concentraron *in vacuo* hasta lograr un residuo que se utilizó en el siguiente paso sin ninguna purificación posterior.

Esquema 3.1



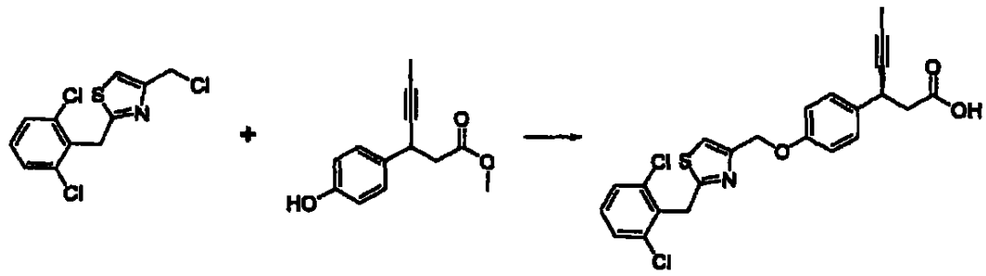
3.2 3

[0319] **Ácido *(S)*-3-[4-(4-Metil-2-p-tolil-tiazole-5-ilmetoxi)-fenilo]-hex-4-inóico (3).** El éster **3.2** se disolvió en una solución de THF/MeOH/10% $NaOH_{(aq)}$ (1:1:1) (15mL). Luego de agitarse a temperatura ambiente por más de 30 minutos, la mezcla se acidificó con 1N HCl (aq.) hasta un pH = 4. La fase acuosa se extrajo con acetato de etilo y las fases orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron. El residuo crudo se trituró con 20% de acetato de etilo en hexanos (20 mL). Se filtró el precipitado y el compuesto 3 se obtuvo como un polvo de color amarillo pálido (315 mg, 0.8 mmol). MS ESI m/e: 406 (M-H). ^1H NMR (500MHz) ($CDCl_3$) δ 7.86 (2H, d, *J*=7.5 Hz); 7.36 (2H, d, *J*=9 Hz); 7.26 (2H5 d, *J*=8 Hz); 6.96 (2H, d, *J*=8.5 Hz); 5.18 (2H, s); 4.1 (1H, m); 2.77 (2H, m); 2.52 (3H, s); 2.42 (3H, s); 1.86 (3H, s).

6.4 Ejemplo 4

[0320] Este ejemplo ilustra la preparación de ácido 3-{4-[2-(2,6-Dicloro-benzol)-tiazol-4-ilmetoxi]-fenil}-hex-4-inóico.

Esquema 4.1



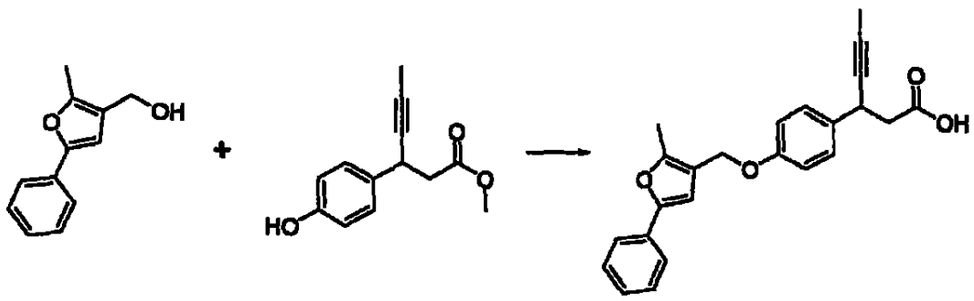
4.1 1.3 4

[0321] **Ácido 3-{4-[2-(2,6-Dicloro-benzol)-tiazol-4-ilmetoxi]-fenil}-hex-4-inóico (4).** Se llevó a cabo la preparación de tiazol **4.1** de acuerdo con el método de Bordwell *et al.* (1990) *J. Amer. Chem. Soc.* 112: 792-797. El compuesto 4.1 (58 mg, 0.2 mmol) y fenol 1 (43.6 nig, 0.2 mmol) se disolvieron en DMF anhidro (2 mL) y se trataron con Cs_2CO_3 molido finamente (65 mg, 0.22 mmol). La mezcla de la reacción se agitó a temperatura ambiente por 14 horas. La reacción se vertió en agua y se extrajo con acetato de etilo (10 mL x 3). Las fases orgánicas combinas se secaron sobre Na_2SO_4, se concentraron *in vacuo* y el residuo se disolvió en una solución de THF/MeOH/10% $NaOH_{(aq)}$ (1:1:1) (6 mL). La mezcla resultante se agitó a temperatura ambiente por 30 minutos. La mezcla se acidificó con 1N $HCl_{(aq.)}$ hasta lograr un pH = 4. La fase acuosa se extrajo con acetato de etilo. Las fases orgánicas se combinaron, se secaron sobre Na2SO4, y se concentraron *in vacuo*. El residuo crudo se trituró con 20% de acetato de etilo en hexanos (10 mL). Se filtró el precipitado y el ácido **4** se obtuvo como un polvo amarillo pálido (55 mg, 0.12 mmol). MS ESI m/e: 460 (M-H). ^{1}H NMR (400MHz) ($CDCl_3$) δ 7.40-7.19 (6H, m); 6.94-6.79 (2H, m); 5.18 (2H, s); 4.73 (2H, s); 4.1-4.06 (1H, m); 2.77 (2H, m); 1.85 (3H, s).

6.5 Ejemplo 5

[0322] Este ejemplo ilustra la preparación de ácido 3-[4-(2-Metil-5-fenilo- furan-3-ilmetoxi)-fenilo]-hex-4-inóico.

Esquema 5.1



5.1 **1.3** **5**

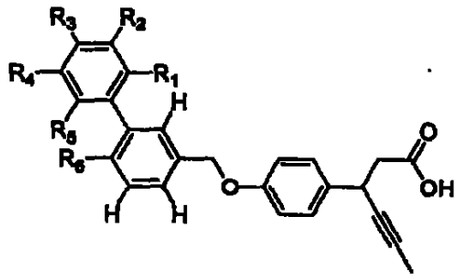
[0323] **Ácido 3-[4-(2-Metil-5-fenilo-furan-3-ilmetoxi)-fenilo]-hex-4-inóico (5).** La reacción Mitsunobu se llevó a cabo de acuerdo con el método de Mikó *et al.* (2003) *J. Med. Chem.*46: 1523-1530. Se agregaron **5.1** (37.6 mg, 0.2 mmol), PPh_3 (52 mg, 0.2 mmol) y fenol 1.3 (43.6 mg, 0.2 mmol), que están disponibles comercialmente, al THF anhidro (3 mL). Luego, gota a gota, se agregó DEAD (45 µL, 0.22 mmol). La mezcla de la reacción se agitó a temperatura ambiente por más de 14 horas. Luego se extrajo la reacción con

acetato de etilo (10mL x 3). Las fases orgánicas se combinaron, se secaron sobre Na_2SO_4, y se concentraron *in vacuo*. El residuo resultante se disolvió en una solución de THF/MeOH/10% $NaOH_{(aq)}$ (1:1:1) (6 mL). La mezcla resultante se agitó a temperatura ambiente por 30 minutos. La mezcla se acidificó con 1N $HCl_{(aq.)}$ hasta lograr un pH = 4. La fase acuosa se extrajo con acetato de etilo. Las fases orgánicas se combinaron, se secaron sobre Na_2SO_4, y se concentraron *in vacuo*. El producto crudo se trituró en 20% de acetato de etilo en hexanos (10 mL). Se filtró el precipitado y se obtuvo el compuesto **5** como un polvo blanco (35 mg, 0.9 mmol). MS ESI m/e: 375 (M-H). ^1H NMR (500MHz) ($CDCl_3$) δ 7.65 (2H, d, J=8 Hz); 7.40-7.24 (5H, m); 6.96 (2H, d, J=8.5 Hz); 6.68 (1H, s); 4.88 (2H, s); 4.1 (1H, s); 2.77 (2H, m); 2.4 (3H, s); 1.86 (3H, s).

6.6 Ejemplo 6

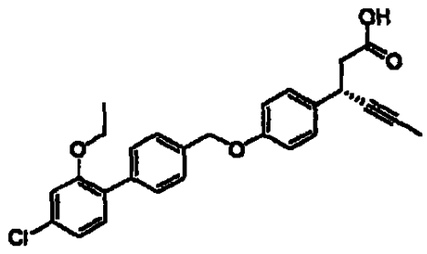
[0324] Los compuestos siguientes se prepararon con métodos similares a los descritos en el Ejemplo 2.

TABLA 1



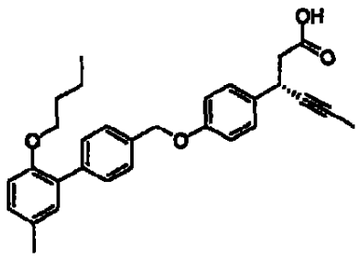
Compuesto	R_1	R_2	R_3	R_4	R_5	R_6
6.1	H	H	H	H	H	H
6.2	OC_2H_5	H	H	H	H	H
6.3	H	H	OC_2H_5	H	H	H
6.4	H	-OCH_2O-		H	H	H
6.5	H	H	CF_3	H	H	H
6.6	H	CN	H	H	H	H
6.7	H	H	CN	H	H	H
6.8	CF_3	H	H	H	H	H
6.9	H	CF_3	H	H	H	H
6.10	H	H	OCF_3	H	H	H
6.11	H	H	CF_3	H	H	OC_2H_5
6.12	OCH_3	H	CF_3	H	H	H

[0325] Los datos NMR y MS para los compuestos **6.13** y **6.14** son de la forma siguiente:



6.13

[0326] ^1H NMR (400MHz) ($(CD_3)_2SO$) δ 12.4 (s, 1H), 7.52 (d, 2H, J= 8.1 Hz), 7.48 (d, 2H, J= 8.1 Hz), 7.28-7.34 (m, 3H), 7.17 (s, 1H), 7.08 (d, 1H, J= 8.1 Hz), 6.98 (d, 2H, J= 8.2 Hz), 5.12 (s, 2H), 4.08 (q, 2H5 J= 7.0 Hz), 3.95 (m, 1H), 2.50-2.60 (m, 2H), 1.78 (s, 3H), 1.27 (t, 3H, J= 7.0 Hz). $[M+H]^+$ Calculado para $C_{27}H_{25}ClO_4$: 449.1. Se encontraron 449.1.



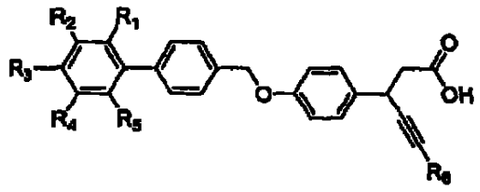
6.14

[0327] ^{1}H NMR (400MHz) ($(CD_3)_2SO$) δ 12.4 (s, 1H), 7.52 (d, 2H, J= 8.0 Hz), 7.46 (d, 2H, J= 8.6 Hz), 7.30 (d, 2H, J= 8.8 Hz), 7.46 (d, 2H, J= 6.0 Hz), 6.98-7.01 (m, 3H), 6.91-6.98 (m, 3H), 5.13 (s, 2H), 3.92-4.04 (m, 3H), 2.61 (d, 2H, J= 7.6 Hz), 2.29 (s, 3H), 1.79 (d, 2H, J= 2.0 Hz), 1.59-1.66 (m, 2H), 1.34-1.40 (m, 2H), 0.88 (t, 3H, J= 7.6 Hz). $[M+Na]^+$ Calculado para $C_{30}H_{32}O_4$: 471.1. Se encontraron 471.1.

6.7 Ejemplo 7

[0328] Los siguientes compuestos se prepararon con métodos similares a los descritos en el Ejemplo 2.

TABLA 2

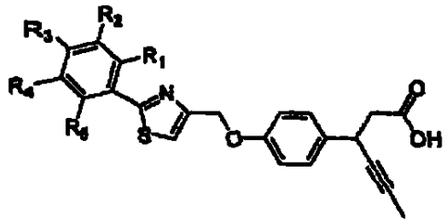


Compuesto	R_1	R_2	R_3	R_4	R_5	R_6
7.1	H	H	H	H	H	H
7.2	CN	H	H	H	H	H
7.3	H	H	H	H	H	CH_3
7.4	CN	H	H	H	H	CH_3
7.5	OC_2H_5	H	H	H	H	CH_3
7.6	Cl	H	H	H	H	CH_3
7.7	F	H	H	H	H	CH_3
7.8	H	OC_2H_5	H	H	H	CH_3
7.9	H	H	OC_2H_5	H	H	CH_3
7.10	H	H	CF_3	H	H	CH_3
7.11	H	$-OCH_2O-$		H	H	CH_3
7.12	OCH_3	OCH_3	H	H	H	CH_3
7.13	H	OCH_3	H	H	H	CH_3
7.14	H	CN	H	H	H	CH_3
7.15	H	H	CN	H	H	CH_3

6.8 Ejemplo 8

[0329] Los siguientes compuestos se prepararon con métodos similares a los descritos en el Ejemplo 3.

TABLA 3

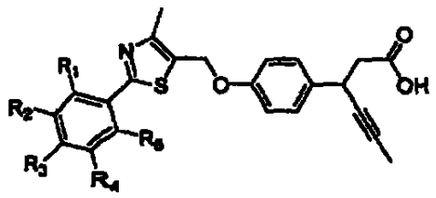


Compuesto	R_1	R_2	R_3	R_4	R_5
8.1	H	H	CF_3	H	H
8.2	H	H	H	H	H
8.3	H	H	Cl	H	H
8.4	H	H	OCH_3	H	H
8.5	H	H	CH_3	H	H
8.6	H	OCH_3	OCH_3	H	H
8.7	Cl	Cl	H	H	H

6.9 Ejemplo 9

[0330] Los siguientes compuestos se prepararon con métodos similares a los descritos en el Ejemplo 3.

TABLA 4



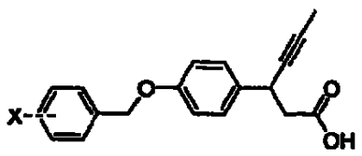
Compuesto	R_1	R_2	R_3	R_4	R_5
9.1	H	H	CF_3	H	H
9.2	H	H	CH_3	H	H
9.3	H	H	H	H	H
9.4	H	OCH_3	OCH_3	H	H
9.5	H	H	Cl	H	H
9.6	Cl	H	H	H	H

6.10 Ejemplo 10

[0331] Los siguientes compuestos se prepararon con métodos similares a los descritos en los Ejemplos 3-5. Los ácidos carboxílicos que corresponden a **10.2** y **10.5** se

prepararon de acuerdo con los métodos de Huang *et al.* (2003) *J. Amer. Chem. Soc.* 22: 6653- 6655, y Admas *et al.* (1973) *Org. Synth.* Coll. Vol. V: 107, 109, respectivamente. 239

TABLA 5

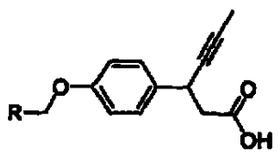


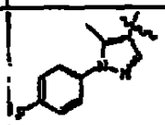
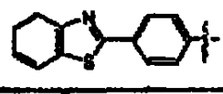
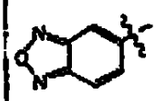
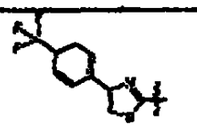
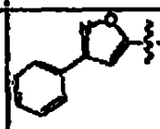
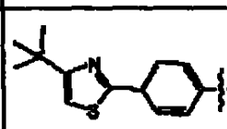
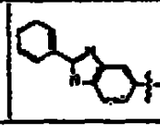
Compuesto	X	Compuesto	X
10.1	3-C(O)Ph	10.8	3-(2)-Piridil
10.2	3-N(C_2H_5)Ph	10.9	3-(3)-Piridil
10.3	3-fenoxi	10.10	3-(4)-Piridil
10.4	4-C(O)Ph	10.11	4-(2)-Piridil
10.5	4-SO_2Ph	10.12	4-(3)-Piridil
10.6	4-CH_2Ph	10.13	4-(4)-Piridil
10.7	4-C_2H_2PH	10.14	4-Pirrole-1-il

6.11 Ejemplo 11

[0332] Los siguientes compuestos se prepararon con métodos similares a los descritos en los Ejemplos 3-5.

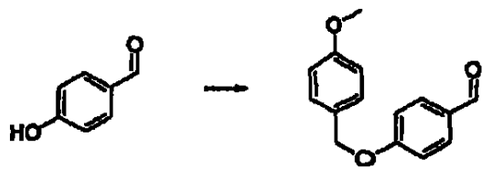
TABLA 6



Compuesto	R	Compuesto	R
11.1		11.5	
11.2		11.6	
11.3		11.7	
11.4		11.8	

[0333] Este ejemplo ilustra la preparación de ácido (+/-)-3-(4-[(4- metoxifenil)metoxi]-fenilo)-hex-4-inóico.

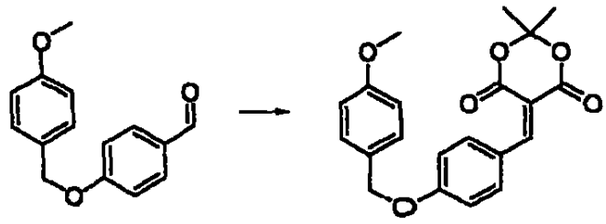
Esquema 12.1



12.1

[0334] 4-[(4-metoxifenil)metoxi]benzaldehido (12.1). Un matraz de fondo redondeado de 500 mL se cargó con 4-hydroxibenzaldehido (40 g, 328 mmol) y se agregó DMF (250 mL). Se agregó 4-metoxibenzilo cloruro (57.8 mL, 426 mmol), seguido de carbonato potásico (90 g, 656 mmol). La mezcla de la reacción se agitó a temperatura ambiente por 5h y luego se vertió en agua con hielo (2.5 L). El producto se recogió por filtración y se enjuagó con agua. Después de secarse completamente se obtuvieron 78 g (98%) del aldehído **12.1** como un polvo de color amarillo claro. ^{1}H NMR(400MHz)(DMSO-d_6) δ 9.88 (s, 1H); 7.88 (d, 2H, J=8.7 Hz); 7.42 (d, 2H, J=8.8 Hz); 7.21 (d, 2H, J-8.8 Hz); 6.97 (d, 2H, J=8.6 Hz); 5.16 (s, 2H); 3.77 (s, 3H). MS ESI (pos.) m/e: 243.1 (M + H).

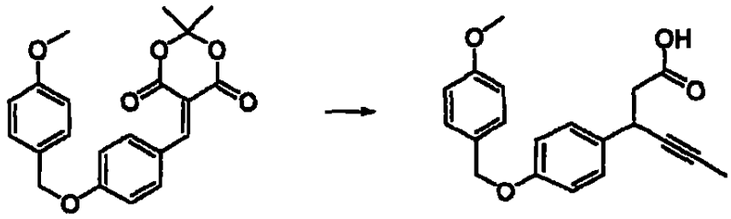
Esquema 12.2



12.1 12.2

[0335] **5-[[4-[(4-metoxifenilo)metoxi] fenil]metileno]-2,2-dimetil- [1,3]dioxan-4,6-diono (12.2).** La Condensación con el ácido de Meldrum se llevó a cabo de acuerdo con el procedimiento de DeWolf *et al.* (1989) *Biochemistry* 28: 3833-3842. Una solución de ácido de Meldrum (18 g, 124 mmol) compuesto **12.1** (30 g, 124 mmol) en tolueno (100 mL) se trató con ácido glacial acético (4 mL) y piperidina (2 mL). La mezcla de la reacción se agitó y se calentó al reflujo hasta que se removió completamente el agua con una trampa Dean-Stark. La mezcla de la reacción se enfrió a temperatura ambiente y el sólido resultante se filtró y se lavó con tolueno frío para producir 28g (62%) de **12.2** como un polvo amarillo brillante. ^{1}H NMR(400MHz)(DMSO-d_6) δ.32 (s, 1H); 8.24 (d, 2H, *J*=8.9 Hz); 7.42 (d, 2H, *J*=8.6 Hz); 7.17 (d, 2H, *J*=9.0 Hz); 6.97 (d, 2H, *J*=8.7 Hz); 5.18 (s, 2H) 3.75 (s, 6H) 1.75 (s, 6H).

Esquema 12.3



12.2 12

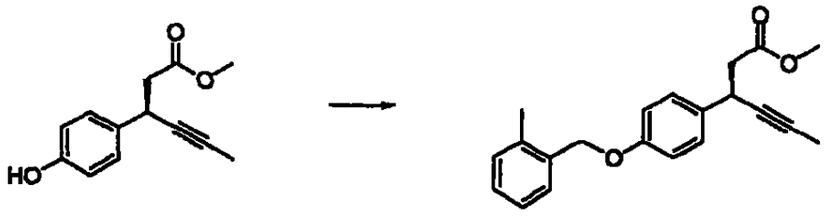
[0336] **Ácido (+/-)-3-(4-[(4-metoxifenilo)metoxi]fenil)-hex-4-inóico (12).** A una solución en agitación de THF (120 mL) del compuesto **12.2** (13.8 g, 37.5 mmol) bajo nitrógeno se agregó bromuro de 1-propinilmagnesio en THF (0.5 N, 97.5 mL) sobre un período de 20 minutos. Tras completarse la adición, la mezcla de la reacción se agitó por 20 minutos, se enfrió rápidamente con NH_4Cl (50 mL) acuoso saturado y se extrajo con

acetato de etilo (3 x 50 mL). Los extractos combinados se lavaron con agua, se secaron sobre $MgSO_4$, se filtraron, y se concentraron hasta lograr un aceite marrón. Se calentó una solución de dicho aceite marrón en 5:1 piridina-agua (360 mL) a 100 °C por 36h. La mezcla de la reacción se enfrió a temperatura ambiente y se colocó en un baño de agua con hielo. Con cuidado se agregó HCl concentrado hasta lograr un pH ~2. La suspensión resultante se extrajo con acetato de etilo (200 mL x 3), se secó sobre $MgSO_4$, se filtró, y se concentró hasta lograr un sólido blanco opaco. La re-cristalización a partir de etanol dio 9.5 g (78%) del compuesto **12** como un polvo blanco. ^{1}H NMR(500MHz)DMSO-d_6) δ 12.2 (s, 1H); 7.37 (d, 2H, *J*=8.5 Hz); 7.27 (d, 2H, *J*=8.5 Hz); 6.95 (d, 2H, *J*=8.0 Hz); 6.94 (d, 2H, *J*=8.5 Hz); 4.99 (s, 2H); 3.95 (m, 1H); 3.76 (s, 3H); 2.60 (m, 2H); 1.78 (d, 3H, *J*=I.5 Hz). MS ESI (neg.) m/e: 323.0 (M -1).

6.13 Ejemplo 13

[0337] Este ejemplo ilustra la preparación de sal sódica de ácido *(3S)*-3-[4-(2-Metil-benciloxi)- fenil]-hex-4-inóico.

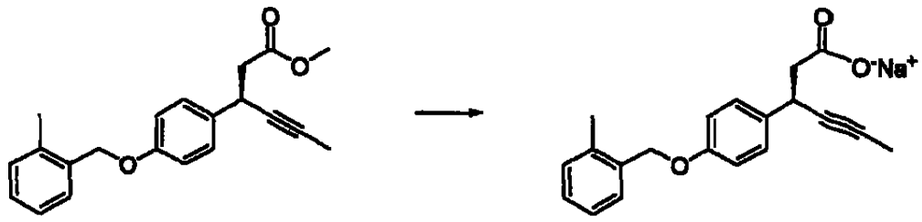
Esquema 13.1



1 13.1

[0338] **Éster metílico de ácido *(3S)*-3-[4-(2-metilo-bencziloxi)-fenil]-hex-4-inoico (13.1).** Se disolvieron bromuro 2-Metilbenzilo (0.98 g, 5.3 mmol) y fenol 1 (0.97 g, 4.4 mmol) en acetona (9 mL) y se condensaron con Cs_2CO_3 (1.45 g, 4.4 mmol). La reacción se agitó a temperatura ambiente por 16 h y luego se filtró y se concentró hasta lograr un aceite que se purificó por cromatografía radial (2 mm placa de gel de sílice, 10% acetato de etilo en hexanos). El eluyente que contiene el compuesto **13.1** se concentró hasta lograr un aceite incoloro (1.37 g, 96%). Este material se analizó por HPLC quiral (columna Daicel ChiralPAK AD-H, eluyente: 0.1% TFA en 95:5 hexanos:2-propanol) y se encontró que contenía 94% ee. ^{1}H NMR(500MHz)(MeOH-d_4) δ 7.39 (d, 1H, *J*=7 Hz); 7.28 (d, 2H, *J*=8.5 Hz); 7.25-7.15 (m, 3H); 5.05 (s, 2H); 4.02 (m, 1H); 3.64 (s, 3H); 2.68 (m, 2H); 2.36 (s, 3H); 1.80 (d, 3H, *J*=2.5 Hz). MS ESI (pos.) m/e: 323.0 (M + H); 245.1 (M + Na).

Esquema 13.2



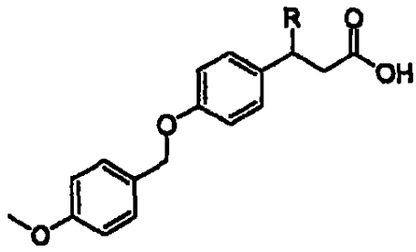
13.1 13

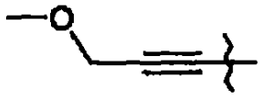
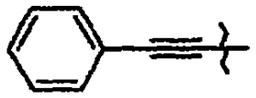
[0339] **Sal sódica de ácido *(3S)*-3-[4-(2-Metil-benciloxi)-fenil]-hex-4-inóico (13).** Se agregó 2N $KOH_{(aq)}$ (3.2 mL) a una solución de **13.1** (1.37 g, 4.25 mmol) en metanol (30 mL). La reacción se agitó a temperatura ambiente durante toda la noche y luego se absorbió en abundante agua. La solución acuosa se ajustó a un pH = 2.0 con IN $HCl_{(aq)}$ y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua y luego con salmuera. El solvente se removió bajo presión reducida y el residuo resultante se disolvió en etanol (4 mL) y se trató con 1 equiv. de bicarbonato de sodio acuoso. Los solventes se removieron bajo presión reducida y el residuo se trituró con éter dietílico. Luego de recogerse por filtración y secarse, se obtuvo la sal de sodio **13** (1.1 g) como un fino polvo blanco. ^1H NMR(500MHz)(D_2O) δ 7.34-7.18 (m, 6H) ; 6.95 (d, 2H, *J*=6.5 Hz); 5.05 (s, 2H); 3.88 (m, 1H); 2.47 (d, 2H, *J*=8.5 Hz); 2.28 (s, 3H); 1.72 (d, 3H, *J*=2.5 Hz). MS ESI (pos.) m/e: 309.1 (M + H); 331.0 (M + Na). $[\alpha]_D$ = +20.6°.

6.14 Ejemplo 14

[0340] Los siguiente compuestos se prepararon utilizando métodos similares a los descritos en el Ejemplo 12.

TABLA 7

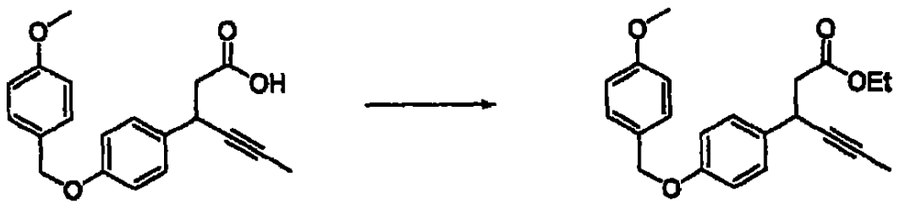


Compuestos	R	Compuestos	R
14.1		14.4	Me
14.2		14.5	
14.3	Et	14.6	

6.15 Ejemplo 15

[0341] Este ejemplo ilustra la preparación de ácido *(3S)*-3-[4-(2-Metil-benciloxi)-fenil]-hex-4-inóico.

Esquema 15.1



12 **15.1**

[0342] **Éster etílico de ácido (+/-)- [4-(4-Metoxi-benciloxi)-fenilo]-hex-4-inóico (15.1).** Se cargó un matraz RB de 100 mL con el compuesto **12** (3.00 g, 9.25 mmol), hidrocloruro de 1-(3- dimetilaminopropil)-3-etilcarbodiimida (2.67 g, 13.9 mmol), 4-dimetilaminopiridina (1.13 g, 9.25 mmol) y diclorometano (30 mL), la mezcla se agitó hasta lograr una solución. Luego de 15 minutos se agregó alcohol etílico (absoluto, 1.00 mL). Luego de 2 h, la reacción se enfrió rápidamente con $NaHCO_3$ acuoso (sat., 100 mL). Las capas se separaron, y la capa orgánica se lavó con $NaHCO_3$ acuoso (2 X 100 mL), se secó sobre $MgSO_4$ y se concentró hasta lograr un polvo blanco (3.19 g, 98%) que se utilizó sin purificación posterior.

Esquema 15.2



15.1 15.2

[0343] Éster etílico de ácido (+/-)- [4-(2-Metil-benciloxi)-fenil]-hex-4-inóico (15.2). El éster **15.1** (3.19 g, 9 mmol) se absorbió en ácido acético glacial (100 mL) en un matraz RB de 250 mL, y la suspensión se calentó al reflujo por 16h. Se removió el solvente bajo presión reducida, y el residuo se disolvió nuevamente en acetato de etilo (200 mL). La solución se lavó con 1 N $HCl_{(aq)}$ (200 mL) y se saturó con salmuera (200 mL), se secó sobre $MgSO_4$ y se concentró hasta lograr un aceite amarillo espeso, al que se agregó bromuro de 2-metilbenilo (2.57 g, 13.9 mmol), carbonato de cesio (6.03 g, 18.5 mmol) y DMF (20 mL). Se calentó la suspensión a 80°C durante toda la noche. Luego de enfriarse, la reacción se aplacó con agua (200 mL) y se extrajo con acetato de etilo (2 X 100 mL). Se lavaron las capas orgánicas combinadas con NaHCO3 (sat. 2 X 100 mL), y NaCl (sat. 3 X 100 mL), se secaron sobre MgSO4, y se concentraron hasta lograr un polvo blanco (2.41 g, 79%).

Esquema 15.3



15.2 15

[0344] Ácido (3S)-3-[4-(2-Metil-benciloxi)-fenil]-hex-4-inóico (15). El compuesto **15.2** se disolvió en una mezcla de 24 mL de metanol y 24 mL de isopropanol con la ayuda de sonicación. La solución se filtró en un vial de 50 mL. El racémico **15.2** se resolvió con una HPLC en fase quiral normal utilizando una columna semi-preparativa ChiralTech AD (2.0 cm X 25.0 cm), eluyendo isocráticamente con hexano/isopropanol (92:8) a una tasa de flujo de 20 mL/min. Cada inyección contenía 50 mg del éster **15** (1 mL). La absorción a 220 nm se utilizó como detección. Se recogieron ambos enantiómeros. Luego de 36 inyecciones, los enantiómeros separados se secaron para dar sólidos blancos. El quiral

analítico HPLC (columna Chiraltech AD-H, 0.4 cm X 25.0 cm, 8% isopropanol/hexano, 1 mL/min) indicó que ambos compuestos eran óptimamente puros. Los enantiómeros se designaron como **A** (tiempo de retención = 11.5 min.) y **B** (tiempo de retención = 15.6 min.).

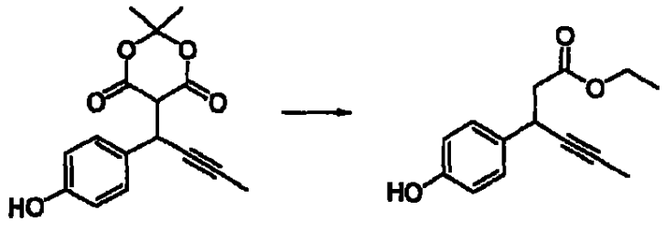
[0345] Se cargó un matraz RB con el enantiómero **A** (0.65 g), etanol (10 mL) y 2N KOH (10 mL). y se agitó por 2 h a temperatura ambiente. Tras la acidificación a un pH~2 con ácido cítrico, se extrajo el producto con acetato de etilo (100 mL). Se lavaron las capas orgánicas con salmera saturada (2 X 50 mL), se secaron sobre $MgSO_4$ y se concentraron hasta lograr un aceite amarillo (0.59 g, 42% global). Se hizo una solución de 1mL de DMF con una parte alícuota (12.0 mg) y se midió la rotación óptica. Este enantiómero se asignó a (S) de acuerdo con DeWolf Jr. *et al.* (1989) *Biochemistry* 28: 3833-3842.

[0346] ^{1}HNMR (400 MHz, acetona-d_6) δ 7.45 (d, 1H, J=7.15 Hz); 7.37 (d, 2H, J=8.66 Hz); 7.25 (d, 1H, J=1.42 Hz); 7.24 (m, 2H); 7.00 (d, 2H, J=8.74 Hz); 5.11 (s, 2H); 4.05 (m, 1H); 2.70 (m, 2H); 2.39 (s, 3H); 2.10 (s, 1H); 1.80 (d, 3H, J=2.41). MS-ESI (neg.) m/e: 307.1 (M-H); 637.2 (2M-H). $[\alpha]_D^{20}$: +16.32 (cl.2, DMF).

6.16 Ejemplo 16

[0347] Este ejemplo ilustra la preparación de etil éster de ácido 3-(4-Hidroxi-fenil)-hex-4-inóico.

Esquema 16.1



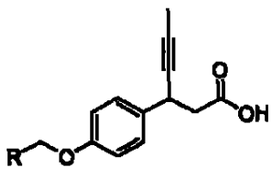
1.2 **16**

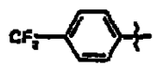
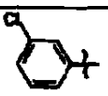
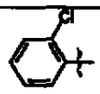
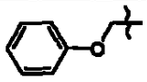
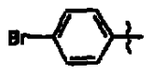
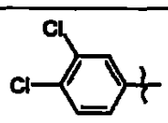
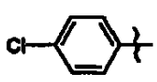
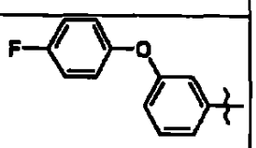
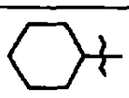
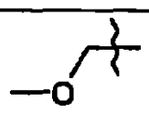
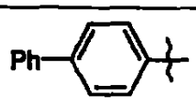
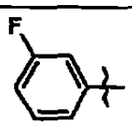
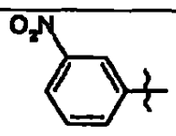
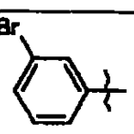
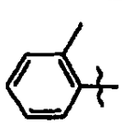
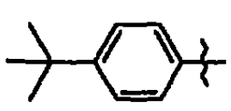
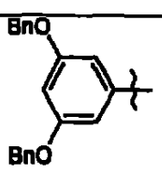
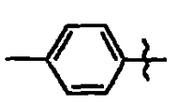
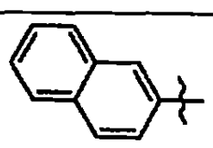
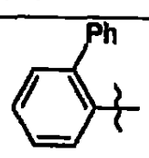
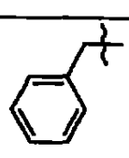
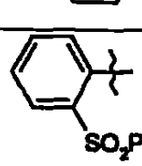
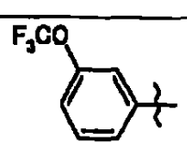
[0348] **Éster etílico de ácido 3-(4-Hidroxi-fenil)-hex-4-inóico (16).** Se disolvió el fenol **1.2** (1.2 g, 4 mmol) en piridina (3 mL) y etanol (1 mL). La mezcla se calentó a 90°C por 16h y luego se concentró hasta lograr un aceite que se purificó por columna de cromatografía (elución con 1-3% MeOH en diclorometano). El fenol **16** (0.88 g, 91%) se obtuvo como un aceite. ^{1}H NMR(500MHz)(acetona-d_6) δ 8.24 (s, 1H); 7.21 (d, 2H, *J*=9.5 Hz); 6.78 (d, 2H, *J*=9.0 Hz); 4.06 (m, 2H); 3.98 (m, 1H); 2.68-2.59 (m, 2H); 1.78 (d, 3H, *J*=2.5 Hz); 1.75 (t, 3H, *J*=7.0 Hz). MS ESI (pos.) m/e: 233.1 (M + H); 255.1 (M + Na).

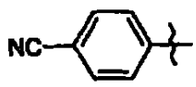
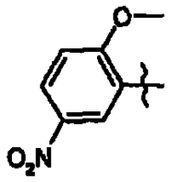
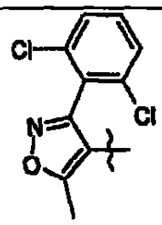
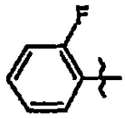
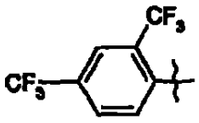
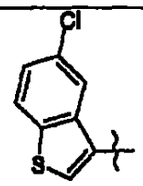
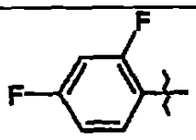
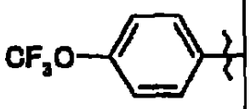
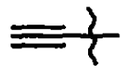
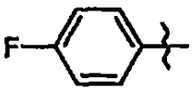
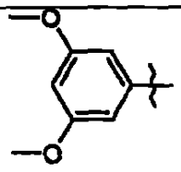
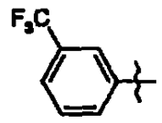
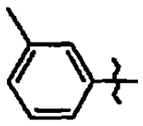
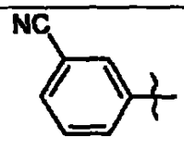
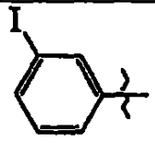
6.17 Ejemplo 17

[0349] Los siguientes compuestos se prepararon con métodos similares a los de los ejemplos 12 y 15.

TABLA 8



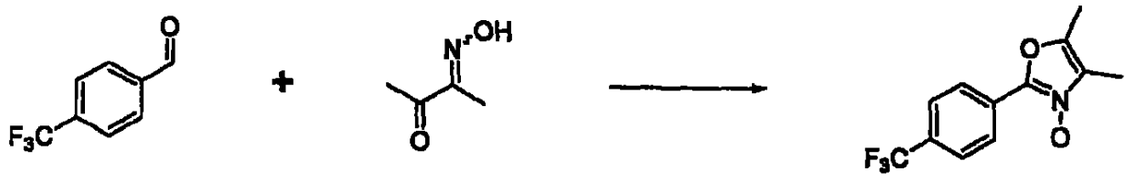
Compuesto	R	Compuesto	R	Compuesto	R
17.1		17.14		17.27	
17.2		17.15		17.28	
17.3		17.16		17.29	
17.4		17.17		17.30	
17.5		17.18		17.32	
17.6		17.19		17.33	
17.7		17.20		17.34	
17.8		17.21		17.35	

Compuesto	R	Compuesto	R	Compuesto	R
17.9		17.22		17.36	
17.10		17.23		17.37	
17.11		17.24		17.38	
17.12		17.25		17.39	
17.13		17.26		17.40	

6.18 Ejemplo 18

[0350] Este ejemplo ilustra la preparación de ácido 3-{4-[5-Metil-2-(4-trifluorometil-fenil)-oxazol-4-ilmetoxil-fenil}-hex-4-inóico.

Esquema 18.1



18.1

[0351] **4,5-dimetil-2-(4-trifluorometil-fenil)-oxazol-3-óxido (18.1).** Un matraz de 100 mL con forma de pera se cargó con butano-2,3-diono monooxime (2.1 g, 20.4 mmol), 4-(trifluorometil)benzaldehído (3.0 mL, 22.4 mmol), y ácido acético (20 mL). La mezcla se enfrió a 0° C. A la reacción se agregó lentamente una solución de 4N HCl en dioxano (7.0 mL, 28.0 mmol) y la mezcla resultante se agitó a 0° C por 20 minutos. Se agregó éster dietílico (30 mL) a la reacción y se dejó que la mezcla se enfriara a temperatura ambiente durante toda la noche. Se removió el solvente bajo presión reducida y el residuo resultante se absorbió en agua (300 mL). Se agregó $NH_4OH_{(aq)}$ concentrado para ajustar el pH a 9.0. La mezcla se extrajo con acetato de etilo (2 x 75 mL), y las capas orgánicas combinadas se lavaron con agua (100 mL), seguida de salmuera saturada (100 mL). Se secó la capa orgánica (Na_2SO_4) y se removió el solvente bajo preaión reducida. El residuo resultante se purificó por cromatografía radial (3% MeOH en DCM) para producir 1.8 g (35%) de 4,5-dimetil-2-(4-trifluorometil-fenil)-oxazol-3-óxido como un sólido blanco. LC/MSD *m/e*: 258.1 (M+H); ^{1}H NMR (400 MHz) (Acetona-d_6) δ 8.68 (d, 2H, *J*=8.0 Hz), 7.89 (d, 2H, *J*=8.0 Hz), 2.45 (s, 3H), 2.16 (s, 3H).

Esquema 18.2

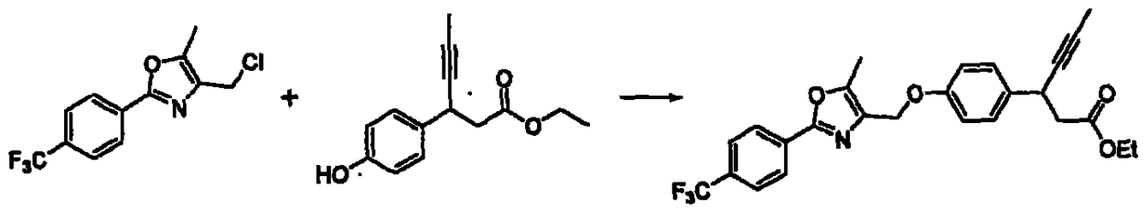


18.1 **18.2**

[0352] **4-clorometil-5-metil-2-(4-trifluorometil-fenil)-oxazol (18.2).** Se agregó gota a gota oxicloruro de fósforo (0.72 niL, 7.8 mmol) a un matraz en forma de pera de 100 mL secado al horno cargado con **18.1** (1.8 g, 7.00 mmol) y diclorometano (20 mL). La reacción se sometió a reflujo bajo atmósfera de nitrógeno por 30 minutos y luego se enfrió a temperatura ambiente. La reacción se lavó con agua (2 x 250 mL) y las capas acuosas combinadas fueron extraídas nuevamente con DCM (2 x 25 mL). Las capas orgánicas combinadas se lavaron con salmuera y se secaron (Na_2SO_4). Se removió el solvente bajo presión reducida y el residuo resultante se purificó por cromatografía radial (15% éter dietílico en hexanos) para producir 216 mg (15%) de 4-clorometil-5-metil-2-(4-trifiuorometil-fenil)-oxazol como un sólido blanco. LC/MSD *m/e*: 276.0 (M+H); ^{1}H NMR

(400 MHz) ($CDCl_3$) δ 8.15 (2H, d, J=8.0 Hz), 7.73 (2H. d, J=8.0 Hz), 4.59 (2H, s), 2.48 (2H, s).

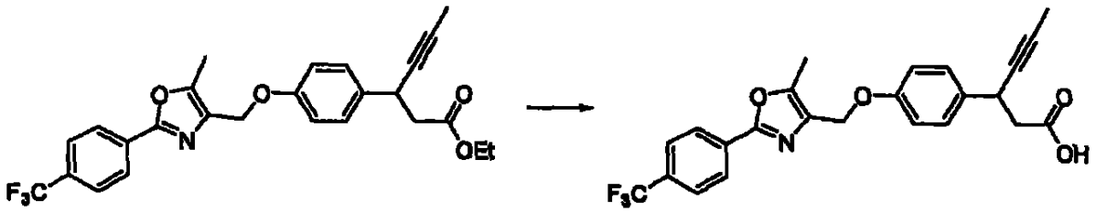
Esquema 18.3



18.2 16 18.3

[0353] Éster etílico de ácido 3-{4-[5-Metil-2-(4-trifluorometil-fenil)-oxazol-4-ylmetoxi]- fenil}-hex-4-inóico (18.3). Se agregaron (0.51 g, 1.57 mmol) de carbonato de cesio a una solución de 18.2 (216 mg, 0.79 mmol) y fenol **16** (220 mg, 0.79 mmol) en DMF (8 mL). La reacción se agitó a temperatura ambiente durante toda la noche y luego se absorbió en agua (500 mL). La solución se ajustó a un pH = 4.0 con 1N $HCl_{(aq)}$ y se extrajo con acetato de etilo (2 x 25 mL). Los orgánicos combinados se lavaron con agua, seguida de salmuera. Se removió el solvente bajo presión reducida y el residuo resultante se purificó por cromatografía radial (20% éter dietílico en hexanos) para producir 304 mg (82%) de éster etílico de ácido 3-{4-[5-Metil-2-(4-trifluorometil-fenil)-oxazol-4-ilmetoxi]-fenil}-hex-4-inóico. LC/MSD *m/e:* 472.0 (M+H); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.16 (2H, d, J=8.0 Hz), 7.73 (2H, d, J=8.0 Hz), 7.33 (2H, m), 6.99 (2H, m), 5.01 (2H, s), 4.14 (3H, m), 2.72 (2H, m), 2.48 (3H, s), 1.85 (3H, s), 1.26 (3H3 1, J=8.0 Hz).

Esquema 18.4



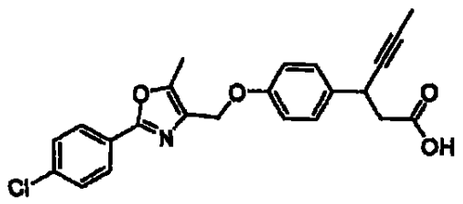
18.3 18

[0354] Ácido 3-{4-[5-Metil-2-(4-trifluorometil-fenil)-oxazol-4-ilmetoxi]-fenil}-hex-4-inóico (18). Se agregó 2N $KOH_{(aq)}$ a una solución de **18.3** (304 mg, 0.65 mmol) en etanol (5 niL). La reacción se agitó a temperatura ambiente durante toda la noche y se absorbió en abundante agua. La solución acuosa se ajustó a un pH = 2.0 con 1N $HCl_{(aq)}$ y se extrajo con acetato de etilo (2 x 25 niL). Las capas orgánicas combinas se lavaron con agua y luego

con salmuera. El solvente se removió bajo presión reducida y el residuo resultante se purificó por cromatografía radial (40% acetato de etilo en hexanos + 0.1% AcOH) para producir 150 mg (52%) del compuesto **18** como un cristal. LC/MSD *m/e*: 444.0 (M+H); ^{1}H NMR (400 MHz) (acetona) ∂ 8.21 (2H, m), 7.89 (2H, d, J=8.0 Hz), 7.38 (2H, m), 7.03 (2H, m), 5.06 (2H, s), 4.06 (1H, m), 2.70 (2H, m), 2.52 (3H, s), 1.81 (3H, s).

6.19 Ejemplo 19

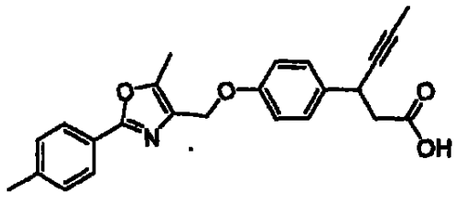
[0355] Los ejemplos 19-22 se prepararon utilizando métodos similares a los descritos en el Ejemplo 18.



19

[0356] **Ácido 3-{4-[5-Metil-2-(4-cloro-fenilo)-oxazol-4-ilmetoxi]-fenil}-hex-4-inóico (19).** LC/MSD *m/e*: 410.0 (M+H). ^{1}H-NMR (400 MHz) (acetona-d_6) δ 8.02 (2H, m), 7.49 (2H, m), 7.35 (2H, m), 7.01 (2H, m), 5.04 (2H, s), 4.09 (1H, m), 2.77 (2H, m), 2.48 (3H, s), 1.86 (3H, s).

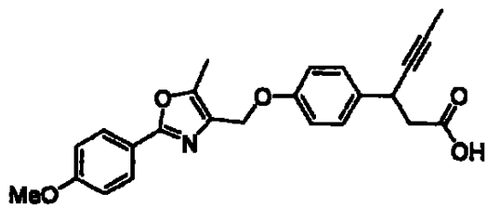
6.20 Ejemplo 20



20

[0357] **Ácido 3-{4-[5-Metil-2-(4-metil-fenil)-oxazol-4-ilmetoxi]-fenil}-hex-4-inóico (16).** LC/MSD *m/e*: 390.2 (M+H). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.96 (2H, m), 7.34 (2H, m), 6.70 (2H, m), 5.02 (2H, s), 4.09 (1H, m), 2.80 (2H, m), 2.47 (3H, s), 1.85 (3H, s).

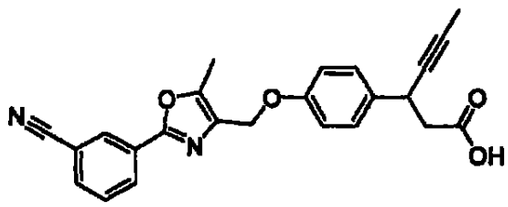
6.21 Ejemplo 21



21

[0358] **Ácido 3-{4-[5-Metil-2-(4-metoxi-fenil)-oxazol-4-ilmetoxi]-fenil}-hex-4-inóico (21).** LC/MSD *m/e*: 406.1 (M+H). ^{1}H NMR (400 MHz) (acetona-d_6) δ 7.89 (2H, d, *J*=9.0 Hz) 7.30 (2H, m), 7.09 (2H, d, *J*=9.0 Hz), 7.00 (2H, m), 4.97 (3H, s), 3.90 (1H, m), 3.84 (3H, s), 2.44 (3H, s), 1.79 (3H, s).

6.22 Ejemplo 22



22

[0359] **Ácido 3-{4-[5-Metil-2-(3-ciano-fenil)-oxazol-4-ilmetoxi]-fenil}-hex-4-inóico (22).** LC/MSD *m/e*: 401.2 (M+H). 1H NMR (400 MHz) (acetona-d_6) δ 8.33 (2H, m), 7.91 (1H, m), 7.79 (1H, m), 7.38 (2H, m), 7.08 (2H, m), 5.06 (2H, s), 4.06 (1H, m), 2.70 (2H, m), 2.51 (3H, s), 1.81 (3H, s).

6.23 Ejemplo 23

[0360] El ejemplo siguiente ilustra la síntesis de 5-{2-[4-(2-Metil-benciloxi)-fenil]-pent-3-inil}-1*H*-tetrazol.

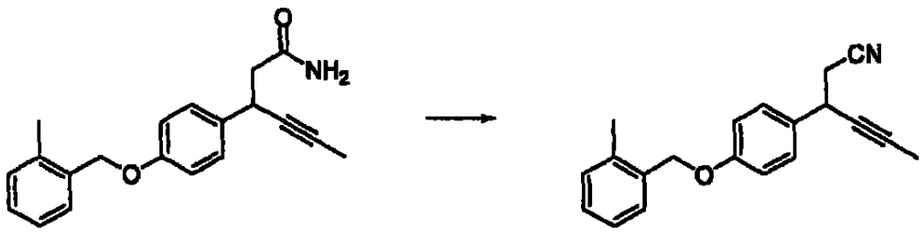
Esquema 23.1



23.1 23.2

[0361] **Amida de ácido 3-[4-(2-Methil-benziloxi)-fenil]-hex-4-inóico (23.2).** Se agregó carbonil diimidazol (0.46 g, 2.84 mmol) a una solución de ácido 3-[4-(2-Metil-benciloxi)-fenil]-hex-4- inóico (véase el Ejemplo 13) (0.73 g, 2.37 mmol) en THF anhidro (10 mL). La mezcla se agitó a temperatura ambiente por 2 horas. Luego se agregó a la mezcla NH_4OH concentrado (10 mL), y la reacción se agitó a temperatura ambiente durante toda la noche. La mezcla de la reacción se vertió en agua (300 mL) y la solución se ajustó a un pH = 7 con HCl concentrado. Luego la capa acuosa se extrajo con 3 x 25 mL de acetato de etilo. Las capas orgánicas combinadas se lavaron con agua, seguida de salmuera. La capa orgánica luego se secó (Na_2SO_4) y se concentró bajo presión reducida para producir 0.48 g (70%) de amida de ácido 3-[4-(2-Metil-benciloxi)-fenil]-hex-4-inóico (23.2) como un sólido amarillo claro. LC/MSD *m/e*: 308.4 (M+H)

Esquema 23.2

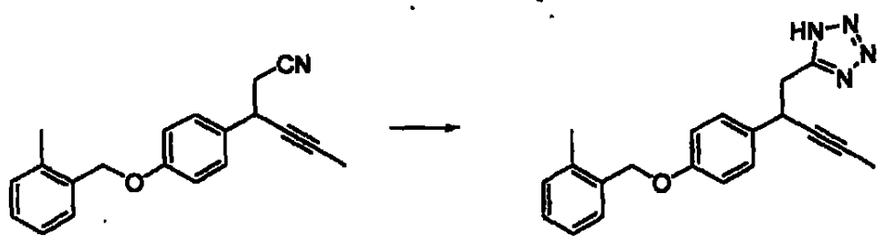


23.2 **23.3**

[0362] **3-[4-(2-Metil-benciloxi)-fenil]-hex-4-inenitrilo (23.3).** Un matraz de 50 mL redondeado en su parte inferior y secado al horno se cargó con DMF (8 mL) y una barra de agitación. La solución se enfrió a 0 °C en un baño de hielo. Lentamente se agregaron (160 µL, 1.0 mmol) de cloruro de tionil por medio de jeringa. La mezcla se agitó a 0 °C por 45 minutos más. Luego a la mezcla se agregaron (300 mg, 0.98 mmol) de nitrilo **23.2** como una solución en DMF (2 mL). La reacción fue agitada a 0° C por una hora, y luego se dejó que se enfriara gradualmente a temperatura ambiente durante toda la noche. La mezcla de la reacción se particionó entre agua fría y acetato de etilo. La capa acuosa se extrajo 2 veces más con 25 mL de acetato de etilo. A la capa acuosa luego se agregó $NaHCO_3$ saturado y se extrajo por tercera vez con acetato de etilo. Las capas orgánicas combinadas se lavaron con $NaHCO_3$ saturado y se concentraron bajo presión reducida. El residuo resultante se purificó por cromatografía radial (15% acetato de etilo en hexanos) para producir 203 mg (72%) de 3-[4-(2- Metil-benciloxi)-fenil]-hex-4-inenitrilo (**23.3**). ^1H NMR

(400 MHz) (acetona-d_6) δ 7.44 (3H, m), 7.24 (3H, m), 7.05 (2H, m), 5.13 (2H, s), 4.09 (1H, m), 2.89 (2H, m), 2.39 (3H, s), 1.88 (3H, s).

Esquema 23.



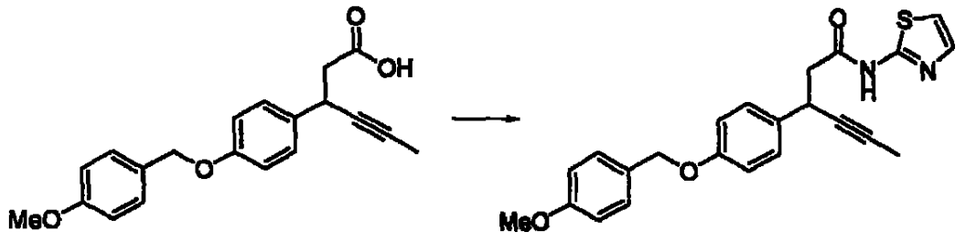
23.3 23

[0363] **5-{2-[4-(2-Metil-benciloxi)-fenil]-pent-3-inil}-1*H*-tetrazol (23).** A una solución de 23.3 (200 mg, 0.51 mmol) en DMF (5 mL) se agregó azida de sodio (35 mg, 0.54 mmol) y cloruro de amonio (29 mg, 0.54 mmol). La solución se mezcló a 110° C por 48 horas. La mezcla de la reacción se vertió en 50 mL de agua y se extrajo con acetato de etilo (2 x 25 mL). Las capas orgánicas combinas se concentraron bajo presión reducida, y el residuo resultante se purificó por medio de HPLC para producir 5 mg (3%) de 5-{2-[4-(2-Metil-benciloxi)-fenil]-pent-3-inil}-1H-tetrazol (**23**) como una película. LC/MSD *m/e*: 333.1 (M+H). ^{1}H NMR (400 MHz) (acetona-d_6) δ 7.45 (1H, m), 7.34 (2H, m), 7.25 (3H, m), 7.00 (2H, m), 5.11 (2H, s), 4.17 (1H, m), 3.37 (2H, d, *J*=7 Hz), 2.39 (3H, s), 1.79 (3H, s).

6.24 Ejemplo 24

[0364] El siguiente ejemplo ilustra la síntesis de tiazol-2-ilamino de ácido 3-[4-(4-Metoxi-benciloxi)-fenil]-hex-4-inóico.

Esquema 24.1



12 24

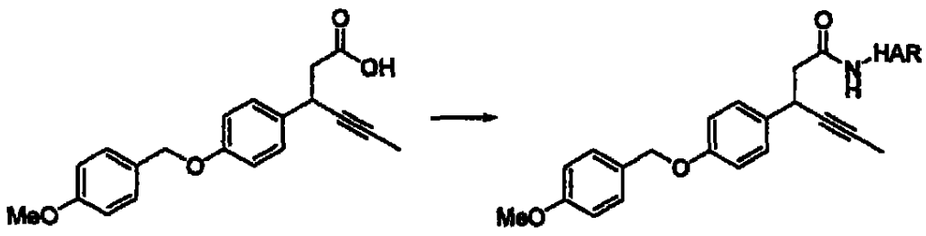
[0365] **Tiazol-2-ilamino de ácido 3-[4-(4-Metoxi-benciloxi)-fenil]-hex-4-inóico (24).** Un matraz en forma de pera se cargó con una barra de agitación, el compuesto **12** (50

mg, 0.154 mmol), carbonil diimidazol (25 mg, 0.154 mmol) y THF (4 mL). La mezcla se refluyó por 1 hora, y luego se agregó 2-amino tiazol (16 mg, 0.154 mmol). La reacción se refluyó por 48 horas, se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se concentró y el residuo resultante se purificó por medio de HPLC para producir 1.0 mg (2%) de tiazol-2-ilamida de ácido 3-[4-(4-Metoxi-benciloxi)-fenil]-hex-4-inóico (**24**) como una película. ^{1}H NMR (400 MHz) (acetona-d_6) δ 7.39 (4H, m), 7.11 (1H, s), 6.95 (3H, m), 5.03 (2H, s), 3.82 (3H, s), 2.95 (2H, m), 1.79 (3H, s).

6.25 Ejemplo 25

[0366] Los compuestos de la tabla siguiente se prepararon utilizando los métodos descritos en el Ejemplo 24.

TABLA 9



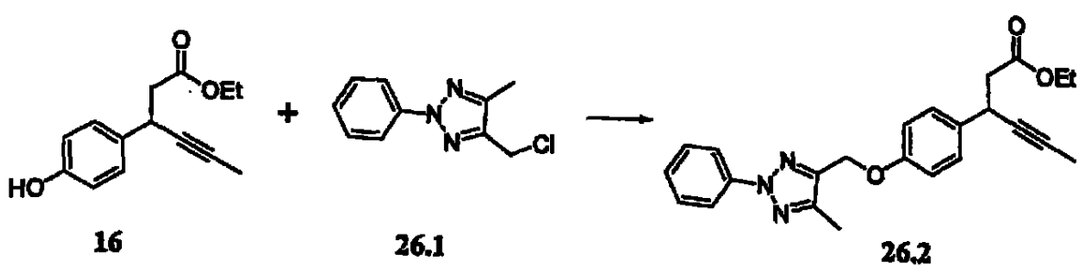
12

Compuesto	HAR
25.1	Tetrazol-5-il
25.2	pirimidin-2-il
25.3	piridin-2-il

6.26 Ejemplo 26

[0367] El siguiente ejemplo ilustra la preparación de ácido 3-[4-(5-Metil-2-fenil-2*H*-[1,2,3]triazol-4-ilmetoxi)-fenil]-hex-4-inóico (**26**).

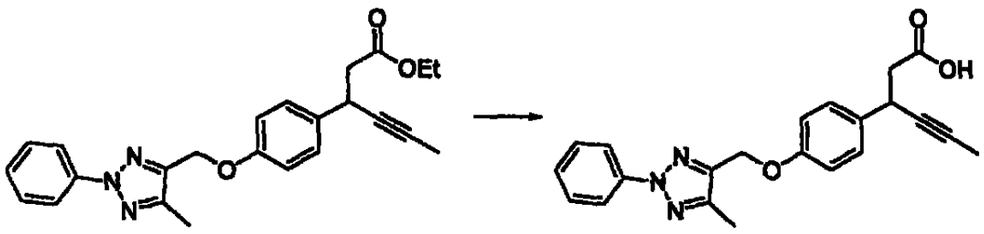
Esquema 26.1



16 **26.1** **26.2**

[0368] **Éster etílico de ácido 3-[4-(5-Metil-2-fenil-2*H*-[1,2,3]triazol-4-ilmetoxi)-fenilo]-hex-4-inóico (26.2).** Se agregaron (107 mg, 0.33 mmol) de carbonato de cesio a una solución de **16** (60 mg, 0.22 mmol) en DMF (5 mL). La mezcla se agitó a temperatura ambiente por 5 minutos, y se agregaron (55 mg, 0.22 mmol) de 4-Clorometil-5-metil-2-fenil-2*H*-[1,2,3]triazol. La reacción se calentó a 60° C y se agitó durante toda la noche. Luego la mezcla de la reacción se vertió en agua abundante. Se agregó 1N $HCl_{(aq)}$ para ajustar el pH a 4.0. La capa acuosa se extrajo con acetato de etilo. La capa orgánica luego se lavó con agua, seguida de salmuera. La capa orgánica se secó (Na_2SO_4) y se concentró. El residuo resultante se purificó por medio de cromatografía radial (20% acetato de etilo en hexanos) para producir 60 mg (66%) de éster etílico de ácido 3-[4-(5-Metil-2-fenilo-2*H*-[1,2,3]triazol-4- ilmetoxi)-fenilo]-hex-4- inóico (26.2). LC/MSD *m/e*: 404.2 (M+H).

Esquema 26.2



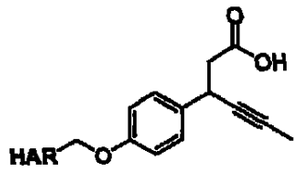
26.2 **26**

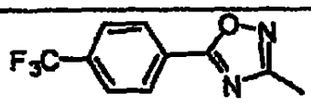
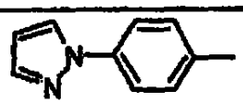
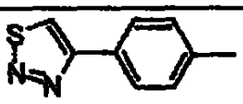
[0369] **Ácido 3-[4-(5-Metil-2-fenilo-2*H*-[1,2,3]triazol-4-ilmetoxi)-fenil]-hex-4-inóico (26).** Se agrego (1 mL) de 2N $KOH_{(aq)}$ a una solución de **26.2** (68 mg, 0.17 mmol) en EtOH (2 mL). La reacción se agitó durante toda la noche y luego se vertió en agua. La mezcla acuosa se acidificó a un pH ≈ 2 con 1N $HCl_{(aq)}$, y luego se extrajo con acetato de etilo. La capa orgánica se lavo con agua, seguida de salmuera. La capa orgánica luego se concentró bajo presión reducida y el residuo resultante se purificó por medio de cromatografía radial (20% acetato de etilo en hexanos) para producir 60.3 mg (95%) del compuesto **26** como un aceite incoloro. LC/MSD *m/e*: 374.0 (M-H); ^{1}H NMR (400 MHz) (acetona-d_6) δ 8.05 (2H, d, J=8.0 Hz), 7.56 (2H, t, J=8.0 Hz), 7.40 (3H, t, *J*=8.0 Hz), 7.06 (2H, d, J=8.0 Hz), 5.28 (2H, s), 4.05 (1H, m), 2.70 (2H, m), 2.44 (3H, s), 1.80 (3H, s).

6.27 Ejemplo 27

[0370] Los compuestos de la tabla siguiente se prepararon utilizando métodos similares a los descritos en el Ejemplo 26.

TABLA 10

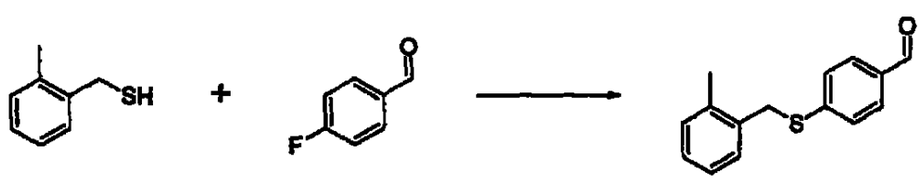


Compuesto	HAR
27.1	
27.2	
27.3	

6.28 Ejemplo 28

[0371] El siguiente ejemplo ilustra la preparación de ácido 3-[4-(2-Metil-benzilsulfanil)-fenil]-hex-4-inóico (**28**).

Esquema 28.1

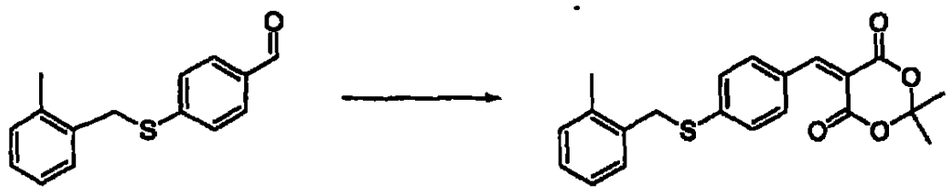


28.1

[0372] **4-(2-Metil-bencilsulfanil)-benzaldehído (28.1).** Gota a gota se agregaron (1.16 g, 9.32 mmol) de 4-fluoro-benzaldehído por más de 2 minutos a una solución de *o*-tolil-metanetiol (1.35 g, 9.79 mmol) y carbonato de cesio (3.19 g, 9.79 mmol) en DMF (20 mL). La solución se agitó a 40 °C durante toda la noche y se vertió en abundante agua. El pH de la solución se ajustó a 4 con 1N $HCl_{(aq)}$, y la solución acuosa se extrajo con acetato de etilo (2 x 35 mL). Las capas orgánicas combinadas se lavaron con agua, seguida de salmuera. Las capas orgánicas combinadas se secaron (Na_2SO_4) y se removió el solvente

bajo presión reducida. El residuo resultante se purificó por medio de cromatografía radial (15% acetato de etilo en hexanos) para producir 1.29 g (54%) de 4-(2-Metil- bencilsulfanil)-benzaldehído (**28.1**). LC/MSD *m/e*: 243.0 (M+H).

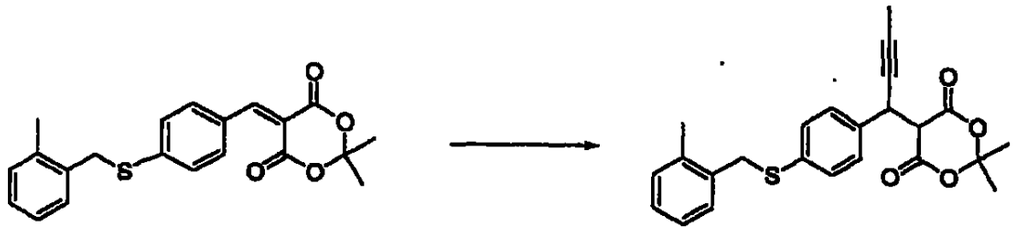
Esquema 28.2



28.1 **28.2**

[0373] 2,2-Dimetil-5-[4-(2-metil-bencilsulfanil)-bencilideno]-[1,3]dioxano-4,6-diono (28.2). Se agregaron (0.45 niL, 5.27 mmol) de pirrolidina a una solución de aldehído **28.1** en éter dietílico (20 mL) y se sonicó la mezcla por 5 minutos. Luego se agregó la mezcla a una solución de (0.73 g, 5.08 mmol) de ácido de Meldrum en éter dietílico (20 mL) y la mezcla resultante se sonicó por 5 minutos, formando un sólido. Se filtró el sólido, se lavó con éter dietílico, y luego se suspendió en DCM (10 mL). Luego se agregaron (0.97 g, 5. 10 mmol) de ácido p-Toluenosulfonico a la suspensión y ésta se sonicó hasta que se aclaró. Se removió el solvente bajo presión reducida, y el residuo resultante se absorbió con éter dietílico y se particionó entre agua y acetato de etilo. La capa acuosa se extrajo 2 veces más con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua, se secaron con (Na_2SO_4), y se concentraron *in vacuo* para producir 1.05 g (54%) de 2,2-Dimetil-5-[4-(2-metil-bencilsulfanil)-bencilideno]-[1,3]dioxano-4,6-diona (**28.2**) como un aceite amarillo. El aceite Amarillo resultante se utilizó sin ninguna purificación posterior. LC/MSD *m/e*: 391.1 (M+Na).

Esquema 28.3



28.2 **28.3**

[0374] **2,2-Dimetil-5-{1-[4-(2-metil-bencilsulfanil)-fenil]-but-2-inil}- [1,3]dioxano-4,6-diono (28.3).** Se cargó un matraz en forma de pera de 100 mL secado al horno, dotado de una barra de agitación también secada al horno, con una solución 0.5 M de bromuro de magnesio 1-propinilo en THF 12.5 mL, 6.27 mmol) por medio de cánula. La solución se enfrió a 0° C, y se luego agregó la solución de **28.2** (1.05 g, 2.85 mmol) en THF anhidro (6 mL) durante 3 minutos por medio de una cánula. La reacción se agitó a 0° C por 5 minutos y luego se agitó a temperatura ambiente por 1.5 horas. La mezcla de la reacción se vertió en $NH4Cl_{(aq)}$ saturado y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua, seguida de salmuera. Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron *in vacuo*. El residuo resultante se purificó por medio de cromatografía radial (20% acetato de etilo en hexanos) seguido de re-cristalización a partir de acetato de etilo caliente y hexanos para producir 162 mg (15%) de 2,2-Dimetil-5-{1-[4-(2-metil-bencilsulfanil)-fenil]-but-2-inil}-[1,3]dioxano-4,6-diono (**28.3**). LC/MSD *m/e*: 409.1 (M+H).

Esquema 28.4



28.3 **28**

[0375] **Ácido 3-[4-(2-Metil-bencilsulfanil)-fenil]-hex-4-inóico (28).** Una solución de **28.3** (20 mg, 0.05 mmol) en 5:1 piridina: agua (6 mL) se calentó a 80° C por 72 horas. La reacción se vertió en 500 mL de agua y la solución se acidificó con 1N $HCl_{(aq)}$ (65 mL). La solución acuosa se extrajo con acetato de etilo y las capas orgánicas combinadas se lavaron con agua, seguida de salmuera. Las capas orgánicas combinadas luego se secaron (Na_2SO_4) y se concentraron *in vacuo*. El residuo resultante se purificó por medio de cromatografía radial (30% acetato de etilo en hexanos) para producir 18 mg (cuantitativo) de ácido 3-[4-(2-Metil-bencilsulfanil)-fenil]-hex-4-inóico (**28**). LC/MSD *m/e*: 323.1 (M-H).

6.29 Ejemplo 29

[0376] El siguiente ejemplo ilustra la preparación de ácido 3-(4-o-Tolilmetanosulfinil-fenil)-hex-4-inóico.

Esquema 29.1



28.3 **29.1**

[0377] **2,2-Dimetil-5-[1-(4-o-tolilmetanosulfinil-fenil)-but-2-inil]- [1,3]dioxano~4,6-diona (29.1).** A una solución a 0° C de **28.3** (20 mg, 0.05 mmol) en AcOH (2 mL) se agregó una solución de peróxido de hidrógeno (20 µL, 0.05 mmol). La reacción se agitó a 80° C por 1.5 horas, luego se enfrió a temperatura ambiente y se agitó por 16 horas. La mezcla de la reacción se vertió en agua fría y la solución resultante se acidificó a un pH = 2 con 6N HCl(aq). La capa acuosa se extrajo con acetato de etilo y secbutanol. Las capas orgánicas combinadas se concentraron para producir 10 mg (50%) de 2,2-Dimetil-5-[1-(4- o-tolilmetanosulfinil-fenil)-but-2-inil]- [1,3]dioxano~4,6-diona (29.1). LC/MSD *m/e*: 383.0 (consistente con di ácido -H).

Esquema 29.1

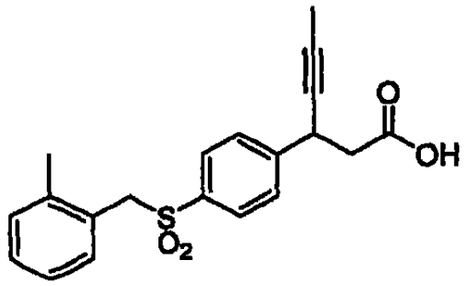


29.1 **29**

[0378] **Ácido 3-(4-o-Tolilmetanosulfinil-fenil)-hex-4-inóico (29).** Se hidrolizaron (10.0 mg, 0.025 mmol) de **29.1** utilizando los métodos descritos en el Ejemplo 28 para producir 3.0 mg (25%) de ácido 3-(4-o-Tolilmetanosulfinil-fenil)-hex-4-inóico (**29**). LC/MSD

m/e: 339.1 (M-H); ^{1}H NMR (400MHz) (acetona-d_6) δ 7.60 (2H, m), 7.49 (2H, m), 7.21 (2H, m), 7.04 (2H, m), 5.63 (2H, s), 4.17 (1H, m), 2.81 (2H, m), 2.22 (3H, s), 1.88 (3H, s).

6.30 Ejemplo 30



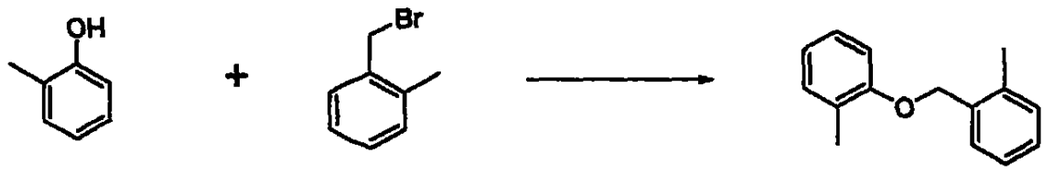
30

[0379] El ácido 3-(4-o-Tolilmetanosulfonilo-fenilo)-hex-4-iónico (**30**) se preparó utilizando métodos similares a los descritos en el Ejemplo 29.LC/MSD *m/e*: 357.2 (M+H); ^{1}H NMR (400MHz) (acetona-d_6) δ 7.69 (3H, m), 7.50 (1H, m), 7.17 (4H, m), 4.53 (2H, s), .4.22 (1H, m), 2.79 (2H, m), 2.27 (3H, s), 1.82 (3H, s).

6.31 Ejemplo 31

[0380] Los siguientes ejemplos ilustran la preparación de ácido 3-[2-Metil-4- (2-metil-benciloxi)-fenil]-hex-4-enoico (**31**).

Esquema 31.1

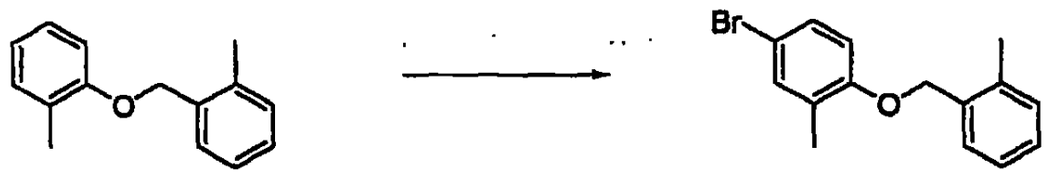


31.1

[0381] **2-(2-metil-benciloxi)tolueno (31.1).** Se agregaron (2.0 g, 10.81 mmol) de α-bromo-*o*-xileno a una solución de 2-metil-fenol (1.06 g, 9.82 mmol) y carbonato de cesio (7.99 g, 24.55 mmol) en DMF (20 mL). La reacción se mezclo a 80° C durante toda la noche. La mezcla de la reacción se acidificó con 25 mL de 1N HCl(aq) y se vertió en abundante agua. La capa acuosa se extrajo con acetato de etilo y la capa orgánica se secó con (Na_2SO_4) y se concentró *in vacuo*. El residuo resultante se purificó por medio de

cromatografía radial (20% acetato de etilo en hexanos) para producir 1.82 g (88%) de 2-(2-metil-benciloxi)tolueno (31.1). LC/MSD *m/e*: 213.2 (M+H).

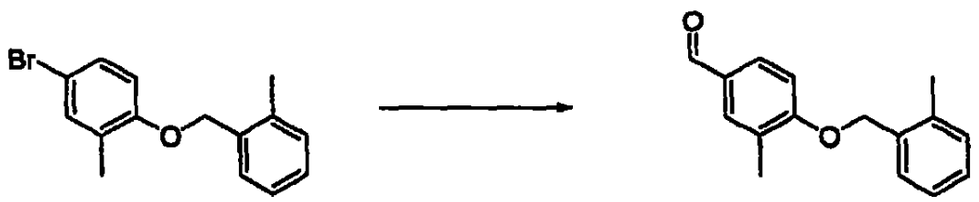
Esquema 31.2



31.1 **31.2**

[0382] **2-(2-metil-beciloxi)-5-bromotolueno (31.2).** Se agregaron (1.46 g, 8.23 mmol) de NBS a una solución de **31.1** (1.59 g, 7.48 mmol) en tetracloruro de carbono (8 mL). La mezcla se agito a 60° C durante toda la noche y se filtró para remover las succinimidas. El filtrado se concentró *in vacuo* y se purificó por medio de cromatografía radial (15% éter dietílico en hexanos) para producir 0.65g (25%) de 2-(2-metil-benciloxi)-5-bromotolueno (**31.2**). LC/MSD *m/e*: 314.2 (M+Na).

Esquema 31.3



31.2 **31.3**

[0383] **2-Metil-4-(2-metil-benciloxi)-benzaldehído (31.3).** Una solución de 2.5M de *n*-BuLi (2.1 mL, 5.26 mmol) en THF se agregó gota a gota a una solución a -78 °C de **31.2** (1.46 g, 5.01 mmol) en THP (25 mL). La reacción se agitó a -78° C por 15 minutos y luego se agregó DMF (3.3 mL). Tras 5 minutos se dejó de enfriar y se dejó que la reacción se calentara a temperatura ambiente. La reacción se particionó entre acetato de etilo y agua y la capa acuosa se extrajo una vez más con acetato de etilo. Las capas orgánicas se secaron (Na2SO4) y se concentraron. El residuo resultante se purificó por medio de cromatografía

radial (5% acetato de etilo en hexanos) para producir 269 mg (22%) de 2-Metil-4-(2-metil-benciloxi)-benzaldehído (**31.3**). LC/MSD *m/e*: 241.2 (M+H).

Esquema 31.4



31.3 **31.4**

[0384] **4-[2-Metil-4-(2-metil-benciloxi)-fenil]-but-3-en-2-ona (31.4).** Se agregaron (0.6 mL) de 2N $NaOH_{(aq)}$ a una solución de **31.3** (100 mg, 0.42 mmol) en acetona (1 mL). La reacción se mezcló a temperatura ambiente durante toda la noche y luego se absorbió en agua. La solución acuosa se acidificó con (1.5 mL) de 1N $HCl_{(aq)}$ y se extrajo con acetato de etilo. Los extractos orgánicos se lavaron con salmuera, se secaron (Na2SO4), y se concentraron *in vacuo*. El residuo resultante se purificó por medio de cromatografía radial (20% acetato de etilo en hexanos) para producir 74 mg (63%) de 4-[2-Metil-4-(2-metil-benciloxi)-fenil]-but-3-en-2-ona (**31.4**). LC/MSD *m/e*. 281.1 (M+H; ^{1}HNMR (400 MHz) (acetona-d_6) δ 7.83 (1H, d, *J*=16), 7.70 (1H, m), 7.46 (1H, m), 7.25 (3H, m), 6.96 (2H, m), 6.63 (1H, d, *J*=16 Hz).

Esquema 31.5

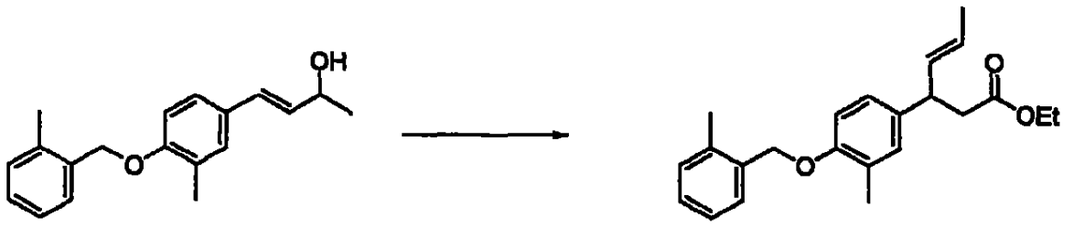


31.4 **31.5**

[0385] **4-[2-Metil-4-(2-metil-benciloxi)-fenil]-but-3-en-2-ol (31.5).** Se agregaron (20 mg, 0.51 mmol) de NaBH4 a una solución de 0.4 M de $CeCl_3$ en MeOH (0.65 mL, 0.26 mmol), 31.4 (74 mg, 0.26 mmol), y THF (1 mL). La reacción se agitó, destapada, hasta que cesó la evolución de gas. La reacción se aplacó con agua (1.5 mL) y se particionó entre agua y éter dietílico. La capa acuosa se extrajo 2 veces con éter dietílico y las capas

orgánicas combinadas se lavaron con salmuera y se concentraron *in vacuo* para producir 69 mg (93%) de 4-[2-Metil-4-(2-metil-benciloxi)-fenil]-but-3-en-2-ol (31.5). LC/MSD *m/e*: 266.3 (M-OH); ^{1}H NMR (400 MHz) (DMSO-d_6) δ 7.44 (2H, m), 7.25 (3H, m), 6.86 (2H, m), 6.75 (1H, m), 6.08 (1H, m), 5.11 (2H, s), 4.40, (1H, m), 2.38 (3H, s), 2.32 (3H, s), 1.29 (3H, m).

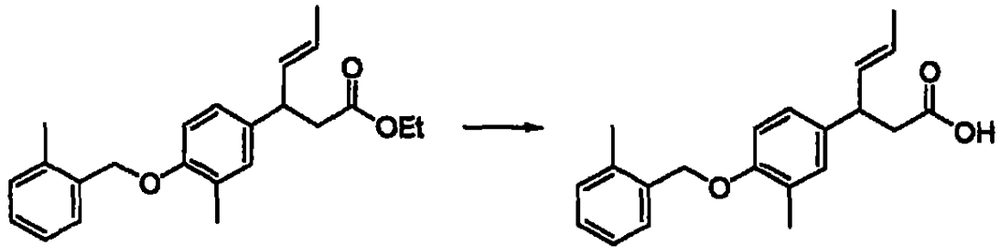
Esquema 31.6



31.5 **31.6**

[0386] Éster etílico de ácido 3-[2-Metil-4-(2-metil-benciloxi)-fenil]-hex-4-enoico (31.6). Se agregó ácido propiónico (cat.) a una solución de 31.5 (69 mg, 0.24 mmol) en 1,1,1 - trietoxi-etano (440 µL, 2.4 mmol). La reacción se agitó a 105 °C durante toda la noche. Se removió el solvente bajo presión reducida y el residuo resultante se purificó por medio de cromatografía radial (5% acetato de etilo en hexanos) para producir 33 mg (39%) de éster etílico de ácido 3-[2-Metil- 4-(2-metil-benciloxi)-fenil]-hex-4-enoico (**31.6**). LC/MSD *m/e*: 375.0 (M+Na).

Esquema 31.7



31.6 **31**

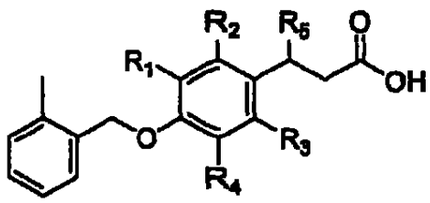
[0387] Ácido 3-[2-Metil-4-(2-metil-benciloxi)-fenil]-hex-4-enoico (31). La hidrólisis de **31.6** (33 mg, 0.094 mmol) se llevó a cabo utilizando métodos similares a los descritos en el Ejemplo 26 para producir 5.7 mg (19%) de ácido 3-[2-Metil-4-(2-metil-benciloxi)-fenil]-

hex-4-enoico (**31**). ^{1}H NMR (400 MHz) (acetona) d 7.44 (2H, m), 7.25 (3H, m), 6.86 (2H, m), 6.73 (1H, m), 6.10 (1H, m), 5.64 (2H, s), 4.42 (1H, m), 2.38 (3H, s), 2.32 (3H, s), 1.29 (3H, d, *J*=7.0 Hz).

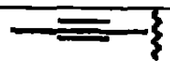
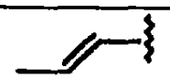
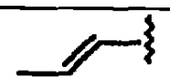
6.32 Ejemplo 32

[0388] Los siguientes compuestos se prepararon utilizando métodos similares a los descritos en los Ejemplos 28 y 31.

TABLA 11



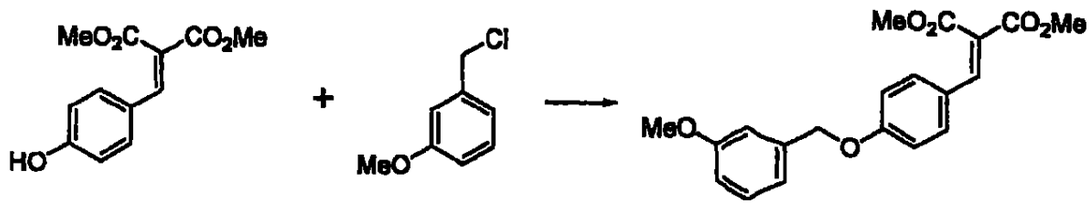
32

Compuesto	R1	R2	R3	R4	R5
32.1	Me	H	Me	H	
32.2	H	Ph	H	H	
32.3	Me	Me	H	H	
32.4	Ph	H	H	H	

3.66 Ejemplo 33

[0389] El siguiente ejemplo ilustra la preparación de ácido 3-[4-(3-Metoxi-benciloxi)-fenil]-5-metil-hex-4-enoico (**33**).

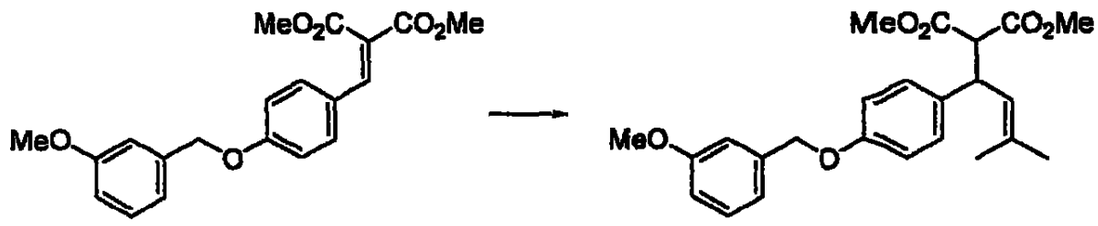
Esquema 33.1



33.1

[0390] **Éster dimetílico de ácido 2-[4-(3-Metoxi-benziloxi)-bencilideno]-malónico (33.1).** Se agregó K_2CO_3 a una solución de éster dimetílico de ácido 4-hidroxibencilidena-malónico (6.95 mmol) y cloruro 4-metioxibencilo (7.64 mmol) en DMF (15 ml). Luego se agitó a temperatura ambiente durante toda la noche. La reacción se vertió en agua, y el producto se extrajo con acetato de etilo por dos veces. La capa orgánica se lavo con agua y salmuera saturada, se secó sobre Na_2SO_4, y se concentro *in vacuo*. El residuo resultante se purificó utilizando cromatografía de columna de gel de sílice (hexano/acetato de tilo = 2/1) para dar el compuesto **33.1** como un sólido blanco (3.2 mmol).

Esquema 33.2



33.1 **33.2**

[0391] **Éster dimetílico de ácido 2-(1-[4-(3-Metoxi-benziloxi)-fenil]-3-metil-but-2-enil)-malónico (33.2).** A una solución del compuesto **33.1** (1.0 mmol) en THF gota a gota se agregó bromuro de 2-metil-1-propenilmagnesio (3 mL, 0.5 M en THF). La mezcla de la reacción se agitó a temperatura ambiente por 1 hora y luego se aplacó con $NH4Cl_{(aq)}$ saturado y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua y salmuera saturada, se secaron sobre Na_2SO_4, y se concentraron *in vacuo*. El residuo resultante se purificó utilizando cromatografía de columna de gel de sílice (hexano/acetato de etilo= 2/1) para dar el compuesto **33.2** como un sólido blanco (0.93 mmol).

Esquema 33.3



33.2 **33.3**

[0392] **Ácido 2-{1[4-(3-Metoxi-benciloxi)-fenil]-3-metil-but-2-enil}-malónico (33.3).** A una solución del compuesto **33.2** (0.50g, 1.21 mmol) en THF (5 ml), metanol (5ml) y agua (2.5 ml) se agregó monohidrato de hidróxido de litio (1.17g, 28 mmol). La mezcla de la reacción se agitó a temperatura ambiente durante toda la noche. La mezcla de la reacción se acidificó con 1N HCl a un pH 2-3, y luego se extrajo con acetato de etilo por dos veces. La capa orgánica se lavo con agua y salmuera, se secó sobre Na_2SO_4, y se concentró *in vacuo*. El residuo resultante se utilizó en el siguiente paso sin purificación.

Esquema 33.4



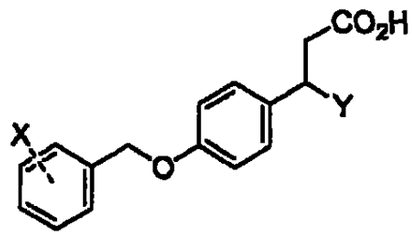
33.3 33

[0393] **Ácido 3-[4-(3-Metoxi-benciloxi)-fenil]-5-metil-hex-4-enoico (33).** Una suspensión del compuesto **33.3** (0.136 mmol) en toluene se sometió al reflujo por 16 h. Luego de remover el solvente, el residuo se purificó utilizando cromatografía de columna de gel de sílice (TFA/ Diclorometano/ acetato de etilo = 1/5/40) para obtener el compuesto **33** como un sólido blanco (0.088 mmol). MS ESI m/e: 339 (M-H) ^{1}H NMR (500MHz) (DMSO-d_6) δ 11.97 (1H, s); 7.31 (1H, t, J=10 Hz); 7.14 (2H, d, J=11 Hz); 6.99 (2H, m); 6.87 (3H, m); 5.22 (1H, m); 5.03 (2H, s); 3.75 (1H, m); 3.75 (3H, s); 2.44-2.53 (2H, m); 1.63 (3H, s); 1.62 (3H, s).

6.34 Ejemplo 34

[0394] Los siguientes compuestos se hicieron utilizando los métodos descritos en el Ejemplo 33.

TABLA 12



Compuesto	X	Y
34.1	4-Metoxi	1-Propenilo
34.2	4-Metoxi	3-Propenilo
34.3	4-Metoxi	Vinilo
34.4	4-Metoxi	2-Propenilo
34.5	4-Metoxi	2-Metil-1-propenilo
34.6	4-Metoxi	1-Metil-1-propenilo
34.7	4-Metoxi	Tiofen-2-ilo
34.9	2-Metoxi	2-Metil-1-propenilo
34.10	3-Metoxi	1-Propinilo
34.11	3-Metoxi	2-Metil-1-propenilo

[0395] Compuesto **34.1.** MS ESI m/e: 325 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.05 (1H, s); 7.36 (2H, d, J=10 Hz); 7.16 (2H, d, J=10 Hz); 6.94 (2H, d, J=10 HZ); 6.90 (2H, d, J=5 Hz); 5.48-5.58 (1H, m); 5.39-5.43 (1H, m); 4.98 (2H, s); 3.99-4.03 (1H, m); 3.76 (3H, s); 2.46-2.60 (2H, m); 1.64 (3H, d, J=5 HZ).

[0396] Compuesto **34.2.** MS ESI m/e: 325 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 11.98 (1H, s); 7.38 (2H, d, J=10 Hz); 7.13 (2H, m); 6.95 (2H, m); 6.09 (2H, m); 5.63 (1H, m); 4.97 (2H, s); 4.92 (2H, d, J=10 Hz); 3.76 (3H, s); 3.03 (1H, m); 2.28-2.56 (4H, m).

[0397] Compuesto **34.3.** MS ESI m/e: 311 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.06 (1H, s); 7.37 (2H, d, J=10 Hz); 7.14 (2H, d, J=10 Hz); 6.92-6.95 (4H, m); 5.92 (1H, m); 5.00 (2H, m); 4.98 (2H, s); 3.76 (3H, s); 3.35 (1H, m); 2.54-2.64 (2H, m).

[0398] Compuesto **34.4.** MS ESI m/e: 325 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.03 (1H, s); 7.37 (2H, d, J=10 Hz); 7.09-7.19 (4H, m); 6.91-6.99 (4H, m); 4.97 (2H, s); 3.76 (3H, s); 3.63 (1H, m); 2.57-2.71 (2H, m); 2.09 (3H, s).

[0399] Compuesto **34.5.** MS ESI m/e: 339 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 11.97 (1H, s); 7.36 (2H, d, J=10 Hz); 7.14 (2H, d, J=10 Hz); 6.94 (2H, d, J=10 Hz); 6.89 (2H, d, J=5 Hz); 5.24 (2H, d, J=10 Hz); 3.85-3.90 (1H, m); 3.76 (3H, s); 2.44-2.57 (2H, m); 1.68 (3H, s); 1.63 (3H, d, J=10 Hz).

[0400] Compuesto **34.6.** MS ESI m/e: 339 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 11.97 (1H, s); 7.37 (2H, d, J=8.5 Hz); 7.10 (2H, d, m); 6.90-6.95 (4H, m); 5.23 (1H, d, J=6.5

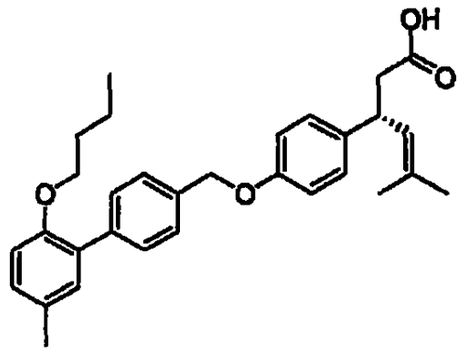
Hz); 4.97 (2H, s); 4.29 (1H, m); 3.76 (3H, s); 2.47-2.75 (2H, m); 1.71 (3H, d5 J=6 Hz); 1.56 (3H, s).

[0401] Compuesto **34.7**. MS ESI m/e: 367 (M-H). 1H NMR (500MHz) (DMSO-d_6) δ 12.18 (1H, s); 7.37 (2H, d, J=5 Hz); 7.32 (1H, m); 7.21 (2H, d, J=10 Hz); 6.92-6.95 (6H, m); 4.98 (2H3 s); 4.58 (1H, m); 3.76 (3H, s); 3.01 (1H, m); 2.94 (1H, m).

[0402] Compuesto **34.9**. MS ESI m/e: 339 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 11.99 (1H, s); 7.37 (2H, m); 7.14 (2H, d, J=10 Hz); 7.04 (2H, d, J=10 Hz); 6.96 (1H, t, J=10 Hz); 6.88 (2H, d, J=10 Hz); 5.24 (2H, d, J=10 Hz); 5.00 (2H, s); 3.87 (1H, m); 3.87(3H, s); 2.45-2.55 (2H, m); 1.63 (3H, s).

[0403] Compuesto **34.10**. MS ESI m/e: 323 (M-H). 1H NMR (500MHz) (DMSO- d6) δ 12.10 (1H, s); 7.25-7.32 (3H, m); 7.01 (2H, d, J=9 Hz); 6.94 (2H, d, J=10 Hz); 6.88 (1H, m); 5.05 (2H, s); 3.92-3.95 (1H, m); 3.75 (3H, s); 2.58 (2H, d, J=10 Hz); 1.77 (3H, s).

[0404] Compuesto 34.11. MS ESI m/e:353.0 (M-H).



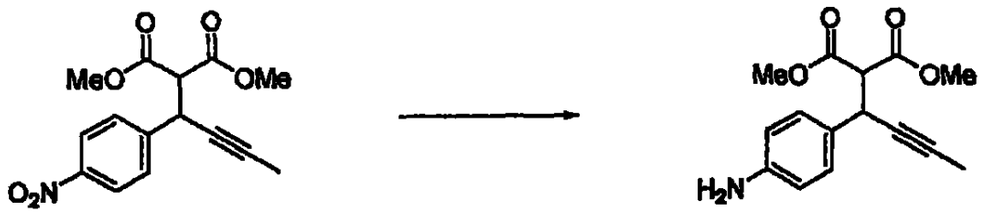
34.12

[0405] ^{1}H NMR (400MHz) ($(CD_3)_2SO$) δ 11.95 (s, 1H), 7.49 (d, 2H, J= 8.2 Hz), 7.15 (d, 2H, J= 8.6 Hz), 7.08-7.10 (m, 2H), 6.91-6.98 (m, 3H), 5.25 (d, 1H, 9.0 Hz), 5.07 (s, 2H), 3.78-3.94 (m, 3H), 2.44-2.59 (m, 2H), 2.26 (s, 3H), 1.55-1.63 (m, 8H), 1.30-1.38 (m, 2H), 0.85 (t, 3H, J= 7.3 Hz). $[M+1]^+$ Calculado para $C_{31}H_{36}O_4$: 473.3. Se encontraron 473.5.

6.35 Ejemplo 35

[0406] El ejemplo siguiente ilustra la preparación de ácido 3-[4-(3-Metoxi- benciloxi)-fenil] -5-metil-hex-4-enoico.

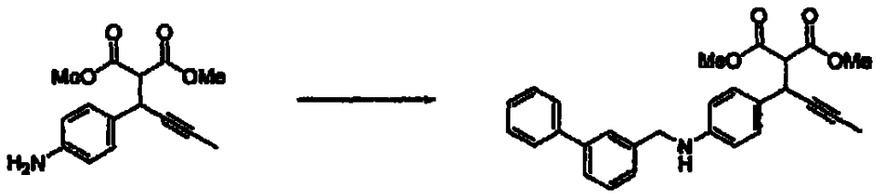
Esquema 35.1



35.1 35.2

[0407] Éster dimetílico de ácido 2-[1-(4-Amino-fenil)-but-2-inil]-malónico (35.2). A la solución del compuesto 35.1 (15.3 mmol, preparada de dimetil-4-nitrobencilidinemalonato y bromuro de 1-propinilmagnesio, disponibles comercialmente, de acuerdo con el método del Ejemplo 33) se agregó cloruro de estaño dihidrato (46 mmol) en etanol (200 ml). La mezcla se agitó a 70 °C por 17 h. Tras remover el solvente bajo presión reducida, se agregó una solución acuosa de carbonato de sodio a la capa acuosa y se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua y salmuera, y se secaron sobre Na_2SO_4 concentrado *in vacuo*. El residuo resultante se filtró a través de un tapón corto de gel de sílice, eluído con acetato de etilo. El eluyente se concentró y se obtuvo el compuesto 35.2 (12.8 mmol).

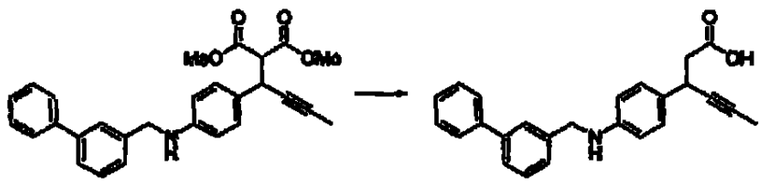
Esquema 35.2



35.2 35.3

[0408] Éster dimetílico de ácido 2-{1-{4-[(Bifenil-3-ilmetil)-amino]-fenilo}-but-2-inil}-malónico (35.3). Se agitó una mezcla del compuesto 35.2 (1.0 mmol), 3-(bromometil)bifenil (1.3 mmol) y K_2CO_3 (2.0 mmol) en DMF (10 ml) a 90 °C por 19 h. Tras diluir con acetato de etilo, se lavó la mezcla con Na_2CO_3 acuoso y luego con salmuera, se secó sobre Na_2SO_4, y se concentró *in vacuo*. El residuo resultante se purificó por cromatografía en columna de gel de sílice (acetato de hexano/etilo = 2/1) para dar el compuesto **35.3**.

Esquema 35.3



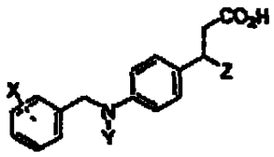
35.3 35

[0409] **Ácido 3-(4-[(Bifenil-3-ilmetil)-amino]-fenilo-hex-4-inóico (35).** El compuesto **35** se preparó a partir del compuesto **35.3** por hidrólisis con base y decarboxilación como se describió en el Ejemplo **33**. MS ESI m/e: 368 (M-H). ^{1}H NMR (500MHz) (DMSO-J6) δ 7.63-7.66 (2H, m); 7.51(1H, m); 7.34-7.44 (6H, m); 7.05 (2H, d, J=10 Hz); 6.60 (2H, d, J=10 Hz); 4.33 (2H, s); 3.79-3.83 (1H, m); 2.44-2.53 (2H, m); 2.09 (1H, s); 1.74 (3H, s).

6.36 Ejemplo 36

[0410] Los siguientes compuestos se prepararon de acuerdo con los métodos descritos en el Ejemplo 35.

TABLA 13



Compuesto	X	Y	Z
36.1	3-Metoxi	H	1-Propinilo
36.2	3-Metoxi	3-Metoxi-bencilo	1-Propinilo
36.3	4-Fenilo	H	1-Propinilo
36.4	4-(2-cianofenilo)	H	1-Propinilo

6.37 Ejemplo 37

[0411] Este ejemplo ilustra la preparación de ácido (+/-)-3-(4-[(4- metoxifenil)metoxi]-fenil)-propanóico.

Esquema 37.1



12.2 37

[0412] **Ácido (+/-)-3-(4-[(4-metoxifenil)metoxi]fenil)-propanóico (37).** A una solución en agitación de acetato de etilo (10OmL) de 5-[[4-[(4-metoxifenil)metoxi]fenil]-metileno]-2,2-dimetil-[l,3]dioxano-4,6-diono (200 mg, 0.543 mmol) se agregó EtOH (4 mL), seguido de NaBH4 (62 mg, 1.63 mmol). La mezcla de la reacción se agitó a temperatura ambiente por 15 minutos, se aplacó con agua (5 mL), se extrajo con EtOAc (10 mL). El extracto se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró hasta lograr un sólido blanco. Se calentó una solución de este sólido blanco en 3:1 piridina-agua (5 mL) a 100 °C por 24h. La mezcla de la reacción se enfrió a temperatura ambiente y se puso en un baño de agua con hielo. Con mucho cuidado se agregó HCl para lograr un pH ~2. La suspensión resultante se extrajo con acetato de etilo (10mL x 3), se secó sobre MgSO4, se filtró, y se concentró hasta lograr un sólido blanco opaco. El HPLC preparatorio dio el compuesto **37** como un sólido blanco. MS ESI (neg.) m/e: 285.0 (M -1).

6.38 Ejemplo 38

[0 13] Este ejemplo ilustra la preparación de ácido (+/-)-3-(4-[(4- metoxifenil)metoxi]-fenil)-3-ciano-propanóico.



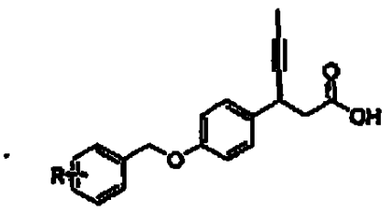
38

[0414] **Ácido (+/-)-3-(4-[(4-metoxifenil)metoxi]fenil)-3-ciano-propanóico (38).** A una solución en agitación de DMF (10mL) de 2-[4-[(4-Metoxifenil)metoxi]fenil]- acetonitrilo (500 mg, 1.97 mmol) se agregó bromoacetato de etilo (330 µL, 2.96 mmol), seguido de K_2CO_3 (820 mg, 5.9 mmol). La mezcla de la reacción se agitó a temperatura ambiente por 2h, se vertió en agua fría (100 mL), se filtró, y se secó. Se agitaron 20 mg de este sólido blanco en 1:1 THF/1N NaOH en MeOH (4 mL) por 5h. La mezcla de la reacción se concentró, se diluyó en agua (10mL), se lavó con EtOAc (5mL x '2): La capa acuosa se

acidificó con 3N HCl a un pH ~2, se extrajo con EtOAc (10mL x 2), se secó sobre $MgSO_4$, se filtró y se concentró hasta lograr un sólido blanco. MS ESI (neg.) m/e: 310.0 (M -I).

6.39 Ejemplo 39

[0415] Los siguientes compuestos se prepararon por los métodos descritos en el Ejemplo 15 usando el enatiómero con el tiempo más corto de retención de la resolución del quiral HPLC.



Compuestos	R	Compuestos	R
15	2-CH_3	39.4	4-(2-CN)Ph
39.1	3-CH_3	39.5	3-CF_3
39.2	3-CF_3O	39.6	4-Br
39.3	3-Cl	39.7	4-CH_3O

[0416] **Ácido (3S)-3-[4-(3-Metil-benciloxi)-fenil]-hex-4-inóico (39.1).** MS-ESI (neg.) m/e: 307.1 (M-H). $[\alpha]^{20}$: +21.26 (cθ.188, DMF).

[0417] **Ácido (3S)-3-[4-(3-Trifluorometoxi-benciloxi)-fenil]-hex-4-inóico (39.2).** MS-ESI (neg.) m/e: 377.0 (M-H). $[\alpha]^{20}$: +18.30 (cθ.259, DMF).

[0418] **Ácido (3S)-3-[4-(3-clorobenciloxi)-fenil]-hex-4-inóico (39.3).** MS-ESI (neg.) m/e: 327.1 (M-H). [α]20: +14.36 (cθ.440, DMF).

[0419] **Ácido (3S)-3-[4-(2'-Ciano-bifenil-4-ilmetoxi)-fenil]-hex-4-inóico (39.4).** MS-ESI (neg.) m/e: 394.1 (M-H). $[\alpha]^{20}$: +16.07 (cθ.331, DMF).

[0420] **Ácido (3S)-3-[4-(2-Tirfluorometil-benciloxi)-fenil]-hex-4-inóico (39.5).** MS-ESI (neg.) m/e: 361.1 (M-H). $[\alpha]^{20}$: +12.80 (cθ.285, DMF).

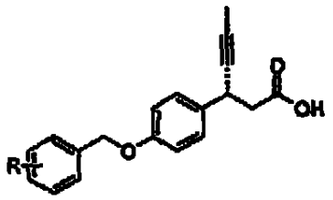
[0421] **Ácido (3S)-3-[4-(4-Bromobenciloxi)-fenil]-hex-4-inóico (39.6).** MS-ESI (neg.) m/e: 371.0, 373.0 (M-H). $[\alpha]^{20}$: +19.19 (cθ.238, DMF).

[0422] **Ácido (3S)-3-[4-(4-Metoxi-benciloxi)-fenil]-hex-4-inóico (39.7).** MS- ESI (neg.) m/e: 323.0 (M-H). $[\alpha]^{20}$: +23.30 (cθ.329, DMF).

6.40 Ejemplo 40

[0423] Los siguientes compuestos se prepararon de acuerdo con el método descrito en el ejemplo 15 utilizando el enatiómero con el tiempo más largo de retención de la resolución del quiral HPLC.

TABLA 15



Compuestos	R	Compuestos	R
40.1	2-CH_3	40.4	3-CF_3
40.2	3-Cl	40.5	4-CH_3O
40.3	4-(2-CN)Ph		

[0424] **Ácido (3R)-3-[4-(2-Metil-benciloxi)-fenil]-hex-4-inóico (40.1).** 1HNMR (400 MHz, acetona-d_6) δ 7.45 (d, 1H, J=7.11 Hz); 7.37 (d, 2H5 J-8.58 Hz); 7.26 (d, 1H, J=I.62 Hz); 7.22-7.27 (m, 2H); 7.00 (d, 2H, J-8.76 Hz); 5.11 (s, 2H); 4.05 (m, 1H); 3.33 (s, 1H); 2.69 (m, 2H); 2.38 (s, 3H); 1.80 (d, 3H, J=2.44). MS-ESI (neg.) m/e: 307.1 (M-H). $[\alpha]^{20}$: -19.78 (cθ.286, DMF).

[0425] **Ácido (3R)-3-[4-(3-clorobenciloxi)-fenil]-hex-4-inóico (40.2).** MS-ESI (neg.) m/e: 327.0 (M-H). $[\alpha]^{20}$: -20.50 (cθ.158, DMF).

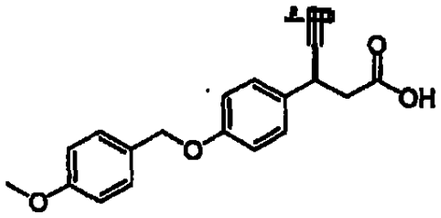
[0426] **Ácido (3R)-3-[4-(2'-Ciano-bifenil-4-ilmetoxi)-fenil]-hex-4-inóico (40.3).** MS-ESI (neg.) m/e: 394.1 (M-H). $[\alpha]^{20}$: -25.04 (cθ.143, DMF).

[0427] **Ácido (3R)-3-[4-(2-Tirfluorometil-benciloxi)-fenil]-hex-4-inóico (40.4).** MS-ESI (neg.) m/e: 361.0 (M-H). $[\alpha]^{20}$: -14.69 (cθ.286, DMF).

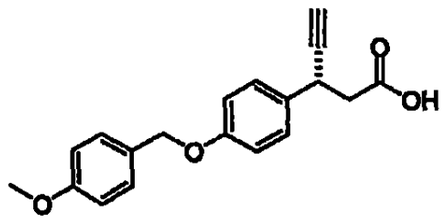
[0428] **Ácido (3R)-3-[4-(4-Metoxi-benciloxi)-fenil]-hex-4-inóico (40.5).** MS- ESI (neg.) m/e: 323.0 (M-H). $[\alpha]^{20}$: -27.20 (cθ.324, DMF).

6.41 <u>Ejemplo 41</u>

[0429] Los siguientes compuestos se prepararon con métodos similares a los del ejemplo 15.



41.1



41.2

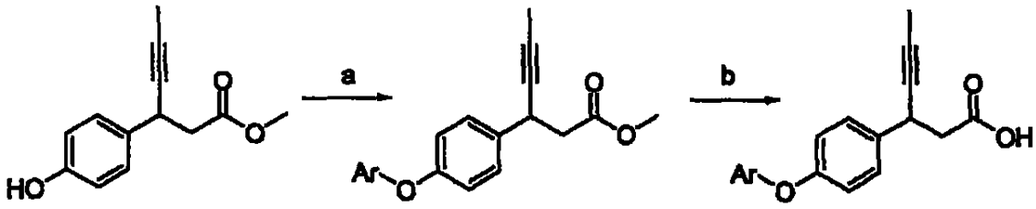
[0430] **Ácido (3S)-3-[4-(4-Metoxi-benciloxi)-fenil]-pent-4-inóico (41.1).** MS- ESI (pos.) m/e: 333.1 (M+H). $[\alpha]^{20}$: +11.80 (c0.166, DMF). 275

[0431] **Ácido (3R)-3-[4-(4-Metoxi-benciloxi)-fenil]-pent-4-inóico (41.2).** MS- ESI (pos.) m/e: 333.1 (M+H). $[\alpha]^{20}$: -10.20 (c0.206, DMF).

6.42 Ejemplo 42

[0432] El Esquema 42.1 presenta un procedimiento general para la preparación de compuestos de éter diarílico.

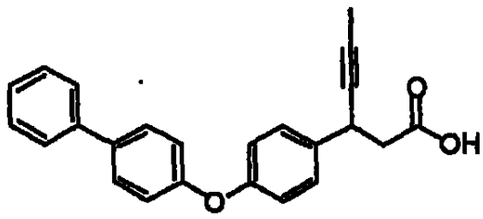
Esquema 42.1



Esquema 42.1. a. $ArB(OH)_2$, $CuO(Ac)_2$, Et_3N, DCM, 4A MS, r.t, 16h; b. LiOH/THF, MeOH, y agua, r.t, 2h.

42.1 **42.2** **42.3**

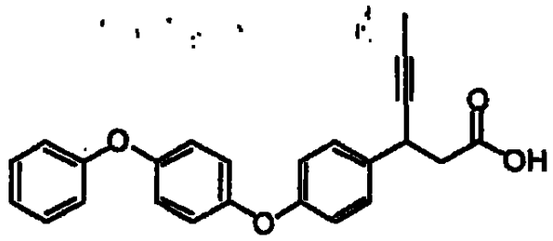
[0433] Procedimiento general para la preparación de compuestos de éter diarílico: Se cargó un matraz con fenol (1.0 equiv.), $Cu(OAc)_2$ (1.0 equiv.), ácido ariloborónico (1.0-3.0 equiv.), támices moleculares 4 Å en polvo. La mezcla de la reacción se diluyó con CH_2Cl_2 para resultar en una solución de aproximadamente 0.1 M en fenol, y se agregó Et_3N (5.0 equiv.). Tras agitar la mezcla heterogénea de la reacción por 16h a 25 °C bajo atmósfera ambiente, la mezcla resultante se filtró y se aisló el éter diarílico del filtrado orgánico por cromatografía flash. El éster resultante fue luego hidrolizado con LiOH (2.0 equiv.) en una mezcla 1:1:1 de MeOH, THF, y agua por 2h a 25 °C. La mezcla de la reacción se acidificó con 1N HCl, se extrajo con CH_2Cl_2 y se concentró para dar el ácido puro.



42.4

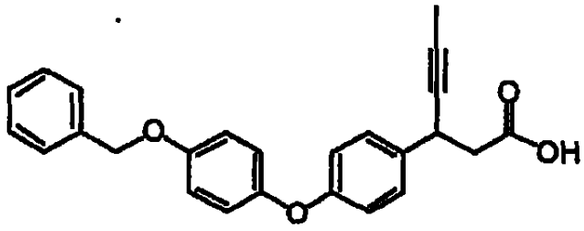
[434] **Ácido 3-[4-(Bifenil-iloxi)-fenil]-hex-4-inóico (42.4).** MS ESI m/e: 357.0 (M + H). ^1H NMR (500 MHz) ($CDCl_3$) δ 7.60-7.57 (4H, m); 7.46 (2H, dd, J=8.0, 8.0 Hz); 7.39 (2H,

d, J-8.5 Hz); 7.36 (1H, d, J=7.3 Hz); 7.09 (2H5 d, J=8.6 Hz); 7.04 (2H, d, J=8.6 Hz); 4.2-4.1 (1H3 m); 2.87 (1H, dd, J=15.8, 8.6 Hz); 2.77 (1H, dd, J=15.8, 6.7 Hz); 1.88 (3H, d, J=2.3 Hz).



42.5

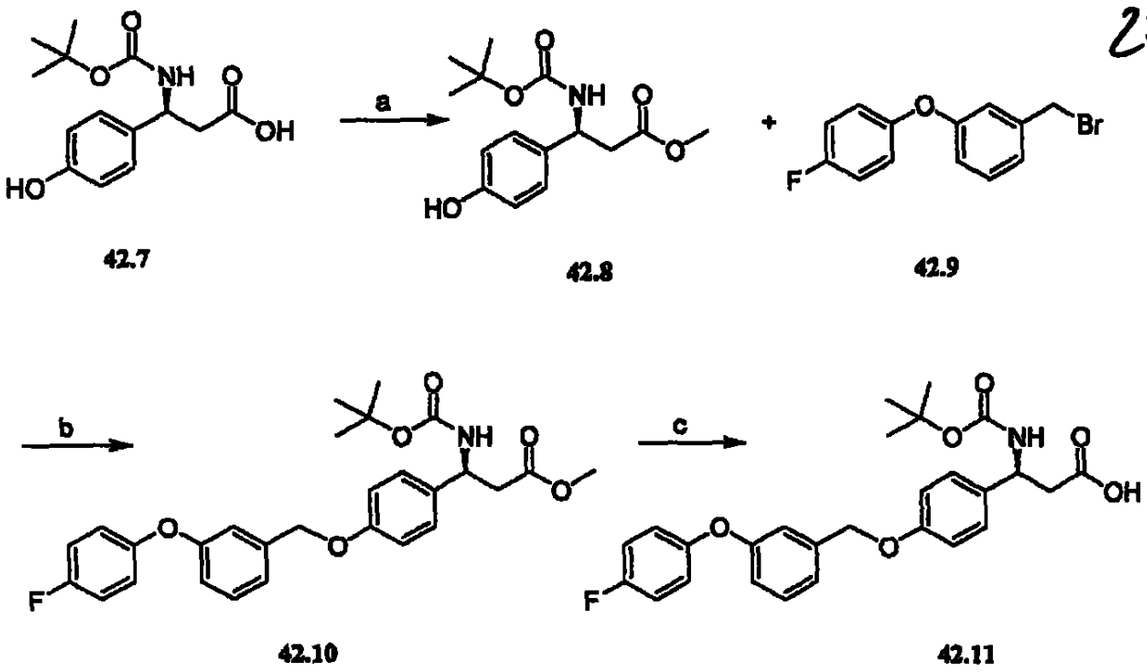
[0435] **Ácido 3-[4-(4-Fenoxi-fenoxi)-fenil]-hex-4-inóico (42.5).** MS ESI m/e: 373.0 (M + H). ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.37-7.32 (5H, m); 7.12 (2H, dd, J=8.0, 8.0 Hz); 7.03 (2H, d, J=7.5 Hz); 7.02 (2H, s); 6.97 (2H, d, J=8.6 Hz); 4.1 (1H, m); 2.85 (1H, dd, J=15.8, 8.6 Hz); 2.75 (1H, dd, J=15.8, 6.7 Hz); 1.87 (3H, d, J=2.3 Hz).



42.6

[0436] **Ácido 3-[4-(4-Benciloxi-fenoxi)-fenil]-hex-4-inóico (42.6).** MS ESI m/e: 387.0 (M + H). ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.47 (2H, d, J=7.2 Hz); 7.42 (2H, dd, J=7.5, 7.5 Hz); 7.37 (1H, d, J=7.3 Hz); 7.33 (2H, d, J=8.7 Hz); 6.98 (4H, br. s); 6.93 (2H, d, J-9.7 Hz); 5.07 (2H, s); 4.10 (1H, m); 2.84 (1H, dd, J=15.7, 8.5 Hz); 2.75 (1H, dd, J=15.7, 6.7 Hz); 1.86 (3H, d, J=2.3 Hz).

Esquema 42.2



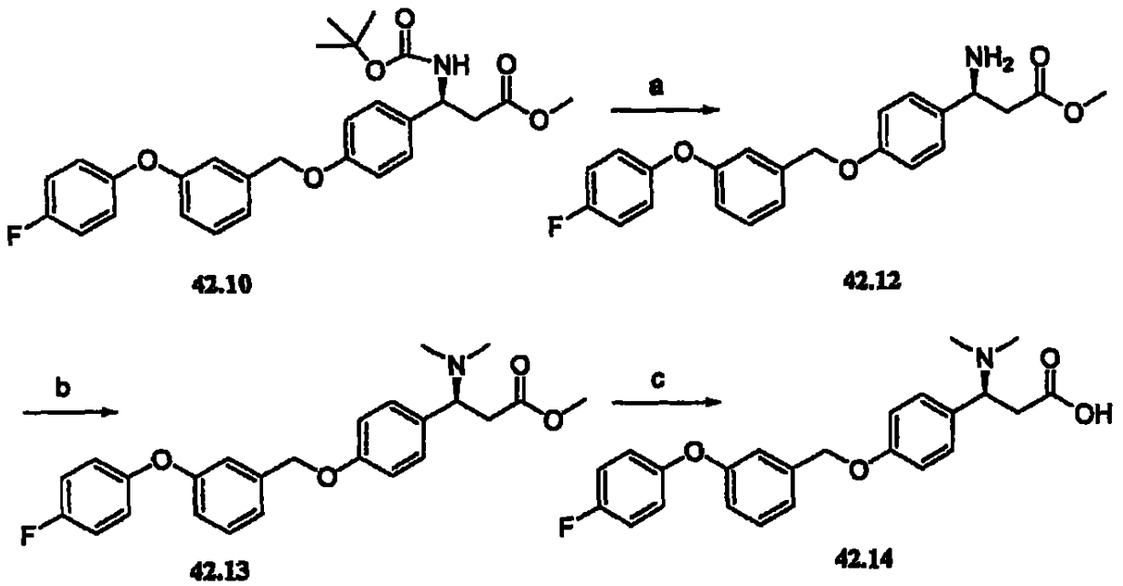
42.7 42.8 42.9

42.10 42.11

Esquema 42.2. a. $TMSCHN_2$, MeOH, benceno, r.t, 1h; b. K_2CO_3, DMF, r.t, toda la noche; c. LiOH/THF, MeOH, y agua, r.t, 2h.

[0437] Ácido (S)-3-tert-Butoxicarbonilamino-3-{4-[3-(4-fluoro-fenoxi)-benciloxi]-fenil}-propiónico (42.11). A una solución de 2.5 niL de 2M de rimetilsilildiazometano en hexano a 25 °C lentamente se agregó ácido 3-Boc-amino-3(4-hidroxifenil)-propanóico (42.7) (703 mg, 2.5 mmol) en 25mL de MeOH/Benceno(4:1). La mezcla de la reacción se agitó por 1h y se concentró *in vacuo* para dar el éster. MS ESI m/e: 296.0 (M + H). A una solución del éster metílico **42.8** (2.5 mmol) y bromuro de 4-fluorofenoxibencilo **42.9** (700 mg, 2.5 mmol) en DMF (10 mL), se agregó K_2CO_3 (414 mg, 3 mmol) y la mezcla resultante se agitó durante toda la noche (14~16h) a 25 °C. La solución se diluyó (20mL0) y se extrajo dos veces con EtOAc (20 mL). Se concentró la extracción orgánica y el producto se purificó por cromatografía flash. MS ESI m/e: 518.0 (M + Na). El metil éster **42.10** (39mg, 0.08 mmol) se hidrolizó con LiOH (10 mg, 0.25 mmol) en una mezcla de 1.5 mL of 1:1:1 de MeOH, THF, y agua por 2h a 25 °C. La mezcla de la reacción se acidificó con 1N HCl, se extrajo con CH_2Cl_2 y se concentró para dar el ácido puro **(42.11)**. MS ESI m/e: 504.0 (M + Na). ^1H NMR (400MHz) ($CDCl_3$) δ 8.5 (1H, br. s); 7.34 (1H5 dd, J=8.0, 8.0 Hz); 7.24 (2H, d, J=8.8 Hz); 7.16 (1H, d, J=7.7 Hz); 7.07-6.98 (5H, m); 6.93 (2H, d, J-11.7 Hz); 6.92 (1H, d); 5.3 (1H, br. s); 5.03 (2H, s); 3.0- 2.8 (2H, m); 2.1-1.9 (1H, m); 1.44 (9H, s).

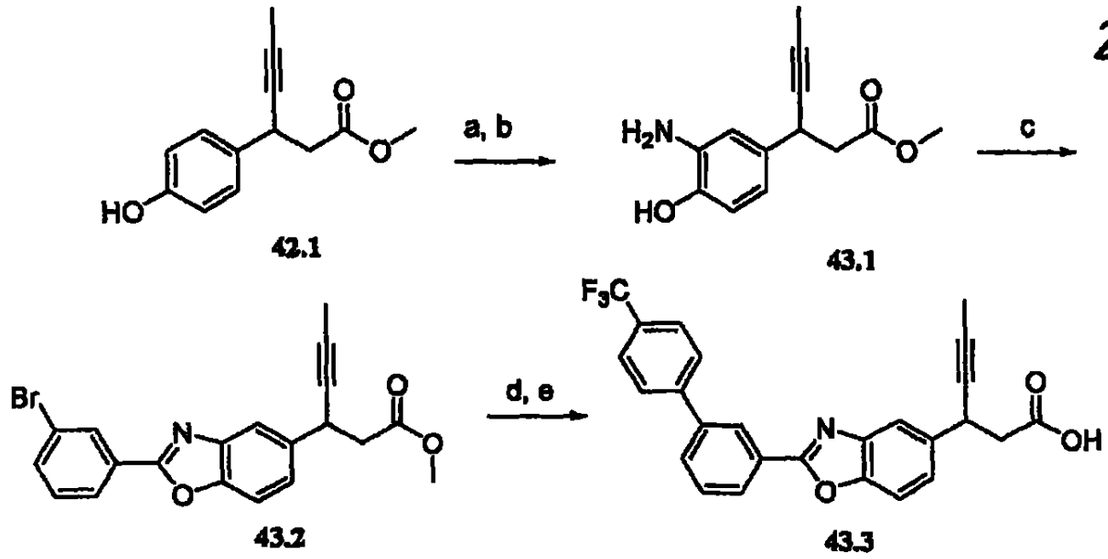
Esquema 42.3



Esquema 42.3. a. TFA, DCM, r.t., Ih; b. formaldehido, $NaBH(OAc)_3$, AcOH5 DMF, r.t, toda la noche; c. LiOH/THF, MeOH, y agua, r.t., 2h.

[0438] Ácido 3-Dimetilamino-3-{4-[3-(4-fluoro-fenoxi)-benciloxi]-fenil}-propiónico (42.14). El ácido (S)-3-tert-Butoxicarbonilamino-3-{4-[3-(4-fluoro-fenoxi)-benciloxi] fenil}-propiónico metil éster (42.10) (1.0 g, 2 mmol) se trató con 10 mL de una solución TFA al 10% en CH_2Cl_2 a 25 °C por 1h. El solvente se concentró *in vacuo* para dar el amino libre (42.12). MS ESI m/e: 418.0 (M + Na). El amino (60 mg, 0.15 mmol) se trató con exceso de formaldehido (2 equiv.), $NaBH(OAc)_3$ (85 mg, 0.4 mmol) y una cantidad catalítica de AcOH en DMF por toda la noche (14-16h) a 25 °C. El producto se purificó por HPLC en fase reversa. MS ESI m/e: 424.1 (M + H). El éster metílico se hidrolizó con LiOH (19mg, 0.45 mmol) en una mezcla de 3 mL de1:1:1 de MeOH, THF, y agua por 2h a 25 °C. La mezcla de la reacción se acidificó con 1N HCl, se extrajo con CH_2Cl_2 y se concentró para dar el ácido puro (42.14) (23 mg). MS ESI m/e: 410.2 (M + H). ^1H NMR (500MHz) ($CDCl_3$) δ 9.46 (1H, br. s); 7.72 (1H, d, J=16.0 Hz); 7.51 (2H, d, J=8.7 Hz); 7.36 (1H, dd, J=8.0, 8.0 Hz); 7.17 (2H, d, J=7.0 Hz); 7.08-6.98 ($5H_2$, m); 6.94 (1H, d, J=8.2 Hz); 6.34 (1H, d, J=16.0 Hz); 5.10 (2H, s); 3.4-2.9 (2H, m); 2.73 (6H, s); 2.1-1.9 (1H, m).

Esquema 43.1



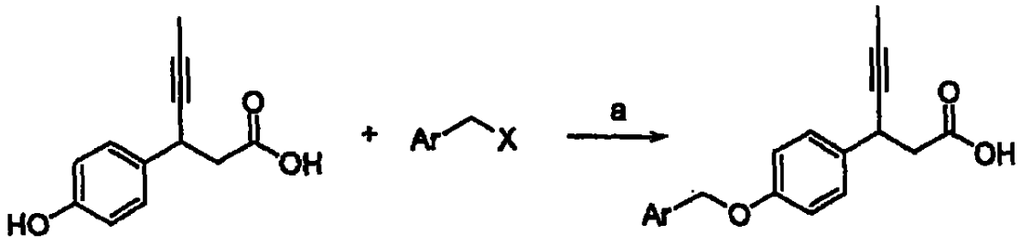
Esquema 43.1. a. HNO3, HOAc, 80 °C, 3h; b. $SnCl_2$, EtOAc/EtOH, 70 °C, 3h; c. 3-bromobenzaldehido, DDQ, DMF, r.t., 2h; d. ácido 4-trifluorometilbecenoborónico, $Pd(PPh_3)4$, DME, Na_2CO_3, 80 °C, 14h; e. LiOH/THF, MeOH, y agua, r.t., 2h.

[0439] **Ácido 3-[2-(4'-Trifluorometil-bifenil-3-il)-benzooxazol-5-il]-hex-4-inóico (43.3).** Se trató el éster metílico de ácido 3-(4-Hidroxi-fenil)-hex-4-inóico (1.32 g, 6 mmol) con HNO_3 (0.30 niL, 7.2 mmol) en AcOH (10 mL) a 80 °C por 3h. El solvente se concentró *in vacuo* y con cromatografía flash se aisló el éster metílico ácido 3-(3-nitro-4-hidroxi-fenil)-hex-4-inóico (613 mg, 2.3 mmol). MS ESI m/e: 264.0 (M + H). El grupo nitro fue luego reducido con $SnCl_2$ (2.62 g, 11.6 mmol) en EtOH (10 mLO y EtOAc (10 mL) a 70 °C por 3h. La mezcla de la reacción se enfrió a 25 °C, lavada con Na_2CO_3 acuoso saturado, agua, salmuera, se secó sobre MgSO4, filtrada y se concentró *in vacuo*. El producto crudo fue luego purificado por HPLC en fase reversa para dar el éster metílico de ácido 3-(3-amino-4-hidroxi-fenil)-hex-4-inóico (174 mg, 0.74 mmol). MS ESI m/e: 234.0 (M + H). Se trataron el éster metílico de ácido 3-(3-amino-4-hidroxi-fenil)-hex-4-inóico (174 mg, 0.74 mmol) y el ácido 3-bromobenzaldehido (278 mg, 1.5 mmol) en DMF (3 mL) con DDQ (204 mg, 0.9 mmol) por 2h a 25 °C. El producto se purificó por HPLC en fase reversa. MS ESI m/e: 398.0 (M + H). Se trataron el éster metílico de ácido 3-[2-(3-Bromo-fenil)-benzooxazol-5-il]-hex-4-inóico (19.6 mg, 0.05 mmol) y el ácido trifluorofenilborónico (38 mg, 0.2 mmol) en DME (1 mL) y 0.2 mL de solución 2M de Na_2CO_3 con $Pd(PPh_3)_4$ a 80 °C por 14h. El producto se aisló por cromatografía flash. MS ESI m/e: 464.0 (M + H). El éster metílico (7.8 mg, 0.017 mmol) se hidrolizó con LiOH (4mg, 0.1 mmol) en un 1 mL de una mezcla 1:1:1

de MeOH, THF, y agua por 2h a 25 °C. La mezcla de la reacción se acidificó con 1N HCl, se extrajo con CH_2Cl_2 y se concentró para dar el ácido puro (7.6 mg). MS ESI m/e: 450.1 (M + H). ^1H NMR (500 MHz) ($CDCl_3$) δ 8.52 (1H,s)-8.30 (lH,d,J-7.8 Hz); 7.91 (1H, s); 7.83 (2H, d, J=8.2 Hz); 7.82 (1H, s); 7.78 (2H, dd, J=8.0, 8.0 Hz); 7.67 (1H, dd, J=7.8, 7.8 Hz); 7.58 (2H, d, J=8.4 Hz); 7.46 (1H, dd, J=SA, 1.5 Hz); 4.29 (1H, m); 2.94 (1H, dd, J=15.8, 8.1 Hz); 2.84 (1H, dd, J=15.8, 6.9 Hz); 1 .89 (3H, d, J=2.3 Hz).

6.44 Ejemplo 44

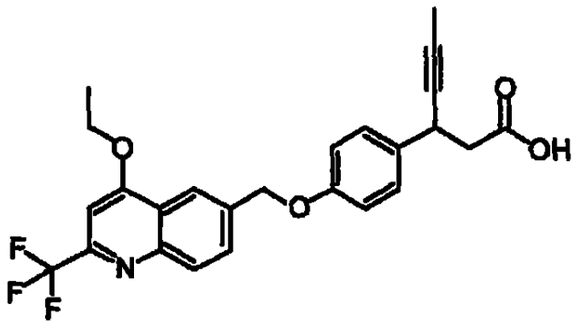
Esquema 44.1



Esquema 44.1. a. NaOH, EtOH, agua, r.t, 3h (X = Br, Cl).

44.1 **44.2**

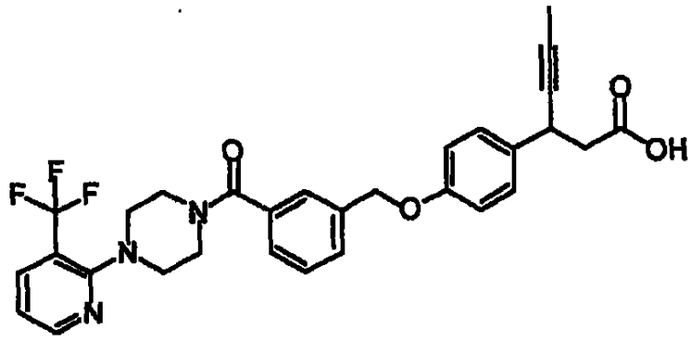
[0440] Procedimiento general para la preparación de éteres de arilo bencilo: se agregó ácido 3-(4-Hidroxi-fenil)-hex-4-inóico en EtOH (0.4M) a una solución de 1N NaOH (3 equiv.) en agua a 25 °C y se agitó por 5 minutos a 70 °C. Lentamente se agregó $ArCH_2X$ (X = Br, Cl, 1 equiv.) en EtOH (0.2M), se agitó por 3h a 70 °C. La mezcla de la reacción se acidificó con 1N HCl y se purificó por HPLC en fase reversa.



44.3

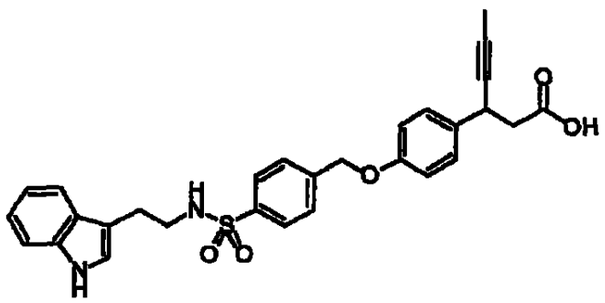
[0441] **Ácido 3-[4-(4-Etoxi-2-trifluorometil-quinolin-6-ilmetoxi)-fenil]-hex-4-inóico (44.3).** MS ESI m/e: 458.0 (M + H). ^1H NMR (400 MHz) (DMSO-d_6) δ 12.6 (1H, br. s); 8.31 (1H, s); 8.12 (1H, d, J=8.7 Hz); 7.95 (1H, dd, J=8.7, 1.3 Hz); 7.41 (1H, s); 7.31 (2H,

d, J=8.5 Hz); 7.03 (2H, d, J=8.5 Hz); 5.36 (2H, s); 4.47 (2H, q, J=8.0 Hz); 3.96 (1H, m); 2.62 (2H, d, J=7.6 Hz); 1.79 (3H, d, J=I.9 Hz); 1.21 (3H, t, J=8.0 Hz).



44.4

[0442] **Ácido 3-(4-{3-[4-(3-Trifluorometil-piridin-2-il)-piperacina-1-carbonil]-benciloxi}-fenil)-hex-4-inóico**. MS ESI m/e: 552.0 (M + H). ^{1}H NMR (400 MHz) (DMSO-d_6) δ 12.5 (1H5 br. s); 8.57 (1H3 d, J=3.5 Hz); 8.12 (1H, dd, J=I.9, 1.6 Hz); 7.56- 7.48 (3H, m); 7.41 (1H, d, J=7.5 Hz); 7.30-7.25 (3H, m); 6.98 (2H, d, J=8.7 Hz); 5.16 (2H, s); 3.95 (1H, m); 3.2 (4H, m); 2.60 (2H, d, J=7.6 Hz); 2.52 (4H, m); 1.77 (3H, d, J=2.4 Hz).



44.5

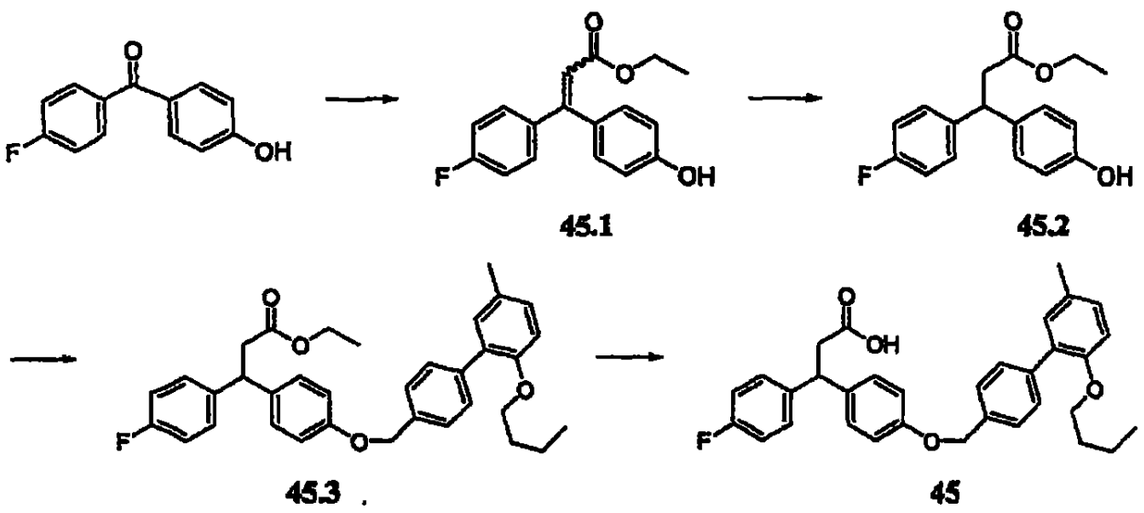
[0443] **Ácido 3-(4-{4-[2-(1H-Indol-3-il)-etilsulfamoil]-benciloxi}-fenil)-hex-4-inóico**. MS ESI m/e: 517.2 (M + H). ^{1}H NMR (400 MHz) (DMSO-d_6) δ 12.5 (1H, br. s); 10.82 (1H, s); 7.83 (2H, d, J=8.3 Hz); 7.77 (1H, dd, J=7.8, 7.8 Hz); 7.39 (1H, d, J=8.0 Hz); 7.32 (1H, d, J=8.0 Hz); 7.29 (2H, d, J=8.7 Hz); 7.13 (1H, d, J=2.2 Hz); 7.06 (1H, dd, J=7.0, 8.0 Hz); 6.97 (2H, d, J=8.7 Hz); 5.19 (2H, s); 3.95 (1H, m); 3.02 (2H, t, J=7.6 Hz); 2.81 (2H, t, J=7.6 Hz); 2.61 (2H, d, J=8.0 Hz); 1.78 (3H, d, J=2.4 Hz).

6.45 Ejemplo 45

[0444] Este ejemplo ilustra la preparación de ácido (+/-)-3-[4-(2'-butoxi-5 '-metil-bifenil-4-ilmetoxi)-fenil]-3-(4-fluorofenil)-propiónico (45).

Esquema 45.1

7



[0445] **Etil 3-(4-fluorofenil)-3-(4-hidroxifenil)-acrilato (45.1).** Se agregó una solución de hexametildisilacido de litio (23.1 mL, IM in THF) a una solución en agitación de (trimetilsilil)acetato de etilo (2.53 mL, 13.9 mmol) en THF (15 mL) en 10 min. a -78 °C. La mezcla de la reacción se agitó aún más a dicha temperatura por 20 min. A la mezcla de la reacción lentamente se agregó una solución de (4-fluorofenil)-(4-hidroxifenil)-metanona (2 g, 9.2 mmol) en THF (30 mL). La mezcla de la reacción se llevó a 0 °C en 5 h. La mezcla de la reacción se aplacó con una solución saturada de cloruro de amoníaco, se extrajo con acetato de etilo y se lavó con una solución diluida de cloruro de amoníaco. La capa orgánica se secó sobre sulfato de magnesio. El solvente se removió al vacío y el producto se purificó por cromatografía flash sobre gel de sílice, dando **45.1** como un aceite (1.405 g).

[0446] **Etil éster de ácido 3-(4-Fluorofenil)-3-(4-hidroxifenil)-propiónico (45.2).** Se agitó una solución de **45.1** (385 mg) en etanol (12 mL) y acetato de etilo (10 mL) con 10% Pd-C (50 mg) bajo una atmósfera de hidrógeno a temperatura ambiente por 3 h. La mezcla de la reacción se filtró y se concentró para obtener **45.2** (350 mg).

[0447] **Éster etílico de ácido 3-[4-(2'-Butoxi-5'-metil-bifenil-4-ylmetoxi)-fenil]-3-(4- fluorofenil)-propiónico (45.3).** Se agitó una mezcla de **45.2** (48 mg, 0.166 mmol), 4'-Bromometil-2-butoxi-5-metil-bifenilo (67 mg, 0.2 mmol) y carbonato de cesio (81 mg, 0.25 mmol) en DMF (2 mL) a temperatura ambiente por toda la noche. La mezcla de la reacción se diluyó con agua y se secó sobre sulfato de magnesio. El residuo obtenido tras la

concentración se sometió a cromatografía flash sobre gel de sílice para obtener **45.3** (71 mg).

[0448] **Ácido (+/-)-3-[4-(2f-Butoxi-5'-metil-bifenil-4-ilmetoxi)-fenil]-3-(4-fluorofenil)-propiónico (45).** Se agitó una mezcla de **45.3** (56 mg, 0.1 mmol) y una solución de 2N $NaOH_{(aq)}$ (0.31 mL, 0.62 mmol) en THF (3 mL) a temperatura ambiente por toda la noche. La mezcla de la reacción se concentró, se trató con HCl diluido, y se extrajo en acetato de etilo. La capa orgánica se lavó con agua y se concentró para dar el producto que fue purificado por cromatografía flash para dar el compuesto **45** (40mg). ^1H NRM (500 MHz, $CDCl_3$, ppm), δ 0.9 (t,3H), 1.4 (m, 2H), 1.65 (m, 2H), 2.35 (s, 3H), 3.05 (m, 2H), 3.9 (t,2H), 4.5 (t,1H), 5.05 (s,2H), 6.8-7.5 (m, 15H). MS ESI (neg.) m/e: 511.0 (M-H).

6.46 Ejemplo 46

[0449] Los compuestos siguientes se prepararon de acuerdo con métodos análogos a los descritos en el Ejemplo 45: Ácido 3-(4-fluorofenil)-3-[4-(4'-trifluorometil-bifenil-3-ilmetoxi)-fenil]-propiónico (**46.1**), ácido 3-(4-fluorofenil)-3-[4-(4-metil-2-p-tolil-tiazol-5-ilmetoxi)-fenil]-propiónico (**46.2**) y ácido 3-(4-fluorofenil)-3-{4-[2-(3-trifluorometil-fenoxi)-etoxi]-fenil}-propiónico (**46.3**).

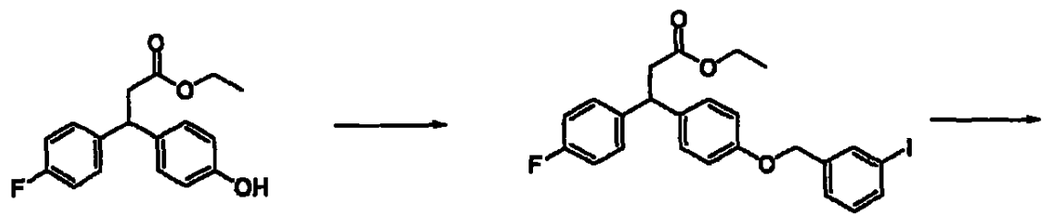
[0450] Los compuestos siguientes se prepararon de acuerdo con los métodos análogos a los descritos en el ejemplo **45**, comenzando con ácido (4-hidroxifenil)-fenil-metanona: 3-[4-(2-metil-benciloxi)-fenil]-3-fenil-propiónico (**46.4**), ácido 3-[4-(2'-butoxi-5'-metil-bifenil-4-ilmetoxi)-fenil]-3-fenil-propiónico (**46.5**), ácido 3-[4-(4- metil-2-p-tolil-tiazol-5-ilmetoxi)-fenil]-3-fenil-propiónico (**46.6**), ácido 3-fenil-3-{ 4-[2-(3-trifluorometil-fenoxi)-etoxi]-fenil}-propiónico (**46.7**), ácido 3-[4-(2'-ciano- bifenil-4-ilmetoxi)-fenil]-3-fenil-propiónico (**46.8**) y 3-fenil-3-[4-(4'- trifluorometil-bifenil-3-ilmetoxi)-fenil]-propiónico (**46.9**).

[0451] Los compuestos siguientes se prepararon de acuerdo con los métodos análogos a los descritos en el ejemplo **45**, comenzando con ácido (4-hidroxifenil)-piridin-4-il-metanona: 3-[4-(2'-butoxi-5'-metil-bifenil-4-ilmetoxi)-fenil]-3-piridin-4-il-propiónico (**46.10**) y ácido 3-piridin-4-il-3-[4-(4'-trifluorometil-bifenil-3-ilmetoxi)-fenil]-propiónico (**46.11**).

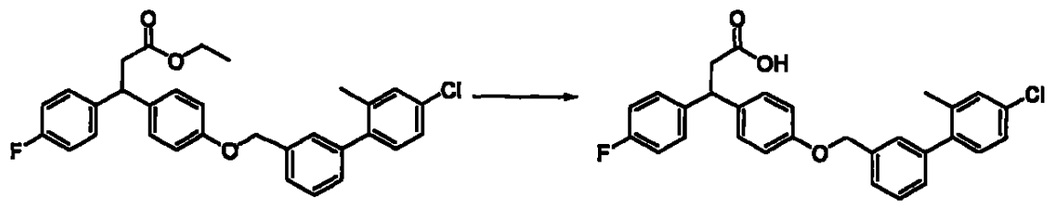
6.47 Ejemplo 47

[0452] Este ejemplo ilustra la preparación de ácido (+/-)-3-(4-[3-(4-cloro-2-metilfenil)benciloxi]fenil)-3-(4-fluorofenil)-propanóico (**47**).

Esquema 47.1



45.2 47.1



47.2 47

[0453] **3-(4-[3-Iodobenciloxi)fenil)-3-(4-fluorofenil)propanoato de etilo (47.1).** En forma sucesiva se agregaron Cs_2CO_3 (4.89g 15mmol) y 1-(bromometil)-3-iodobenceno (4.45g, 15mmol) a una solución seca de DMF (20 niL) de **45.2** (2.88g, 10mmol). La mezcla de la reacción se agitó durante toda la noche a temperatura ambiente, se diluyó con acetato de etilo (200mL), se lavó con agua (100 mL x 2) y salmuera (100 niL), y se secó sobre Na_2SO_4. El solvente se removió al vacío y el residuo se purificó por cromatografía flash para dar el compuesto **47.1** como un aceite incoloro. MS ESI (pos.) m/e: 505.0 (M+H).

[0454] **3-(4-[3-(4-Cloro-2-metilfenil)benciloxi]fenil)-3-(4-fluorofenil)-propanoato (47.2).** En forma sucesiva se agregaron CsF (96 mg, O.βmmol), ácido 4-cloro-2-metilfenilborónico (102 mg, 0.6 mmol) y Pd(PPh3)4 (70 mg, 0.06mmol) a una solución seca de 1,2- dimetoxietano (DME, 2 mL) de 47.1 (108 mg, 0.2 mmol) bajo agitación en una atmósfera de nitrógeno. La mezcla de la reacción se agitó a 80 °C durante toda la noche. El solvente se removió bajo un flujo de nitrógeno y el residuo se disolvió en CH_2Cl_2 (2 mL) y se purificó por cromatografía flash. El compuesto **47.2** se obtuvo como un aceite incoloro. MS ESI (pos.) m/e 503.0 (M+l).

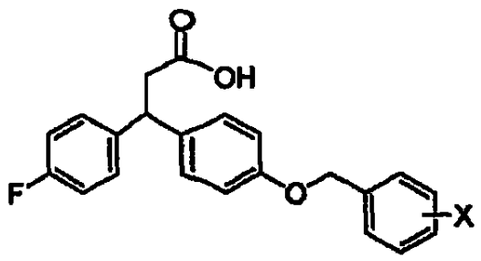
[0455] **Ácido (+/-)-3-(4-[3-(4-Cloro-2-metilfenil)fenil]-metoxil)fenil}-3-(4-fluorofenil)-propanóico (47).** Se agregó LiOH (48 mg, 2 mmol) a una solución THF-H2O (1/1, 4mL) del compuesto **47.2** (104 mg, 0.2 mmol). La mezcla de la reacción se agitó a temperatura ambiente durante toda la noche. Se agregó 1N HCl(aq) para acidificar la mezcla a un pH 3 a 0 °C. La mezcla se extrajo con acetato de etilo (20 mL x 2), se lavó con agua y salmuera, se secó sobre Na_2SO_4, y se purificó por cromatografía flash para obtener

el compuesto 47 (82 mg) como un aceite incoloro. ^{1}H NMR (400 MHz)($CDCl_3$) δ 2.22 (s, 3H), 3.05 (dd, J = 7.8, 1.1 Hz, 2H), 4.49 (t, J = 8.0 Hz, 1H), 5.09 (s, 2H), 6.92-7.43 (m, 12H). MS ESI (neg.) m/e 473.0 (M-H).

6.48 Ejemplo 48

[0456] Los compuestos siguientes se prepararon de acuerdo con los métodos descritos en el Ejemplo 47.

Tabla 16



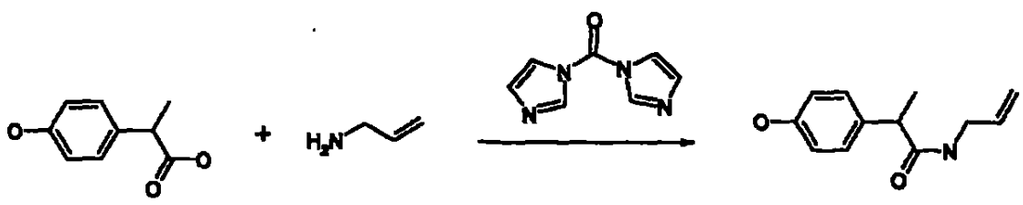
Compuesto	X
48.1	4-iodo
48.2	3-iodo
48.3	4-(3-benciloxifenilo)
48.4	4-(3-butoxifenilo)
48.5	4-(5-etoxi-2-fluorofenilo)
48.6	4-(2-etoxi-6-fluorofenilo)
48.7	4-(2-butoxi-5-fluorofenilo)
48.8	4-(3-isoproxifenilo)
48.9	4-(2-fluoro-5-propoxifenilo)
48.10	4-(4-cloro-2-metilfenilo)
48.11	4-(4-metoxi-2-metilfenilo)
48.12	4-(4-metoxi-2,6-dimetilfenilo)
48.13	4-(2,4,6-trimetilfenilo)
48.14	4-(4-cloro-2-etoxifenilo)
48.15	4-(4-fluoro-2-etoxifenilo)
48.16	4-(2- isoproxifenilo)
48.17	3-(2,5-dimetilfenilo)
48.18	3-(3-benciloxifenilo
48.19	3-(5-etoxi-2-fluorofenilo)
48.20	3-(4-cloro-2-metilfenilo)
48.21	3-(2-etoxi-5-metilfenilo)

48.22	3-(4-cloro-2-metilfenilo)
48.23	3-(2-butoxi-5-metilfenilo)
48.24	3-(2-butoxi-5-fluorofenilo)
48.25	3-(4-etoxifenilo)
48.26	3-(5-fluoro-2-metoxifenilo)
48.27	3-(3-isopropoxifenilo)

6.49 Ejemplo 49

[0457] Este ejemplo ilustra la preparación de ácido (+/-)-3-(4-(3-(4-(trifluorometil)fenil)benciloxi)fenil)-4-(dietilamino)-3-metil-4-oxobutanoico.

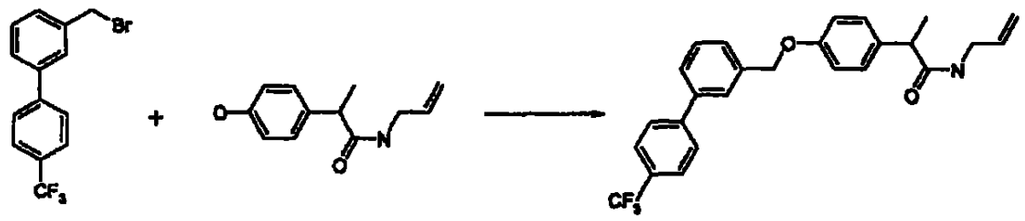
Esquema 49.1



49.1

[0458] **N-Alil-2-(4-hidroxifenil)propanamido (49.1).** Se agregó N1N'-Carbonildiimidazol (22.65g, 140mmol) al ácido 2-(4-hidroxifenil)propiónico (21g, 127mmol) en THF (100mL), disponible en el comercio. Se observó un calentamiento ligero y evolución de gas. La mezcla resultante se agitó por 3 h. Gota a gota se agregaron Allilamina (10.9 g, 190.5 mmol) y Et_3N (19.2 mL, 190.5 mmol), y la mezcla se agitó durante toda la noche. La reacción se aplacó con agua (200mL) y la fase orgánica se extrajo con acetato de etilo (50 mLx3). Los extractos orgánicos combinados se secaron sobre MgSO4 y se concentraron *in vacuo*. El producto se purificó por cromatografía flash (elución con acetato de etilo). Se obtuvo fenol **49.1** como un sólido blanco. MS ESI m/e: 206 (M-H).

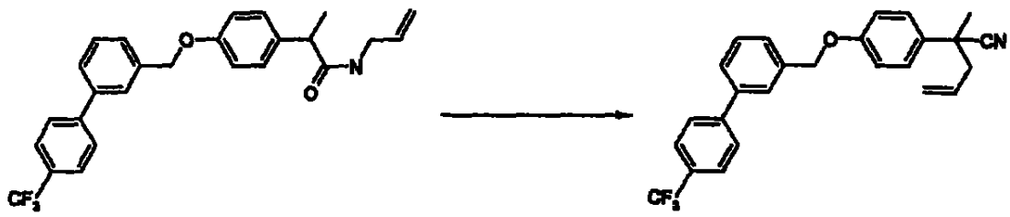
Esquema 49.2



49.2 49.1 49.3

[0459] **2-(4-(3-(4-(Trifluorometil)fenil)benciloxi)fenil)-N-alilpropanamida (49.3).** Se agregó Cs_2CO_3 (23.1g, 71 mmol) a una mezcla del compuesto **49.2** (20.33g, 64.5mmol) y fenol **49.1** (13.23g 64.5mmol) en DMF (50mL). La mezcla resultante se agitó durante toda la noche. La reacción se aplacó con agua (500mL). La fase orgánica se extrajo con acetato de etilo (75mLx3). Las fases orgánicas combinadas se secaron sobre MgSO4 y el solvente se removió bajo presión reducida. El residuo resultante se purificó por cromatografía flash (10% Acetona en diclorometano) para resultar en 15.9 g de **49.3**. MS ESI m/e: 440 (M-H).

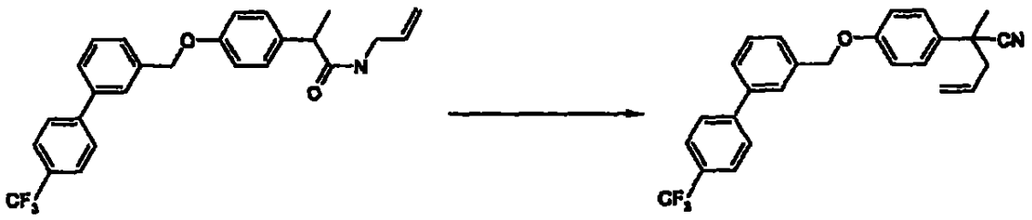
Esquema 49.3



49.3 49.4

[0460] **2-(4-(3-(4-(Trifluorometil)fenil)benciloxi)fenil)-2-metilpent-4-enenitrilo (49.4).** La reacción 3-aza-claisen se llevó a cabo de acuerdo con el método de Walters et al. (1991) Tetrahedron Lett. 2: 179-182. Se disolvieron amida 49.3 (15.9g, 36.2mmol) y PPh_3 (21g, 80mmol) en diclorometano anhidro (160 mL). Gota a gota se agregaron Et_3N (12g, 119.5mmol) y CCl_4 (18.4g, 119.5mmol). La mezcla resultante se agitó durante toda la noche. La reacción se aplacó con salmuera concentrada (250 mL). La fase orgánica se extrajo con acetato de etilo (50mLx3). Las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. El residuo resultante se purificó por cromatografía flash (25% acetato de etilo en hexanos) para dar 12.3 g de 49.4. ^1H NMR (400MHz) ($CDCl_3$) δ 7.73 (4H, s); 7.70 (1H, s); 7.61-7.51 (3H, m); 7.41 (2H, d, J=8.9Hz); 7.05 (2H, d, J=8.9Hz); 5.76-5.72 (1H, m); 5.21-5.17 (4H, m); 2.71-2.59 (2H, m); 1.72 (3H, s).

Esquema 49.4



49.3 49.4

[0461] **Ácido 2-(4-(3-(4-(Trifluorometil)fenil)benciloxi)fenil)-2-metilpent-4-enoico (49.5).** Se agregó **49.4** a una mezcla de etileno glicólico (8 mL), H2O (0.25 mL) y KOH (750 mg). La mezcla resultante se calentó a 190°C por 6 h. La mezcla de la reacción se enfrió a temperatura ambiente. La fase acuosa se extrajo con acetato de etilo (10 mLx3). Los extractos se combinaron, se secaron sobre MgSO4 y se concentraron bajo presión reducida. El residuo resultante se purificó por cromatografía flash (10% de acetona en diclorometano) para dar 632 mg de **49.5**. MS ESI m/e: 441 (M-H).

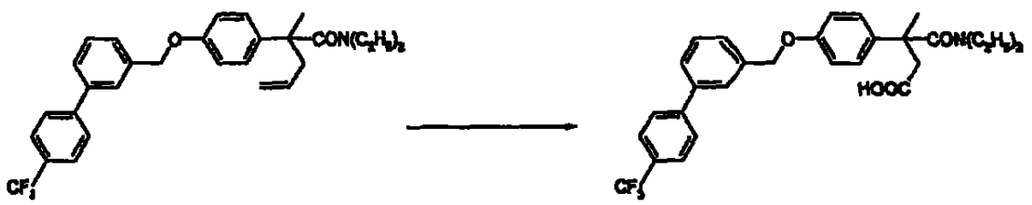
Esquema 49.5



49.5 49.6

[0462] **2-(4-(3-(4-(Trifluorometil)fenil)benciloxi)fenil)-N,N-dietil-2-metilpent-4-enamida (49.6).** Gota a gota se agregó cloruro de oxalilo (57.7mg, 0.45inmol) a **49.5** (100 mg, 0.23 mmol) en diclorometano anhidro (4 mL). La mezcla resultante fue sometida a reflujo en un tubo sellado a 50 °C durante toda la noche. El diclorometano se removió bajo un chorro de N_2. Gota a gota se agregó éter anhidro (2 mL), seguido de amino dietílico (50 mg, 0.69 mmol) y Et3N (70 mg, 0.69 mmol). La mezcla fue sometida a reflujo durante toda la noche. La mezcla de la reacción se concentró durante presión reducida, y el residuo resultante se purificó por cromatografía flash (25% acetato de etilo en hexanos). Se obtuvieron 82 mg de **49.6**. MS ESI m/e: 496 (M-H). ^{1}H NMR (500MHz) ($CDCl_3$) δ 7.72 (4H, s); 7.69 (1H, s); 7.6-7.5 (3H, m); 7.14 (2H, d, J=8.5Hz); 7.05 (2H, d, J=8.5Hz); 5.7-5.6 (1H, m); 5.15 (2H, s); 5.03-5 (2H, m); 3.5-3.2 (2H, m); 3.0-2.9 (2H, m); 2.74-2.64 (2H, m); 1.62 (3H, s); 1.13 (3H, s); 0.72 (3H, s).

Esquema 49.6

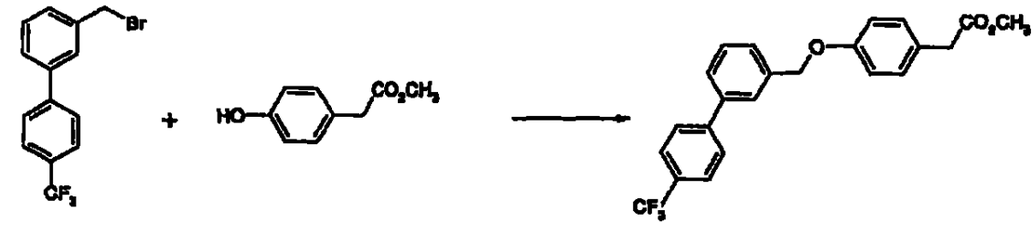


49.6 49

0463] Ácido (+/-)-3-(4-(3-(4-(Trifluorometil)fenil)benciloxi)fenil)-4-(dietilamino)-3-metil-4-oxobutanoico (49). La reacción de oxidación se llevó a cabo de acuerdo con el método de Henry et al. (1993) J Org. Chem. 58: 4745. Se agregó una cantidad catalítica de OsO_4 a una solución de **49.6** (50 mg, 0.1 mmol) en acetona (4 mL), seguida de un exceso de reactivo Jones (0.25 mL). La mezcla de la reacción se agitó a temperatura ambiente durante toda la noche. La reacción se aplacó con agua (2 mL), y la fase acuosa se extrajo con diclorometano (2 mLx3). Los extractos orgánicos combinados se secaron sobre $MgSO_4$ y se removieron bajo presión reducida. El residuo resultante se purificó en una fase invertida de HPLC. MS ESI m/e: 514 (M-H).

[0464] Este ejemplo ilustra la preparación de ácido 3-{4-[4'-(1 ,1-difluoro-etil)-bifenil-3-ilmetoxi]-fenil}-N,N-dimetil-succínico.

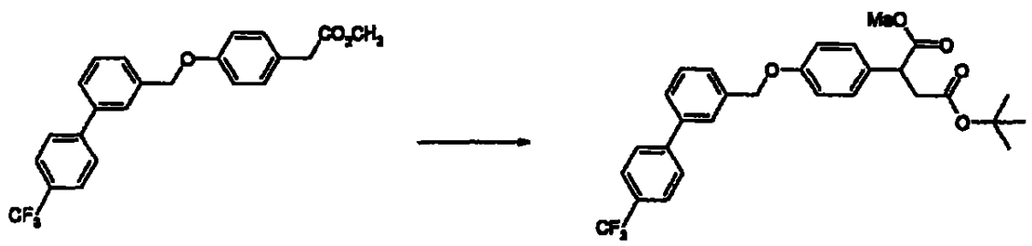
Esquema 50.1



49.2 50.1

[0465] Éster metílico de ácido [4-(4'-Trifluorometil-bifenil-3-ilmetoxi)-fenil]-acético (50.1). Se agregó el compuesto **49.2** (15.8 g, 50.1 mmol) a 4-hidroxifenilacetato de metilo (8.3 g 50 mmol) en DMF (30 mL), seguido de Cs_2CO_3 (17.9 g, 55 mmol). La mezcla resultante se agitó durante toda la noche. La reacción se aplacó con agua (300 mL). La fase orgánica se extrajo con acetato de etilo (50 mL x 3). La fase orgánica saturada se enjuagó con salmuera saturada, se secó sobre $MgSO_4$, y se concentró bajo presión reducida. El producto (16.3 g) se usó en el paso siguiente sin ninguna purificación posterior. MS ESI (pos.) m/e: 423 (M+Na).

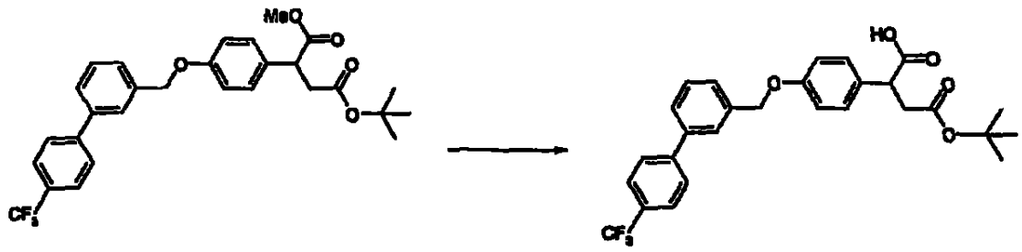
Esquema 50.2



50.1 50.2

[0466] **Éster 4-tert-butílico de 1-metil éster de ácido 2-{4-[4'-Trifluorometil-bifenil-3-ilmetoxi]-fenil}-succínico (50.2)**. El compuesto **50.1** (4 g, 10mmol) en THF (12 mL) se agregó gota a gota a LDA en THF (IM, 12 mL) a -78 °C. La mezcla resultante se agitó por 30 min. antes de agregarse bromoacetato de tert-butilo (2.15 g, 11 mmol) en THF (2 mL) por un período de 10 min. La mezcla de la reacción se agitó por 2 h a -78 °C y se dejó calentar lentamente hasta 0 °C. La reacción se aplacó con NH_4Cl acuoso saturado (20 mL). La fase orgánica se extrajo con acetato de etilo (25 mLx3). Los extractos orgánicos se combinaron, se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. El residuo resultante se purificó por cromatografía flash (50% acetato de etilo en hexanos) para dar 3.3 g de **50.2**. MS ESI (pos.) m/e: 537 (M+Na). ^1H NMR (400MHz) ($CDCl_3$) δ 7.72 (4H, s); • 6E l ; -7Λ (ή)r .25-7.24 (2H3 m); 6.98-6.97 (2H5 m); 5.14 (2H, s); 4.04- 4.0 (1H3 m); 3.7 (3H, s); 3.1 (1H, m); 2.63 (IK3 m); 1.42 (9H3 s).

Esquema 50.3

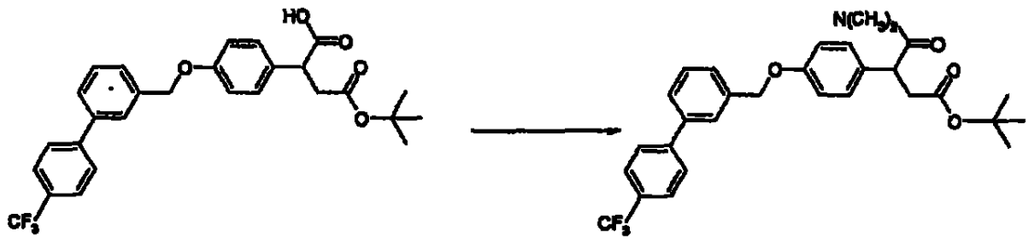


50.2 50.3

[0467] **Éster 4-tert-butílico de ácido 2-{4-[4'-Trifluorometil-bifenil-3-ilmetoxi]-fenil}-succínico (50.3)**. Se agregó hidróxido de litio (121mg, 5mmol) a una solución de **50.2** en MeOH/THF/H_2O (1:1:1, 90mL). La mezcla resultante se agitó a temperatura ambiente durante toda la noche. El solvente orgánico se removió bajo presión reducida. La mezcla de la reacción se extrajo con diclorometano (10 mLx3). Los extractos orgánicos se combinaron, se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. El residuo resultante se purificó por cromatografía flash (50% acetato de etilo en hexanos) para dar el

ácido **50.3** (860 nig). MS ESI (pos.) m/e: 523 (M+Na). ^{1}H NMR (4001MHz) ($CDCl_3$) δ 7.72 (4H_3 s); 7.67 (1H, s); 7.59-7.47 (3H, m); 7.29-7.25 (2H_3 m); 6.98-6.97 (2H, m); 5.14 (2H, s); 4.04-4.0 (1H, m); 3.1-3.053 (1H_3 m); 2.64-2.60 (1H, m); 1.4 (9H3 s). 291

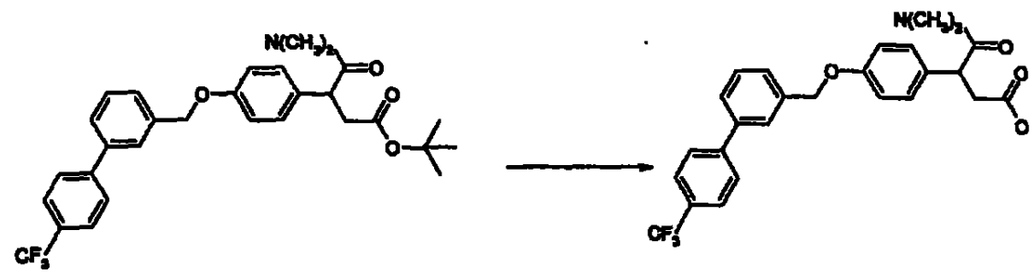
Esquema 50.4



50.3 **50.4**

[0468] **Éster tert-butílico de ácido 3-{4-[4'-Trifluorometil-bifenil-3-ilmetoxi]-fenil}-N,N-dimetil-succinámico (50.4)**. De forma secuencial se trató una solución del compuesto **50.3** (50mg, 0.1mmol) en diclorometano (2mL) con 1-hidroxibenzotriazol (15 mg, 0.11mmol) y EDC (21 mg, 0.11mmol). La mezcla resultante se agitó por 1 h. antes de que gota a gota se agregara dimetilamina (9 mg, 0.2mmol). 30 minutos más tarde se aplacó la reacción con agua (5 mL). La mezcla de la reacción se extrajo con diclorometano (2 mLx3). Los extractos orgánicos se combinaron, se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida para dar la amida **50.4** (48 mg). El producto se uso en el paso siguiente paso sin ninguna purificación posterior. MS ESI (pos.) m/e: 527 (M+).

Esquema 50.5



50.4 **50**

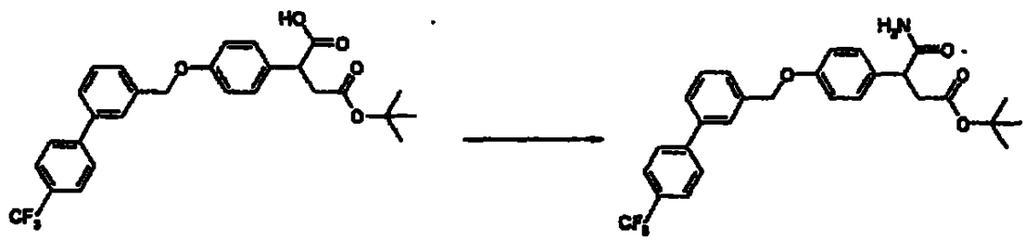
[0469] **Ácido (+/-)-3-{4-[4'-Trifluorometil-bifenil-3-ilmetoxi]-fenil}-N,N-dimetil-succinámico (50)**. El éster **50.4** (48mg, 0.09mmol) se disolvió en una solución de diclorometano/TFA (3:1, 2 mL). La mezcla resultante se agitó a temperatura ambiente por 2 h. El solvente se removió bajo presión reducida, y el producto se purificó en una fase invertida de HPLC para dar el ácido **50** (30mg). MS ESI (pos.) m/e: 472 (M+H). ^{1}H NMR

(400MHz) ($CDCl_3$) δ 7.72 (4H, s); 7.67 (1H, s); 7.59-7.28 (3H, m); 7.2 (2H, d, J=8.6Hz); 7.0 (2H, d, J=8.6Hz); 5.13 (2H, s); 4.24-4.21 (1H, m); 3.20-3.13 (1H, m); 3.0 (3H, s); 2.95 (3H, s); 2.76-2.71 (1H, m).

6.51 Ejemplo 51

[0470] Este ejemplo ilustra la preparación de ácido 3-(4-metil-tiazol-2-il)-3-[4-(4'-trifluorometil-bifenil-3-ilmetoxi)-fenil]-propiónico.

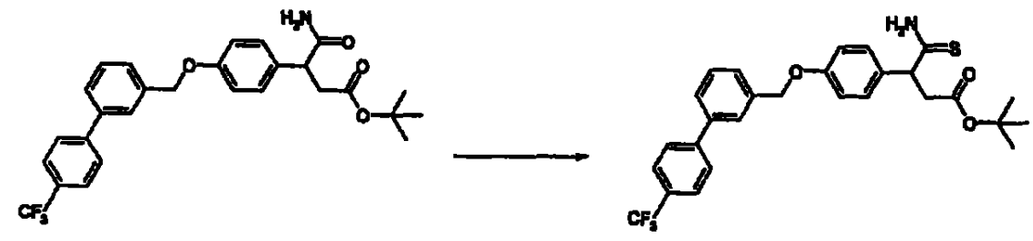
Esquema 51.1



50.3 **51.1**

[0471] **Éster *tert*-butílico de ácido 3-[4-(4'-Trifluorometil-bifenil-3-ilmetoxi)-fenil]-succinámico (51.1).** De forma secuencial se agregaron 1-hidroxibenzotriazol (225 mg, 1.65 mmol) y EDC (315 mg, 1.65 mmol) al compuesto **50.3** (750 mg, 1.5 mmol) en diclorometano (25 mL). La mezcla resultante se agitó por 1 h antes de que gota a gota se agregara hidróxido de amoníaco (25% en agua, 630 mg, 4.5 mmol). Después de 30 min. la reacción se aplacó con agua (10 mL). La mezcla de la reacción se extrajo con diclorometano (10 mLx3). Los extractos orgánicos se combinaron, se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. El producto se purificó por cromatografía (50% acetato de etilo en hexanos) para dar **51.1** (720 mg) como un sólido blanco. MS ESI (pos.) m/e: 500 (M+H). ^1H NMR (400MHz) (CDCl3) δ 7.72 (4H, s); 7.68 (1H, s); 7.57-7.48 (3H5 m); 7.29-7.25 (2H, m); 7.0-6.97 (2H, d, J=6,8Hz); 5.14 (2H, s); 3.91-3.88 (1H5 m); 3.19-3.13 (1H5 m); 2.60-2.55 (1H5 m); 1.4 (9H, s).

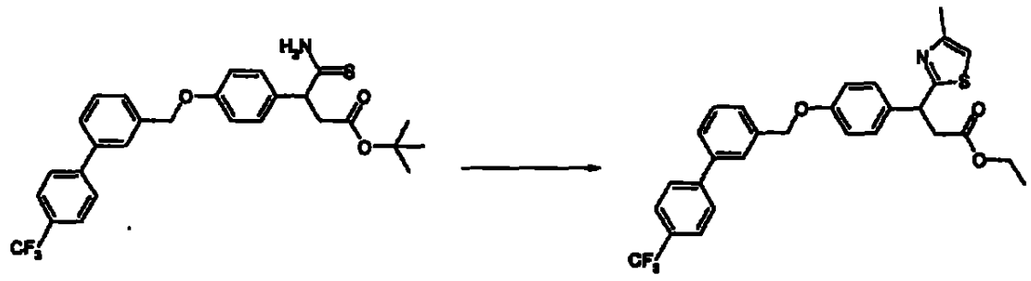
Esquema 51.2



51.1 **51.2**

[0472] **Éster *tert*-butílico de ácido 3-Tiocarbamoil-3-[4-(4'-trifluorometil-bifenil-3-ilmetoxi)-fenil]-propiónico (51.2).** A una solución del compuesto 51.1 (50 mg, 0.1 mmol) en THF (2mL) se agregó el reactivo de Lawesson (81 mg, 0.2 mmol). La mezcla resultante se agitó a temperatura ambiente por 6 h. La reacción se aplacó con agua (5 mL). La mezcla de la reacción se extrajo con diclorometano (3 mLx3). Los extractor orgánicos se combinaron, se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. El producto se purificó por cromatografía flash (50% acetato de etilo en hexanos) para dar el compuesto **51.2** (40 mg) como una película clara. MS ESI (pos.) m/e: 516 (M+H). ^1H NMR (400MHz) ($CDCl_3$) δ 7.72 (4H, s); 7.67 (1H5 s); 7.51-7.48 (3H5 m); 7.31-7.28 (2H5 m); 7.0- 6.97 (2H5 m); 5.14 (2H5 s); 4.25-4.22 (1H, m); 3.51-3.46 (1H, m); 2.78-2.72 (1H, m); 1.38 (9H, s).

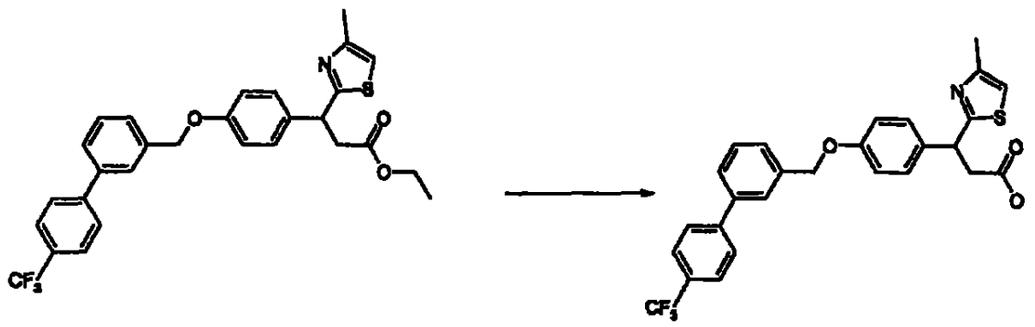
Esquema 51.3



51.2 **51.3**

[0473] **3-(4-Metil-tiazol-2-il)-3-[4-(4'-trifluorometil-bifenil-3- ilmetoxi)-fenil]-propanoato de etilo (51.3).** Se trató una solución de 51.2 (100 mg, 0.19 mmol) en EtOH (3 mL) con cloroacetona (88mg, 0.95mmol). La mezcla resultante se sometió a reflujo por 5 h. A la mezcla de la reacción anterior se agregó HCl (6N, 25µL) acuoso y la reacción se calentó a 50 °C durante toda la noche. El solvente se removió bajo presión reducida. El producto se purificó por cromatografía flash (50% acetato de etilo en hexanos) para dar **51.3** (50mg). MS ESI (pos.) m/e: 526 (M+H).

Esquema 51.4



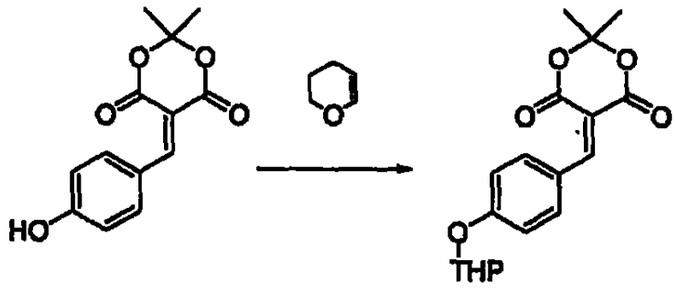
51.3 51

[0474] Ácido (+/-)-3-(4-Metil-tiazol-2-il)-3-[4-(4'-trifluorometil-bifenil-3-ilmetoxi)-fenil]-propiónico (51). El compuesto **51.3** (50 mg, 0.1 mmol) se disolvió en MeOH/THF/H_2O (1:1:1, 3 mL). La mezcla resultante se agitó a temperatura ambiente por 2 h. La mezcla de la reacción se acidificó a un PH=4 y se extrajo con diclorometano (3 mLx3). El producto se purificó en una fase inversa de HPLC para dar el compuesto **51** (40 mg). MS ESI (pos.) m/e: 498 (M+H). ^{1}H NMR (400MHz) (DMSO) δ 7.92 (2H, d, J=8.1Hz); 7.84 (3H, d, J=8.8Hz); 7.71 (1H, t, J=5.1Hz); 7.54 (2H, d, J=7Hz); 7.29 (2H, d, J=8.7Hz); 7.09 (1H, s); 7.01 (2 H, d, J=8.7Hz); 5.18 (2H, s); 4.66 (1H5 m); 3.2 (1H, m); 2.93 (1H, m); 2.33 (3H, s).

6.52 Ejemplo 52

[0475] Este ejemplo ilustra la preparación de ácido (+/-)-3-(4-((4-metil-2-p-toliltiazol-5-il)metoxi)fenil)-3-(tiofen-2-il)propanóico.

Esquema 52.1

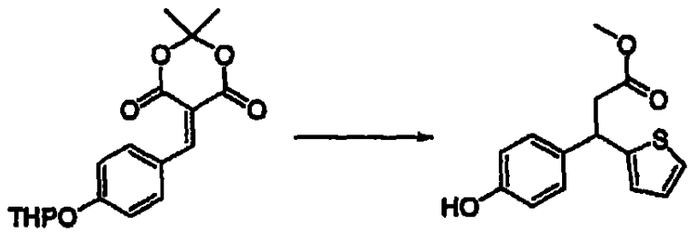


1.1 52.1

[0476] 2,2-Dimetil-5-[4-(tetrahidro-piran-2-iloxi)-bencilidena]-[1,3]dioxana-4,6-diono (52.1). Se llevo a cabo la protección del fenol con dihidropirano en base al método dado en Miyashita et al. (1977) J. Org. Chem. 42: 3772. El compuesto 1.1 se disolvió en diclorometano (4 L). A la suspensión se agregó 3,4-Dihidro-2H-piran (250 g, 3 mol) seguido de PPTS (5 g, 20 mmol). La mezcla de la reacción se calentó hasta un reflujo suave (3.5 h).

El HPLC mostró ~90% de perfección de la reacción. La reacción se concentró bajo presión reducida a ~2L de volumen. Se agregó un 1 L de acetona, y bajo presión reducida se removieron 2 L del solvente. Se agregaron 0.5 L de acetona, y se removieron 0.5 L de solvente bajo presión reducida. De forma secuencial la mezcla resultante de cristales muy finos amarillo claro se filtró y se enjuagó con dos porciones de acetona de 500 mL. El producto se secó en un horno al vacío a 50 °C hasta que en las trampas no se obtuvo más solvente. El compuesto **52.1** (528 g) se obtuvo como cristales finos amarillo claro. ^{1}H NMR(400MHz)(DMSO-<4) δ 8.29 (s, 1H); 8.18 (d, 2H, J=8.9 Hz); 7.13 (d, 2H, J=8.9 Hz);. 5.67 (m, 1H); 3.70 (m, 1H); 3.60 (m, 1H).1.9-1.5 (m, 12H). MS ESI (pos.) m/e: 355.1 (M + Na).

Esquema 52.2

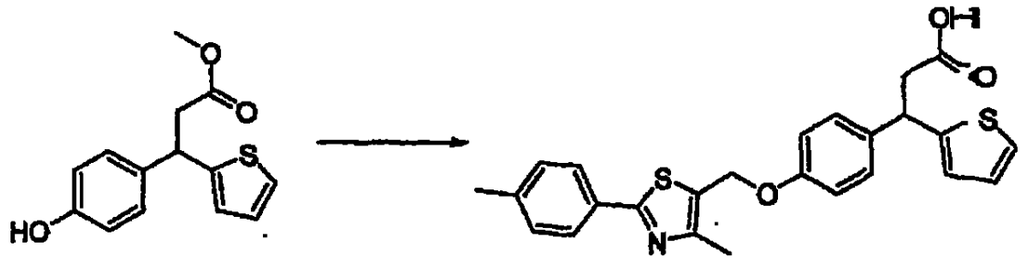


52.1 **52.2**

[0477] **3-(4-hidroxifenil)-3-(tiofen-2-il)propanoato de (+/-)-metilo (52.2)**. Se equipó un matraz de 500 mL con una barra magnética de agitación, una entrada de nitrógeno , una salida de nitrógeno y se colocó a temperatura ambiente en un baño de agua. Al matraz se agregó el compuesto **52.1** (5.00 g, 15.1 mmol) junto con THF anhidro (150 mL). Tras purgar con nitrógeno por 30 min, por medio de una cánula se agregó una solución de bromuro de tiofen-2-pl-magnesio en THF (1 M, 18.1 mL). Una vez que se completó la adición, la mezcla de la reacción se agitó por 1.5 h y se aplacó con NH_4Cl (1 M, 100 mL) acuoso diluido con acetato de etilo (100 mL). La capa acuosa se acidificó a un pH ~2 con HCl concentrado y se extrajo con acetato de etilo (150 mL x 2). El extracto se lavó con salmuera y se concentró. El residuo se disolvió en 100 mL de 10:1 DMFa-agua calentada a 100 °C por 8 h. La reacción se enfrió y se diluyó con 500 mL de agua y se extrajo con acetato de etilo (150 mL x 3). El orgánico se secó con $MgSO_4$, se filtró y se concentró en un evaporador rotativo. El residuo se disolvió en MeOH (200 mL) y se agregaron 5 gotas de H_2SO_4 concentrado y la solución se sometió a reflujo por 24 h. La solución se concentró hasta lograr un residuo en un evaporador rotativo y se purificó por

columna cromatográfica flash con 30% acetato de etilo/hexanos como diluyente. Las fracciones se concentraron para lograr 2.69 g (10.3 mmol) de **52.2** como un aceite viscoso.

Esquema 52.3



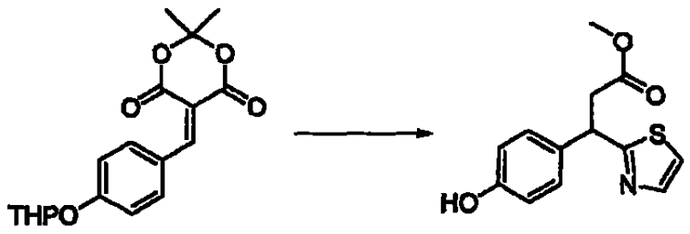
52.2 **52**

[0478] **Ácido (+/-)-3-(4-((4-Metil-2-p-tolil tiazol-5-il)metoxi)fenil)-3-(tiofen- 2-il)propanóico (52).** Se disolvieron cloruro de tiazol **3.1** (108 mg, 0.457 mmol) y fenol **52.2** (100 mg, 0.381 mmol) en DMF (1 mL) y se trataron con Cs_2CO_3 (371 mg, 1.14 mmol). La reacción diluida con agua (15 mL) y cloruro de metileno (15 mL) se agitó a 50 °C por 16 h. La capa orgánica se lavó con agua, se secó con $MgSO_4$, se filtró y se concentró. El residuo se purificó por columna cromatográfica (gel de sílice, 33% a 66% acetato de etilo en hexanos). Un eluyente que contiene el compuesto deseado se concentró disuelto en una solución de THF/MeOH/2N $LiOH_{(aq)}$ (1:1:1) (2 mL). La mezcla se agitó a temperatura ambiente por 90 min., y se vertió la solución en 0.65 N $HCl_{(aq.)}$ (2 mL). La fase acuosa se extrajo con diclorometano (3 x 10 mL) y las fases orgánicas combinadas se secaron sobre Na_2SO_4. Tras filtrarse y secarse, se obtuvieron 1:56 mg (0.323 mmol) de ácido carboxílico **52**. ^1H NMR (400MHz) (CDCl3) S 7.77 (d, 2H, J= 8.1 Hz), 7.23-7.30 (m, 5H), 6.89-6.97 (m, 4H), 5.24 (s, 2H), 4.58 (t, 1H, J= 7.8 Hz), 3.02 (m, 1H), 2.92 (m, 1H), 2.40 (s, 3H), 2.33 (s, 3H).

6.53 Ejemplo 53

[0479] Este ejemplo ilustra la preparación de ácido (+/-)-3-[4-(4'-trifluorometil-bifenil-3-ilmetoxi)-fenil]-3-(tiazol-2-il)-propiónico.

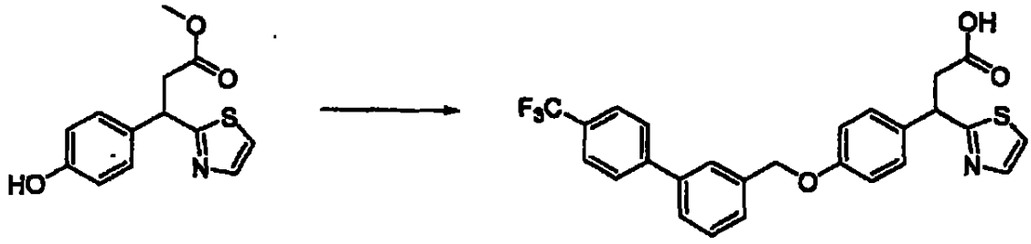
Esquema 53.1



52.1 53.1

[0480] **(+/-)-Metil 3-(4-hidroxifenil)-3-(tiazol-2-il)propanoato (53.1).** Un matraz de 500 mL se equipó con una barra de agitación magnética, entrada de nitrógeno, salida de nitrógeno y se colocó a temperatura ambiente en un baño de agua. Al matraz se agregó el compuesto **52.1** (5.00 g, 15.1 mmol) junto con THF anhidro (150 mL). Tras purgar con nitrógeno por 30 min, se agregó por medio de cánula una solución de bromuro de tiozol-2-il-magnesio en THF (1 M, 18.1 mL). Una vez que se completó la adición, se agitó la mezcla de la reacción por 1.5 h, se extinguió con NH_4Cl acuoso (1 M, 100 mL) diluido con acetato de etilo (100 mL). La capa acuosa se acidificó a un pH ~2 con HCl concentrado y se extrajo con acetato de etilo (150 mL x 2). El extracto se lavó con salmuera y se concentró. El residuo se disolvió en 100 mL de 10:1 DMF-agua y se calentó a 100 °C por 8 h. La reacción se enfrió y se diluyó con 500 mL de agua y se extrajo con acetato de etilo (150 mL x 3). Lo orgánico se secó con $MgSO_4$, se filtró, y se concentró en un evaporador rotativo. El residuo orgánico se disolvió en MeOH (200 mL), se agregaron 5 gotas de H_2SO_4 concentrado y la solución se sometió a reflujo por 24 h. La solución se concentró en un evaporador rotativo hasta obtener un residuo y se purificó por columna cromatográfica flash con acetato de etilo/hexanos 50% como eluyente. Se combinaron las fracciones y se concentraron para obtener 1.90 g (7.25 mmol) de **53.1** como un aceite viscoso.

Esquema 53.2



53.1 53

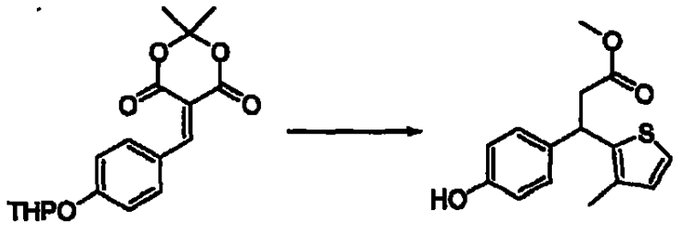
[0481] **Ácido (+/-)-3-[4-(4'-Trifluorometil-bifenil-3-ilmetoxi)-fenil]-3-(tiazol- 2-il)-propiónico (53).** Se disolvieron cloruro de bencilo **2.3** (123 mg, 0.456 mmol) y fenol **53.1**

(100 mg, 0.380 mmol) en acetona (1 mL) y se trataron con Cs_2CO_3 (371 mg, 1.14 mmol). La reacción se agitó a 50 °C por 16 h, se filtró y se concentró. El residuo se concentró por columna cromatográfica (gel de sílice, 30% a 70% acetato de etilo en hexanos). Se concentró un eluyente que contenía los compuestos deseados y se disolvió en una solución de THF/MeOH/2N LiOH(aq) (1:1 :1) (2 mL). La mezcla se agitó a temperatura ambiente por 90 min., y se vertió la solución en 0.65 N HCl (aq.) (2 mL). La fase acuosa se extrajo con diclorometano (3 x 10 mL) y las fases orgánicas combinadas se secaron sobre Na_2SO_4. Tras filtrarse y secarse se obtuvieron 150 mg (0.311 mmol) de ácido carboxílico **53**. ^1H NMR (400MHz) ($CDCl_3$) δ 7.47-7.77 (m, 9H), 7.24-7.27 (m, 3H), 6.99-7.00 (m, 2H), 5.14 (s, 2H), 4.78 (dd, 1H, J- 6.8, 4.4 Hz), 3.47 (dd, 1H, J= 12.8, 6.8 Hz), 3.09 (dd, 1H, ./=12.8, 4.4 Hz).

6.54 Ejemplo 54

[0482] Este ejemplo ilustra la preparación de ácido (+/-)-3-[4-(4'-Trifluorometil-bifenil-3-ilmetoxi)-fenil]-3-(3-metitiofen-2-il)-propiónico.

Esquema 54.1

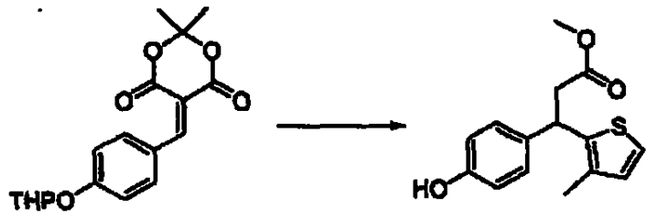


52.1 **54.1**

[0483] **(+/-)-Metil 3-(4-hidroxifenil)-3-(3-metitiofen-2-il)propanoato (54.1).** Un matraz de 500 mL se equipó con una barra magnética de agitación, entrada de nitrógeno, salida de nitrógeno, y se colocó a temperatura ambiente en un baño de agua. Al matraz se agregó el compuesto **52.1** (5.00 g, 15.1 mmol) junto con THF anhidro (150 mL). Tras purgar con nitrógeno por 30 min, por medio de cánula se agregó una solución de bromuro de 3-metitiofen-2-il-magnesio en THF (1 M, 18.1 mL). Tras completar la adición, la mezcla de la reacción se agitó por 1.5 h, se aplacó con NH_4Cl (1 M, 100 mL) acuoso y se diluyó con acetato de etilo (100 mL). La capa acuosa se acidificó a un pH ~2 con HCl concentrado y se extrajo con acetato de etilo (150 mL x 2). El extracto se lavó con salmuera y se concentró. El residuo se disolvió en 100 mL de 10:1 DMF-agua y se calentó a 100 °C por 8 h. La mezcla de la reacción se enfrió, se diluyó con 500mL de agua, y se extrajo con acetato de etilo (150 mL x 3). Las capas orgánicas combinadas se secaron con $MgSO_4$, se filtró, y se concentró en un evaporador rotativo. El residuo se disolvió en MeOH (200 mL) y se

agregaron 5 gotas de H_2SO_4 concentrado y la solución se sometió a reflujo por 24 h. La solución se concentró en un evaporador rotativo hasta lograr un residuo y se purificó por columna cromatográfica flash con 30% acetato de etilo/hexanos como el eluyente. Las fracciones se combinaron y se concentraron para lograr 2.33 g (7.25 mmol) de **54.1** como un aceite viscoso. 299

Esquema 54.2



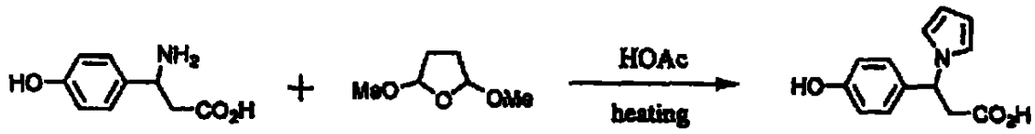
52.1 **54.1**

[0484] **Ácido (+/-)-3-(4-(4-Trifluorometil-bifenil-3-ilmetoxi)-fenil]-3-(3-metitiofen-2-il)-propiónico (54).** En acetona (1 mL) se disolvieron cloruro de bencilo **2.3** (113 mg, 0.434 mmol) y fenol 54.1 (100 mg, 0.362 mmol) y se trataron con Cs_2CO_3 (371 mg, 1.14 mmol). La reacción se agitó a 50 °C por 16 h, se filtró y se concentró. El residuo se purificó por columna cromatográfica (gel de sílice, acetato de etilo en hexanos al30% a 60%) . Un eluyente que contenía el compuesto deseado se concentró y se disolvió en una solución de THF/MeOH/2N $LiOH_{(aq)}$ (1:1:1) (2 mL). La mezcla se agitó a temperatura ambiente por 90 min., la solución se vertió en 0.65 N $HCl_{(aq.)}$ (2 mL). La fase acuosa se extrajo con diclorometano (3 x 10 mL) y las capas orgánicas combinadas se secaron sobre Na_2SO_4. Tras filtrarse y secarse se obtuvieron 154 mg (0.311 mmol) de ácido carboxílico **54**. ^1H NMR (400MHz) (CDCl3) δ 7.43-7.70 (m, 8H), 7.21 (d, 2H, J= 8.6 Hz), 7.05 (d, 1H, J= 5.0 Hz), 6.92 (d, 2H, J= 8.6 Hz), 6.76 (d, 1H, 5.0 Hz), 5.09 (s, 2H), 4.74 (t, 1H, J= 7.8 Hz), 3.05 (d, 2H, J= 7.8 Hz), 2.15 (s, 3H).

6.55 Ejemplo 55

[0485] Este ejemplo ilustra la preparación de 3-(4-hidroxifenil)-3- (1H-pirrol- 1-il)propanoato de etilo.

Esquema 55.1



55.1

[0486] **Ácido 3-(4-Hidroxifenil)-3-(1*H*-pirrol-1-il)propanóico (55.1).** A 100 °C, a una mezcla de ácido 3-amino-3-(4- hidroxifenil) propanóico (7.7 mmol) y acetato de sodio (46 mmol) en ácido acético (34 mL) se agregó 2,5-dimetoxitetrahidrofurano (8.5 mmol). Tras agitar por 1 h, se removió el ácido acético bajo presión reducida. El residuo se extrajo con acetato de etilo (300 mL). La capa orgánica se lavó con salmuera y se secó sobre Na_2SO_4 anhidro y se concentró. El residuo se purificó por columna cromatográfica (10% metanol en diclorometano) para dar el compuesto **55.1**. LC-MS (neg.) m/e: 230.2 (M-H).

Esquema 55.2



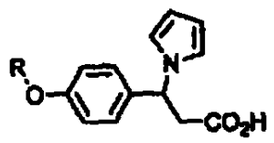
55.1 **55**

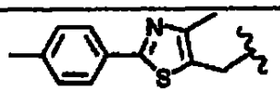
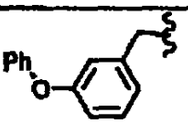
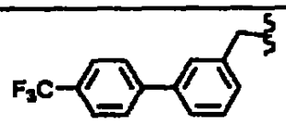
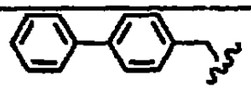
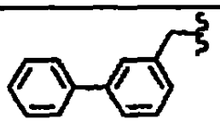
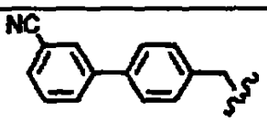
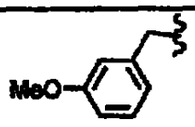
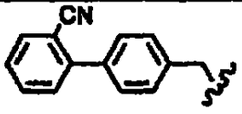
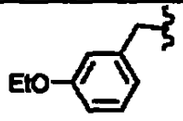
[487] **(+/-)-Metil3-(4-hidroxifenil)-3-(1*H*-pirrol-1-il)propanoato (55).** A una solución de **55.1** (7 mmol) en metanol se agregó trimetisilildiazometano (8 mL, 2M en éter dietílico, 16 mmol). Tras 10 min., el solvente se removió para dar el compuesto **55** metilo. MS ESI (pos.) m/e: 246.1 (M+H).

6.56 Ejemplo 56

[0488] Los siguientes compuestos se prepararon a partir del compuesto **55** de acuerdo con los métodos descritos en el Ejemplo 18.

Tabla 17



Compuesto	R	Compuesto	R
56.1		56.6	
56.2		56.7	
56.3		56.8	
56.4		56.9	
56.5			

[0489] Compuesto **56.1**. MS ESI (neg.) m/e: 431 (M-H). ^{1}H NMR (500MHz) (DMSOd_6) δ 12.3 (1H, s); 7.81 (2H, d, J=8 Hz); 7.30 (4H, m); 6.99 (2H, d, J=9Hz); 6.92 (2H, m); 5.98 (2H, m); 5.56 (1H, t, J=8Hz), 5.29 (2H, s); 3.18 (2H, m); 2.44 (3H, s); 2.38 (3H, s).

[0490] Compuesto **56.2**. MS ESI (neg.) m/e: 464 (M-H). ^{1}H NMR (SOOMHZ) (DMSOd_6) δ 7.92 (2H, m); 7.84 (3H, m); 7.72 (1H, d, J=8Hz); 7.53 (2H, m); 7.26 (2H, d, J=9Hz); 7.00 (2H, d, J=9Hz), 6.91 (2H, m); 5.55 (1H, d, J=8Hz); 5.19 (2H, s); 3.16 (2H, m).

[0491] Compuesto **56.4**. MS ESI (neg.) m/e: 396 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 12.37 (1H, s); 7.65-7.77 (4H, m); 7.41-7.51 (5H, m); 67.27 (2H, m); 7.01 (2H, d, J=5Hz)); 6.92 (2H, m); 5.99(2H, m), 5.56 (1H, m); 5.18 (2H, s), 3.21 (2H, m).

[0492] Compuesto **56.4**. MS ESI (neg.) m/e: 350 (M-H). ^{1}H NMR (500MHz) (DMSO-d6) δ 12.4 (1H5 s); 7.30-7.34 (1H,t, J=8Hz); 7.26 (2H, d5 J=9Hz); 7.01 (2H, m); 6.96 (2H, d, J=9Hz)); 6.90-6.92 (3H, m); 5.98 (2H, m), 5.55 (1H,t,J=8Hz); 5.07(2H, s); 3.78 (3H, s); 3.21(2H, m).

[0493] Compuesto **56.5**. MS ESI (neg.) m/e: 364 (M-H). ^{1}H NMR (500MHz) (DMSOd_6) δ 7.24-7.31 (3H, m); 6.99 (2H, m); 6.88 (3H, m); 5.97 (2H, s); 5.55 (1H, m); 5.06(2H, s), 4.04 (2H, q, J=7Hz); 3.16 (2H, m); 1.34 (3H, t, J=7Hz).

[0494] Compuesto **56.6**. MS ESI (neg.) m/e: 412 (M-H). ^{1}H NMR (500MHz) (DMSOd_6) δ 7.40-7.43 (3H, m); 7.16-7.26 (4H, m); 7.08 (1H, s); 7.03 (2H,d, J=8Hz)); 6.90-6.97 (5H, m); 5.98(2H, s), 5.54 (1H, t,J=8Hz); 5.09 (2H,s); 3.17 (2H, m)

[0495] Compuesto **56.7**. MS ESI (neg.) m/e: 396 (M-H). ^{1}H NMR (500MHz) (DMSOd_6) δ 7.70-7.71 (4H, m); 7.41-7.55 (4H,m); 7.39 (1H, m); 7.25 (2H,d,J=8Hz)); 6.98 (2H,d, J=9Hz); 6.89 (2H,s)5 5.97 (2H,s); 5.55 (1H,t, J=8Hz); 5.12 (2H,s); 3.10 (2H,m).

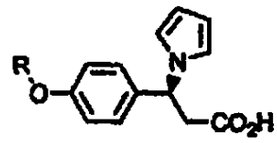
[0496] Compuesto **56.8**. MS ESI (neg.) m/e: 421 (M-H). ^{1}H NMR (500MHz) (DMSOd_6) δ 8.19 (1H, s); 8.05 (1H,d, J=8Hz); 7.87 (1H,d,J=SHz); 7.80 (2H,d J=8Hz); 7.71 (1H,t, J=8Hz); 7.56 (2H,d,J=8Hz); 7.26 (2H, d, J=8Hz); 6.98 (2H,d, J=SHz); 6.90 (2H,d, J=8Hz); 5.98 (2H, m); 5.55 (2H,t,J=8Hz)); 5.17 (2H,s); 3.13 (2H, m).

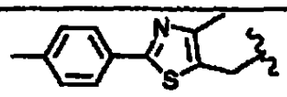
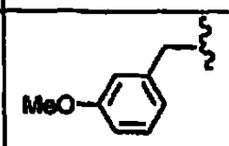
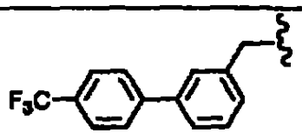
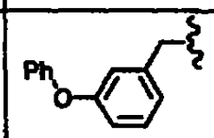
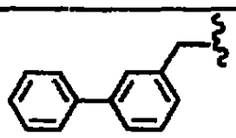
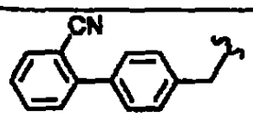
[0497] Compuesto **56.9**. MS ESI (neg.) m/e: 421 (M-H). ^{1}H NMR (500MHz) (DMSO-d6) δ 7.99 (1H5 d, J=8Hz); 7.84 (1H,t,J=8Hz); 7.68 (1H,d,J=8Hz); 7.58-7.64 (5H, m); 7.17 (2H, d, J=8Hz); 6.96 (2H, d, J=8Hz); 6.81 (2H, m); 5.95 (2H, m); 5.55 (1H, t, J=7Hz); 5.18 (2H, s); 2.73 (2H, d, J=7Hz).

6.57 Ejemplo 57

[0498] Los siguientes compuestos se prepararon de acuerdo con los métodos descritos en los Ejemplos 55 y 56.

Tabla 18



Compuesto	R	Compuesto	R
57.1		57.4	
57.2		57.5	
57.3		57.6	

[0499] Compuesto **57.1**. MS ESI (neg.) m/e: 431 (M-H). ^{1}H NMR (500MHz) (DMSOd_6) δ 7.81 (2H, m); 7.28-7.32 (4H, m); 7.00 (2H, d, J=8Hz); 6.92 (2H, s); 5.99 (2H, s); 5.57 (1H, m); 5.30 (2H, s); 3.23 (2H, m); 2.44(3H, s); 2.38 (3H, s).

[0500] Compuesto **57.2**. MS ESI (neg.) m/e: 464 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.93 (2H, d, J=8Hz); 7.83-7.86 (3H, m); 7.72 (1H, d, J=8Hz); 7.56 (2H, m); 7.27 (2H, d, J=9Hz); 7.01 (2H, d, J=9Hz); 6.91 (2H, m); 5.98 (2H, s); 5.55 (1H, d, J=8Hz); 3.14 (2H, m).

[0501] Compuesto **57.3**. MS ESI (neg.) m/e: 396 (M-H). ^{1}H NMR (500MHz) ($CDCl_3$) δ 1.63-1.16 (4H, m); 7.39-7.59 (5H, m); 7.15 (2H, d, J=8Hz); 6.77 (2H, s); 6.19 (2H, s); 5.64 (1H, s); 5.13 (2H, s); 3.22-3.26 (2H, m).

[0502] Compuesto **57.4**. MS ESI (neg.) m/e: 350 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.33 (1H, t, J=8Hz); 7.25 (2H, d, J=8Hz); 7.01 (2H, m); 6.95 (2H, d, J=9Hz); 6.90 (3H, m); 5.98 (2H, s); 5.55 (1H, t, J=8Hz); 5.07 (2H, s); 3.78 (3H, s); 3.16 (2H, m).

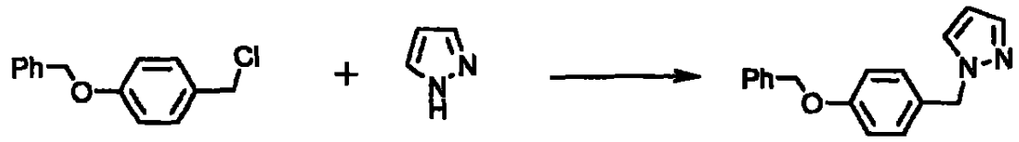
[0503] Compuesto **57.5**. MS ESI (neg.) m/e: 412 (M-H). ^{1}H NMR (5OOMHZ) (DMSO-d_6) δ 7.40-7.43 (3H, m); 7.24-7.26 (3H, m); 7.20 (1H, m); 7.10 (1H, s); 7.03 (2H, d, J=9Hz); 6.90-6.93 (5H, m); 5.98 (2H, m); 5.55 (1H, m); 5.10 (2H, s); 3.18 (2H, m).

[0504] Compuesto **57.6**. MS ESI (neg.) m/e: 421 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.99 (1H3 d, J=8Hz); 7.81(1H, m); 7.68 (1H, d, J=SHz); 7.61-7.65 (5H, m); 6.92 (2H, m); 5.99 (2H, s); 5.56 (1H, t, J=8Hz); 5.20(2H, s); 3.19 (2H, m).

6.58 Ejemplo 58

[0505] Este ejemplo ilustra la preparación de ácido (+/-)-3-(-4-(Benciloxi)fenil)-3-(1*H*-pirazol-l-il)propanoico (**58.3**).

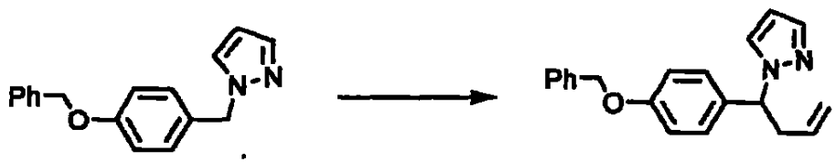
Esquema 58.1



58.1

[0506] **1-(4-(Benziloxi)bencilo)-1*H*-pirazol (58.1).** Luego de que una mezcla de pirazol (7.73 mmol) e hidróxido de potasio (7.73 mmol) en DMF (35 niL) se agitara a temperatura ambiente por 30 min., se agregó gota a gota una solución de l-(benciloxi)-4-(clorometilo)benceno(6.44 mmol) en DMF (7 niL). La mezcla de la reacción se agitó a temperatura ambiente durante toda la noche y el producto se obtuvo a partir de procesamiento acuoso estándar. La cromatografía de columna (1:2 acetato de etilo / hexano) del residuo produjo el compuesto **58.1** como un sólido blanco. LC-MS ESI (pos.) m/e: 265 (M+H); ^{1}HNMR (500MHz) (DMSO-d_6) δ 7.79 (1H, m); 7.46 (3H, m); 7.40 (2H, m); 7.36 (1H, m); 7.21 (2H, d, J=9Hz)); 5.27 (2H, s); 5.11 (2H, m).

Esquema 58.2

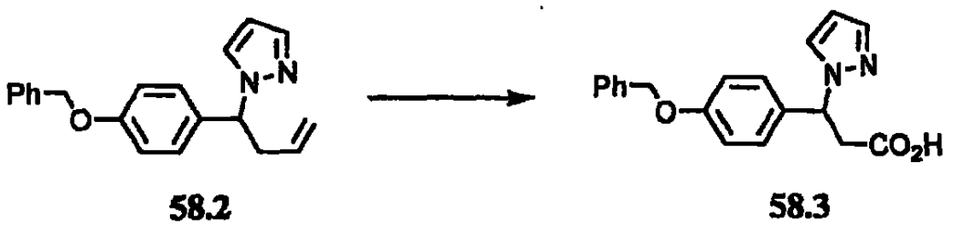


58.1 **58.2**

[0507] **1-(4-(Benciloxi)fenil)but-3-enil)-1*H*-pirazol (58.2).** A una solución del compuesto **58.1** (3.41 mmol) en THF (30 mL) a -78 °C se le agregó gota a gota n-butillitio en hexanos (3.75 mmol). La mezcla se agito por 10 min. y a continuación se agregó bromuro de alilo (3.75 mmol). Se dejó que la mezcla de la reacción se enfriara durante toda la noche, se aplacó con la adición de agua. Luego de la extracción con acetato de etilo, la capa orgánica se lavo con salmuera, se seco sobre Na_2SO_4, y se concentró bajo presión

reducida. La cromatografía de columna (1:3 acetato de etilo/hexano) del residuo produjo el compuesto **58.2** como un sólido blanco. LC-MS ESI (pos.) m/e: 305 (M+H).

Esquema 58.3



58.2 **58.3**

[0508] **Ácido 3-(4-(Beciloxi)fenil)-3-(1H-pirazol-1-il)propanoico (58.3).** A una solución de $KMnO_4$ (1.68 mmol) en agua (19 niL) se le agregó gota a gota a una mezcla del compuesto **58.2** (1.08 mmol), $NaIO_4$ (2.2 mmol), acetona (6mL), y ácido acético (6mL). Luego de que se agitara a temperatura ambiente por 1 h, se agregaron (2 mL) de etilenglicol y se agitó por 1 h más. El MnO_2 se removió por filtración por medio de gel de sílice (eluida con 1:9 metanol: diclorometano). Luego de concentrarse bajo presión reducida, el residuo se purificó por medio de cromatografía de columna (1:9 metanol: diclorometano), lo que produjo el compuesto **58.3** (243 mg, 0.75 mmol). LC-MS ESI (pos.) m/e: 323 (M+H).

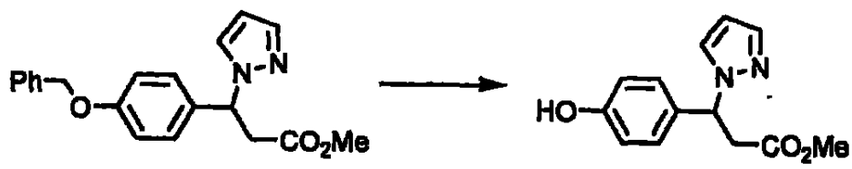
Esquema 58.4



58.3 **58.4**

[0509] **3-(4-(benciloxi)fenil)-3-(1H-pirazol-1-il)propanoato de metilo (58.4).** El compuesto **58.3** se esterificó de forma similar al método discutido en conexión con el Esquema 55.2.

Esquema 58.5



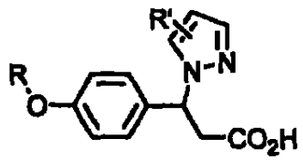
58.4 **58**

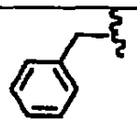
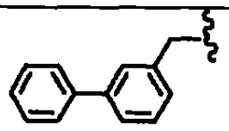
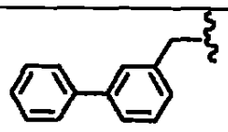
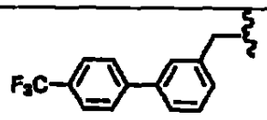
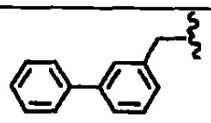
[0510] **(+/-)-Metilo 3-(4-hidroxifenil)-3-(1*H*-pirazo-1-il)propanoato (58).** Una mezcla del compuesto **58.4** (0.37 mmol) y una pequeña cantidad de Pd-C en metanol (8 mL) se agitaron a temperatura ambiente bajo atmósfera de nitrógeno por 20 min. Luego de que se filtrara y concentrara, el residuo se purificó por cromatografía de columna. Se obtuvieron (81 mg, 0.33 mmol) del compuesto **58**. LC-MS ESI (pos.) m/e: 247 (M+H).

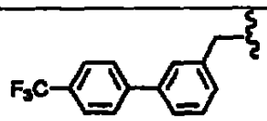
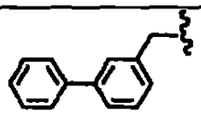
6.59 Ejemplo 59

[0511] Los siguiente compuestos se prepararon a partir del compuesto **58** de acuerdo con los métodos descritos en el Ejemplo 18.

Tabla 19



Compuesto	R	R'
59.1		H
59.2		H
59.3		H
59.4		3-metilo
59.5		3-metilo

Compuesto	R	R'
59.6		5-metilo
59.7		5-metilo

[0512] Compuesto **59.1.** MS ESI (neg.) m/e: 321 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.84 (1H, d, J=2Hz); 7.40-7.50 (5H, m); 7.35 (1H, m); 7.27(2H, d, J=9Hz); 6.97 (2H, d, J=9Hz); 6.24 (1H, s); 5.79 (1H, m); 5.06 (2H, s); 3.3(1H, m); 3.12 (1H, m).

[0513] Compuesto **59.2.** MS ESI (neg.) m/e: 397 (M-H). ^{1}H NMR (5OOMHZ) . (DMSO-d_6) δ 7.85 (1H, s); 7.64-7.77 (4H, m); 7.41-7.50 (6H, m); 7.29(2H, d, J=8Hz); 7.01 (2H, d, J=9Hz); 6.24 (1H, s); 5.80 (1H, m); 5.18 (2H, s); 3.3(1H, m); 3.12 (1H, m).

[0514] Compuesto **59.3.** MS ESI (neg.) m/e: 465 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.93 (2H, d, J=8Hz); 7.85 (4H, m); 7.73 (1H, d, J=7Hz); 7.54(2H, m); 7.29 (1H, s); 7.28 (2H, m); 7.00 (2H, m); 6.23(1H, s); 5.80 (1H, m); 5.20 (2H, s); 3.3(1H, m); 3.14 (1H, m).

[0515] Compuesto **59.4.** MS ESI (neg.) m/e: 479 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.92 (2H, m); 7.82-7.86 (3H, m); 7.72 (1H, m); 7.52-7.56 (2H, m); 7.36 (1H, s); 7.20 (2H, d, J=9Hz); 6.99 (2H, d, J=9Hz); 6.02 (1H, m); 5.69 (1H, m); 5.14 (2H, s); 3.3 (1H, m); 2.98 (1H, m); 2.24 (3H, s).

[0516] Compuesto **59.5.** MS ESI (neg.) m/e: 411 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.63-7.73 (4H, m); 7.36-7.52 (6H, m); 7.20 (2H, d, J=8Hz); 6.99 (2H, d, J=8Hz); 6.01 (1H, s); 5.70 (1H, m); 5.17 (2H, s); 3.3 (1H, m); 2.99 (1H, m); 2.24 (3H, s).

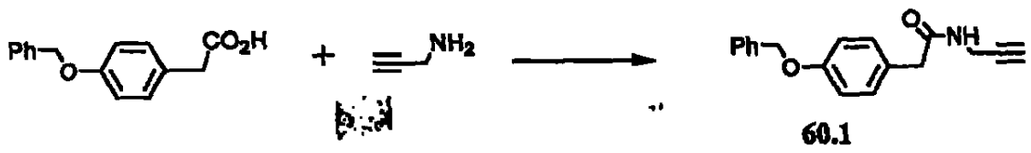
[0517] Compuesto **59.6.** MS ESI (neg.) m/e: 479 (M-H). ^{1}H NMR (5OOMHZ) (DMSO-d_6) δ 7.93 (2H5 m); 7.84 (3H, m); 7.71 (2H, m); 7.55 (2H, m); 7.26(2H, d, J=9Hz); 7.00 (2H, d, J=9Hz); 6.00 (1H, s); 5.69 (1H, m); 5.19 (2H, s); 3.3 (1H, m); 3.05 (1H, m); 2.15 (3H, s).

[0518] Compuesto **59.7.** MS ESI (neg.) m/e: 411 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.64-7.74 (5H, m); 7.39-7.52 (5H, m); 7.26 (2H, d, J=9Hz); 6.99 (2H, d, J=9Hz); 5.99 (1H, s); 5.68 (1H, m); 5.17 (2H, s); 3.3 (1H, m); 3.06 (1H, m); 2.15 (3H, s).

6.60 Ejemplo 60

[0519] Este ejemplo ilustra la preparación de 3-(4-hidroxifenil)-3-(5- metilooxazol-2-il)propanoato etílico.

Esquema 60.1



60.1

[0520] **2-(4-(Benciloxi)fenil)-*N*-(prop-2-inil)acetamida (60.1).** Una mezcla de ácido 4-(benciloxi)fenilacético (20.7 mmol), hidrato de 1-hidroxibenzotriazol (37 mmol), 1-(3-dimetilaminopropil)-3- etilcarbodiimida (37 mmol), propargilamina (20.7mmol) y N-metilmorfolina (62 mmol) en DMF (60 mL) se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se diluyó con acetato de etilo (400 mL), se lavo con 1N HCl, agua, solución saturada de Na_2CO_3, salmuera y se seco sobre Na_2SO_4. Luego de remover el solvente bajo presión reducida, el residuo se trituró con diclorometano. El compuesto **60.1** se obtuvo como un sólido blanco luego de filtrarse y secarse. LC-MS ESI (pos.) m/e: 280 (M+H).

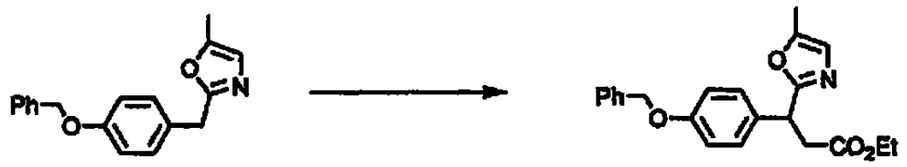
Esquema 60.2



60.1 60.2

[0521] **Oxazole 2-(4-Benciloxi)bencilo)-5-metil (60.2).** Una mezcla del compuesto **60.1** (10.1 mmol), $AuCl_3$ (1 mmol) en diclorometano (100 mL) se agitó a temperatura ambiente durante toda la noche. Se agregaron 100 L de diclorometano y la mezcla de la reacción se lavó con una solución de $NaHCO_3$ y salmuera saturada. Luego de secarse sobre Na_2SO_4 y de concentrarse bajo presión reducida, el residuo se purificó por medio de cromatografía de columna (1:2 acetato de etilo-hexanos) para obtener el compuesto **60.2.** LC-MS ESI (pos.) m/e: 280 (M+H).

Esquema 60.3



60.2 **60.3**

[0522] **3-(4-(benciloxi)fenil)-3-(5-metiloxazol-2-il)propanoato de etilo (60.3).** El compuesto **60.3** se obtuvo del compuesto **60.2** de acuerdo con el método del Ejemplo 58.

Esquema 60.4



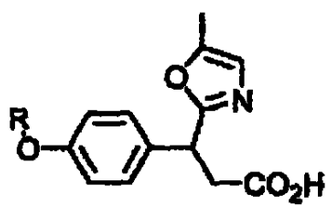
60.3 **60**

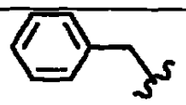
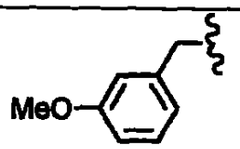
[0523] **3-(4-hidroxifenil)-3-(5-metiloxazol-2-il)propanoato de (+/-)-Etilo (60).** El compuesto **60** se obtuvo a partir del compuesto **60.3** de acuerdo al método del Ejemplo 58.

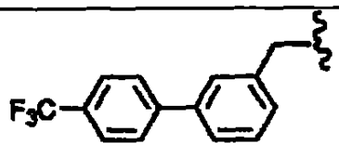
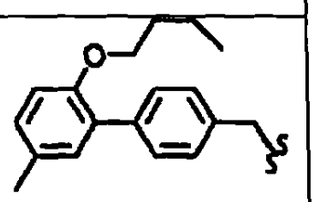
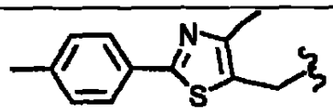
6.61 Ejemplo 61

[0524] Los siguientes compuestos se prepararon a partir del compuesto **60** de acuerdo con los métodos descritos en el Ejemplo 18.

Tabla 20



Compuesto	R	Compuesto	R
61.1		61.4	

Compuesto	R	Compuesto	R
61.2		61.5	
61.3			

[0525] Compuesto **61.1.** MS ESI (neg.) m/e: 336 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.41-7.46 (4H, m); 7.36 (1H, m); 7.17 (2H, d, J=9Hz); 6.97 (2H, d, J=9Hz); 6.73 (1H, s); 5.09 (2H, s); 4.44 (1H, m); 3.08 (1H, m); 2.71 (1H, m); 2.22 (3H, s).

[0526] Compuesto **61.2.** MS ESI (neg.) m/e: 480 (M-H). ^{1}H NMR (5OOMHZ) (DMSO-d_6) δ 7.91-7.93 (2H, m); 7.82-7.85 (3H, m); 7.72 (2H, d, J=7Hz); 7.54 (2H, m); 7.18 (2H, d, J=8Hz); 6.99 (2H, d, J=8Hz); 6.72 (1H, s); 5.17 (2H, s); 4.44 (1H, m); 3.08 (1H, m); 2.74 (1H, m); 2.21 (3H, s).

[0527] Compuesto **61.3.** MS ESI (neg.) m/e: 447 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.80 (2H, d, J=8Hz); 7.30 (2H, d, J=8Hz); 7.19 (2H, d, J=8Hz); 7.00 (2H, d, J=8Hz); 6.73 (1H, s); 5.27 (2H, s); 4.44 (1H, m); 3.10 (1H, m); 2.73 (1H, m); 2.43 (3H, s); 2.34 (3H, s); 2.21 (3H, s).

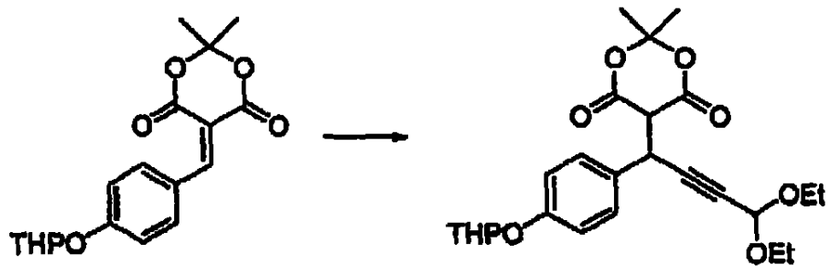
[0528] Compuesto **61.4.** MS ESI (neg.) m/e: 366 (M-H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.32 (1H, t, J=8Hz); 7.16 (2H, d, J=8Hz); 7.00(2H, m); 6.96 (2H, m); 6.89 (1H, m); 6.72 (1H, s); 5.05 (2H, s); 4.42 (1H, m); 3.76 (3H, s); 3.06 (1H, m); 2.76 (1H, m); 2.21 (3H, s).

[0529] Compuesto **61.5.** MS ESI (pos.) m/e: 500 (M+H). ^{1}H NMR (500MHz) (DMSO-d_6) δ 7.50 (2H, d, J=8Hz); 7.44 (2H, d, J=8Hz); 7.11-7.18 (4H, m); 6.97 (3H, m); 6.71 (1H, s); 5.10 (2H, s); 4.43 (1H, m); 3.93 (2H, t, J=7Hz); 3.06 (1H, m); 2.70 (1H, m); 2.20 (3H, s); 1.61 (2H, m);1.36 (2H, m); 0.86 (3H, t, J=7Hz).

6.62 Ejemplo 62

[0530] Este ejemplo ilustra la preparación de ácido 3-(4-(3-(4-(trifluorometil)fenil) benciloxi)fenil)-3-(isoxazol-5-il)propanoico (**62**).

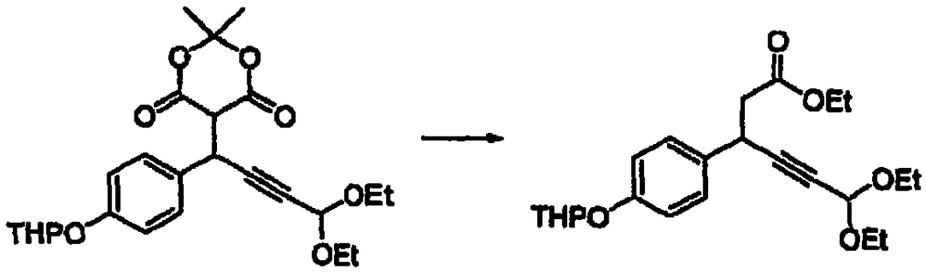
Esquema 62.1



52.1 62.1

[0531] **5-(4,4-Dietoxi-1-(4-(tetrahidro-2H-piran-2-iloxi)fenil)but-2-inil)- 2,2-dimetil-1,3-dioxano-4,6-diona (62.1).** Se enfrió propionaldehido de acetal dietílico (5 g, 39 mmol) en THF anhidro (65 mL) a -5 °C y gota a gota se trató por 10 minutos con bromuro de etilmagnesio (39 mmol en 14 mL de anhidro THF). Luego de 45 min., al compuesto **52.1** en THF anhidro (50 mL) se agregó la solución del reactivo Grignard. Luego de agitar por 1 h, la reacción se aplacó con $NH4Cl_{(aq)}$ saturado (20 mL) y se diluyó con hexanos (100 mL). Luego de mezclarse vigorosamente, las capas se separaron y se descartó la capa orgánica. Se acidificó la capa acuosa y se extrajo dos veces con éter dietílico. Las capas orgánicas combinadas se lavaron con salmuera saturada, se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El residuo se utilizó inmediatamente sin ninguna purificación posterior. MS ESI (pos.) m/e: 478.3 $(M+NH4)^+$.

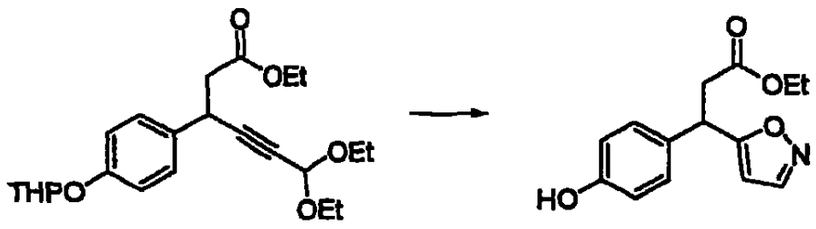
Esquema 62.2



62.1 62.2

[0532] **6,6-dietoxi-3-(4-(tetrahidro-2H-piran-2-iloxi)fenil)hex-4-inoato de etilo (62.1).** La etanólisis y decarboxilación se llevaron a cabo de acuerdo con el método del Ejemplo 16. Se obtuvo el éster **62.2** como un aceite Amarillo claro (8 g).

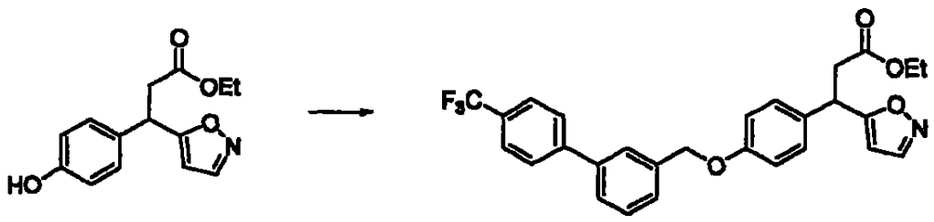
Esquema 62.3



62.2 62.3

[0533] 3-(4-hidroxifenil)-3-(isoxazol-5-il)propanoato de etilo (62.3). Se disolvieron (1 g, 2.5 mmol) del compuesto **62.2** e hidrocloruro de hidroxilamina (0.43 g, 6.2 mmol) en una mezcla de etanol (10 mL) y agua (1 mL). Luego del reflujo por 2 h, la mezcla de la reacción se diluyó con 200 mL de agua y se extrajo con éter dietílico (2 x 100 mL). Las capas orgánicas combinadas se lavaron con salmuera saturada, se secaron sobre $MgSO_4$, se filtraron, y se concentraron bajo presión reducida. El residuo se purificó por medio de cromatografía flash (gel de sílice, 5% metanol en eluyente de diclorometano). El compuesto **62.3** se obtuvo como un aceite espeso (0.38 g). ^1H NMR (500MHz) ($CDCl_3$) δ 8.14 (d, J=I.5 Hz, 1H); 7.12 (d, J=8.5 Hz, 2H); 6.77 (d, J=8.5, 2H); 5.98 (d, J=1.0 Hz, 1H); 5.30 (s, 1H); 4.64 (t, J= 8.0 Hz, 1H); 4.06 (m, 2H); 3.15 (dd, J=16, 7.5 Hz, 1H); 2.95 (dd, J=16, 8.0 Hz, 1H); 1.17 (t, J= 7.2 Hz, 3H).

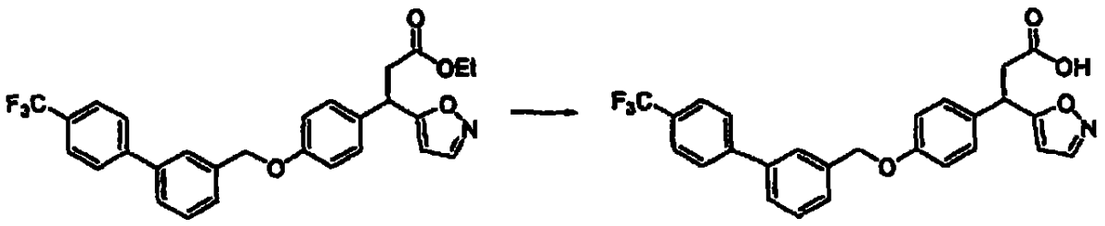
Esquema 62.4



62.3 62.4

[0534] 3-(4-(3-(4-(trifluorometil)fenil)benciloxi)fenil)-3-(isoxazol- 5-il)propanoato de etilo (62.4). El compuesto **62.3** se alquilizó de acuerdo con el procedimiento del Ejemplo 2. LC-MS ESI (pos.) m/e: 496.1 (M+H). ^1H KMR (500MHz) ($CDCl_3$) δ 8.14 (s, 1H); 7.70 (s, 4H); 7.66 (s, 1H); 7.56 (d, J= 7.5 Hz, 1H); 7.50-7.45 (m, 2H); 7.22 (d, J=8.5 Hz, 2H); 6.96 (d, J=8.5, 2H); 5.99 (s, 1H); 5.12 (s, 2H); 4.67 (t, J= 7.7 Hz, 1H); 4.08 (m, 2H); 3.16 (dd, J=16, 7.5 Hz, 1H); 2.95 (dd, J=16, 8.0 Hz, 1H); 1.17 (t, J= 7.2 Hz, 3H).

Esquema 62.5



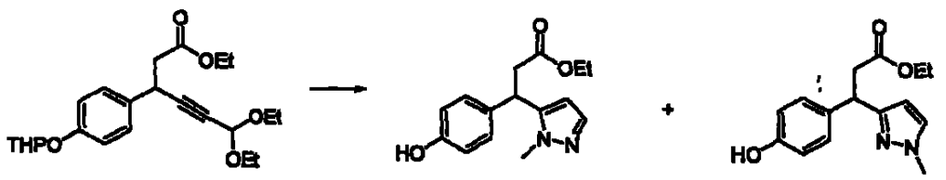
62.4 62

[0535] **Ácido (+/-)-3-(4-(3-(4-(Trifluorometil)fenil)benciloxi)fenil)-3-(isoxazol- 5-il)propanoico (62).** El compuesto **62.4** se disolvió en ácido acético glacial (1 mL) y agua (0.3 mL) y se calentó a 95 °C por 16 h. Se agregó 1N HCl (0.1 mL) y la mezcla de la reacción se calentó por otras 16 h. La mezcla de la reacción se vertió en agua desionizada (50 mL) y se extrajo dos veces con éter dietílico. Las capas orgánicas combinadas se lavaron con salmuera saturada, se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. Se purificó el residuo por medio de cromatografía flash (gel de sílice, 5% metanol en eluyente de diclorometano). El compuesto **62** se obtuvo como un aceite espeso (26 mg). LC-MS ESI (pos.) m/e: 468.1 (M+H). ^{1}H NMR (500MHz) ($CDCl_3$) δ 8.14 (s, 1H); 7.70 (s, 4H); 7.66 (s, 1H); 7.56 (d, J= 7.5 Hz, 1H); 7.50-7.45 (m, 2H); 7.22 (d, J=8.5 Hz, 2H); 6.96 (d, J=8.5, 2H); 5.99 (s, 1H); 5.12 (s, 2H); 4.67 (t, J= 7.7 Hz, 1H); 4.08 (m, 2H); 3.16 (dd, J=16, 7.5 Hz, 1H); 2.95 (dd, J=16, 8.0 Hz, 1H); 1.17 (t, J= 7.2 Hz, 3H).

6.63 Ejemplo 63

[0536] Este ejemplo ilustra la preparación de ácido 3-[4-(2' -butoxi-5' -metil-bifenil-4-ilmetoxi)-fenil]-3-(l-metil-1*H*-pirazol-5-il) propiónico y ácido 3-[4-(2'-butoxi-5'- metil-bifenil-4-ilmetoxi)-fenil]-3-(1-metil- 1*H*-pirazol-3-il) propiónico.

Esquema 63.1

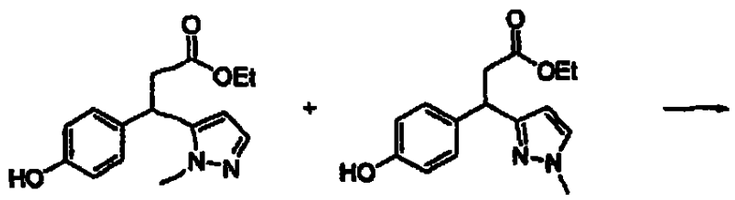


62.2 63.1 63.2

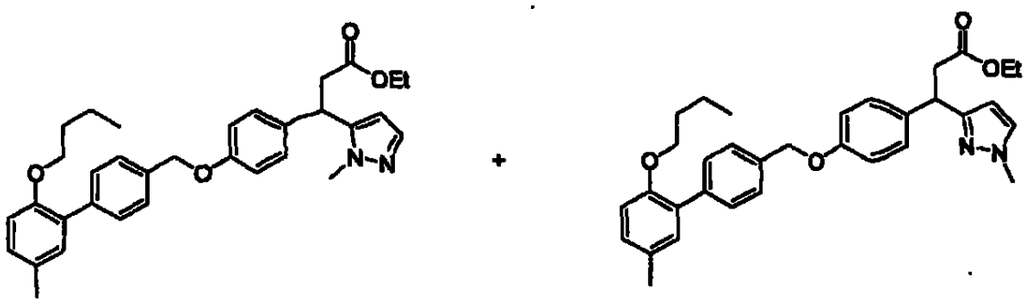
[0537] **3-(4-hidroxifenil)-3-(1-metil-1H-pirazol-5-il)propanoato de etilo (63.1) y 3-(4-hidroxifenil)-3-(1-metil-1H-pirazol-3-il)propanoato de etilo (63.2).** El compuesto **62.2**

se disolvió en etanol absoluto (6 mL). Se agregó una solución de metilhidracina (173 mg, 3.7 mmol) en 6N $HCl_{(aq)}$ (0.6 mL) y la mezcla de la reacción se calentó al reflujo. Luego de 2 h, la mezcla de la reacción se diluyó con 200 mL de agua, se neutralizó con $NaHCO_3$ acuoso saturado, y se extrajo con éter dietílico (2 x 100 mL). Las capas orgánicas combinadas se lavaron con salmuera saturada, se secaron sobre $MgSO_4$, se filtraron, y se concentraron bajo presión reducida. El residuo se purificó por medio de cromatografía flash (gel de sílice, 5% metanol en diclorometano). Los compuestos **63.1** y **63.2** se obtuvieron como una mezcla inseparable en una razón ~4:5 por 1H-NMR. LC-MS ESI (pos.) m/e: 275.2 (M+H).

Esquema 63.2



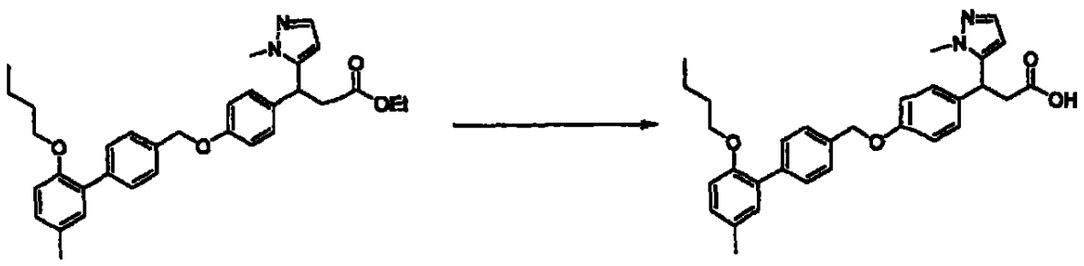
63.1 **63.2**



63.3 **63.4**

[0538] **Etil 3-[4-(2'-Butoxi-5'-metil-bifenil-4-ilmetoxi)-fenil]-3-(1-metil-1*H*-pirazol-5-il) propiónico (63.3) y 3-[4-(2'-butoxi-5'-metil-bifenil-4-ilmetoxi)-fenil]-3-(1-metil-1*H*-pirazol-3-il) propanoato de etilo (63.4).** La mezcla de **63.1** y **63.2** se alquilizó con bromuro 4-(2-butoxi-5-metil)fenil)bencilo de acuerdo con el método del Ejemplo 2. La separación de **63.3** y **63.4** se puede llevar a cabo por medio de cromatografía flash (gel de sílice, 3% acetona en diclorometano).

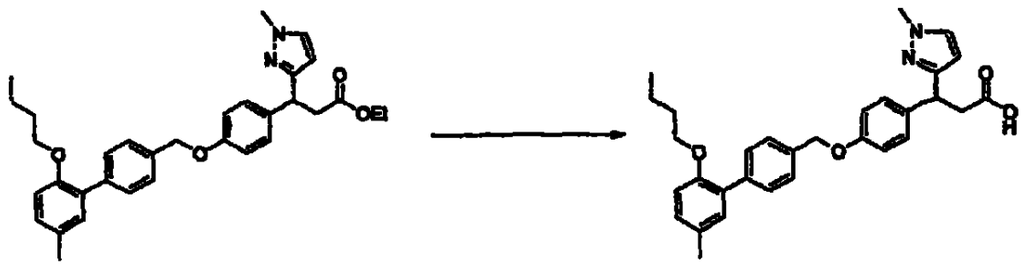
Esquema 63.3



63.3 63.5

[0539] **Ácido (+/-)-3-[4-(2'-Butoxi-5'-metil-bifenil-4-ilmetoxi)-fenil]-3-(1-metil-1*H*-pirazol-5-il) propiónico (63.5).** Un matraz de forma de pera de 25 mL se llenó con 1 mL de etanol, el compuesto **63.3** (20 mg, 0.04 mmol), y 2N $NaOH_{(aq)}$ (2 mL, 4.0 mmol). La mezcla resultante se agitó durante toda la noche a temperatura ambiente. La mezcla se acidificó a un pH de 3 con 1N HCl y se extrajo con acetato de etilo (2 x 10 mL). Los extractos combinados se lavaron con salmuera y se concentraron. El residuo resultante se purificó por medio de TLC preparatorio (30% acetona en diclorometano) para producir el compuesto **63.5** (4.0 mg). ^1H NMR(400MHz)($CDCl_3$) δ 7.55 (d, 2H, J=2 Hz); 7.42 (d, 2H, J=2 Hz); 7.29 (m, 1H); 7.19-7.08 (m, 4H); 6.95-6.86 (m, 3H); 5.98 (s, 1H); 5.05 (s, 2H); 4.46 (m, 1H); 3.94 (s, 3H); 3.31 (m, 1H); 3.01 (m, 1H); 2.33 (s, 3H); 1.67 (m, 3H); 1.40 (m, 3H); 0.90 (t, 3H, J=6 Hz). MS ESI (neg.) m/e: 497.2 (M - H).

Esquema 63.4

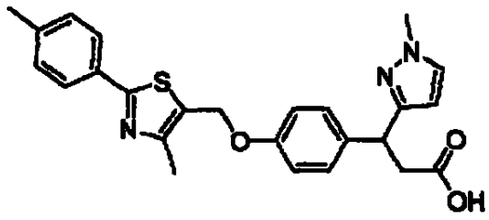


63.4 63.6

[0540] **Ácido (+/-)-3-[4-(2'-Butoxi-5'-metil-bifenil-4-ilmetoxi)-fenil]-3-(1-metil-1*H*-pirazol-3-il) propiónico (63.6).** La hidrólisis de **63.4** se llevó a cabo en la forma descrita anteriormente. MS ESI (neg.) m/e: 497.2 (M - H).

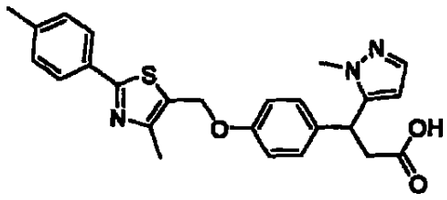
6.64 Ejemplo 64

[0541] Los siguientes compuestos se prepararon a partir de los compuestos **63.1** y **63.2** de acuerdo con los métodos descritos en el Ejemplo 63.



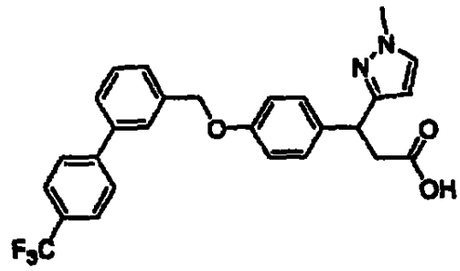
64.1

[0542] **Ácido (+/-)-3-(1-Metil-1*H*-pirazol-3-il)-3-(4-((4-metil-2-*p*-toliltiazol-5-il)metoxi)fenil)propanóico (64.1).** ^{1}H NMR (400MHz) ($CDCl_3$) δ 7.84 (m, 2H); 7.12 (m, 5H); 6.89 (m, 2H); 5.92 (s, 1H); 5.13 (s, 2H); 4.46 (q, 1H, J=6 Hz); 3.88 (s, 3H); 3.23 (m, 1H); 2.98 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H). MS ESI (neg.) m/e: 446.2 (M - H).



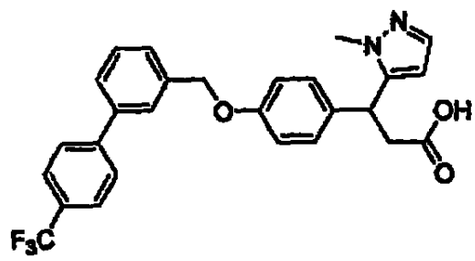
64.2

[0543] **Ácido (+/-)-3-(1-metil-1*H*-pirazol-5-il)-3-(4-((4-metil-2-*p*-toliltiazol-5-il)metoxi)fenil) propanóico (64.2).** MS ESI (neg.) m/e: 446.2 (M - H).



64.3

[0544] **Ácido (+/-)-3-(1-Metil-1*H*-pirazol-3-il)-3-[4-(4'-trifluorometil-bifenil-3-ilmetoxi)-fenil]-propiónico(64.3).** ^{1}H NMR (400MHz) ($CDCl_3$) δ 7.69-7.46 (m, 8H); 7.26-6.92 (m, 5H); 5.96 (s, 1H); 5.01 (s, 2H); 4.47 (m, 1H); 3.91 (s, 3H); 3.25 (m, 1H); 2.99 (m, 1H). MS ESI (neg.) m/e: 479.2 (M - H).



64.4

[0545] **Ácido (+/-)-3-(1-Metil-1*H*-pirazol-5-il)-3-[4-(4'-trifluorometil-bifenil-3-ilmetoxi)-fenil]-propiónico (64.4).** ^{1}H NMR (400MHz) ($CHCl_3$-d_3) δ 7.85-7.44 (m, 8H); 7.06 (d, 2H, J=6 Hz); 6.92 (s, 1H); 5.10 (s, 2H); 4.46 (m, 1H); 3.71 (s, 3H); 3.05 (m, 1H); 2.96 (m, 1H). MS ESI (neg.) m/e: 479.2 (M - H).

6.65 Ejemplo 65 (Ensayo celular de Aequorina)

[0546] Se puede utilizar un ensayo celular de aequorina para caracterizar la actividad modulatoria de los compuestos en las vías de señalización del GPR40. En un ensayo de ejemplo, se transfirieron células CHO a una placa de 15 cm que contiene 14 millones de células con 5 µg de expresión vectorial de GPR40 y 5 µg de expresión vectorial aequorina (Euroscreen) utilizando Lipofectamine 2000 (Invitrogen). Tras 17-24 horas de post-transfección, las células se lavaron con una suspensión en buffer fosfato (PBS) y se separaron de la placa de cultivo de tejido con 2 mL de tripsina (0.25%(w/v)). La tripsinización de detuvo con 28 mL de una solución de sal tamponada de Hanks que contenía 20 mM de Hepes (H/HBSS) y 0.01% de albúmina sérica bobina (BSA) grasa libre de ácido o 0.625% de albúmina sérica humana (HSA) grasa libre de ácido. A 1 ug/mL se agregó coelantrazina y las células se incubaron por 2 horas a temperatura ambiente. Las células se mezclaron gentilmente cada 15 minutos. Los compuestos se disolvieron en sulfóxido de dimetilo para la preparación de 10 mM de soluciones madre. Los compuestos se diluyeron en H/HBSS que contenían ya sea 0.01% BSA o 0.625% HSA. Para determinar las dosis de respuesta se prepararon diluciones seriadas de los compuestos.

[0547] Las medidas de luminiscencia aequorina se tomaron usando un luminómetro EG&G Berthold 96-well y la respuesta se midió en intervalos de 20 segundos tras la mezcla de las células y los compuestos. El área bajo la curva de 2-20 segundos se grafica para determinar la dosis de respuesta. El EC50 (concentración efectiva para alcanzar un respuesta máxima de 50%) se determina de la gráfica de la dosis de respuesta.

[0548] La Tabla 21 presenta datos representativos (valores EC50) obtenidos a partir de compuestos ejemplares de la invención para la activación relativa del GPR40 humano.

[0549] Los estereoisómeros de la Tabla 21 son como se especifican, i.e., *S*-enatiómeros o *R*-enatiómeros, y si no se especifican, son mezclas de *S*-enatiómeros y *R* enatiómeros. Además, la presente invención proporciona los *S*-enatiómeros, *R*-enatiómeros y mezclas de ambos *S*-enatiómeros y *R*- enatiómeros incluyendo los racematos de cada compuesto preparado de acuerdo con los métodos sintéticos descritos aquí o adaptados con las modificaciones mínimas necesarias de estos compuestos.

6.66 Ejemplo 66: Ensayo de Secreción de Insulina

[0550] Con gas de dióxido de carbono se cometió eutanasia en ratones C57/B16. El conducto biliar se pinzó en proximidad al duodeno y luego se canalizó. Luego, a través de la cánula, en infusión se administró H/HBSS que contenía 0.75 mg/ml colagenasa XI (Sigma) al páncreas. El páncreas se escindió y luego se incubó a 37°C por 13 minutos para completar la digestión enzimática. La digestión de colagenasa se aplacó en H/HBSS que contenía 1% BSA y se lavó una vez con el mismo amortiguador. Los islotes se pueden purificar por medio de centrifugación por gradiante de densidad utilizando Histopaque (Sigma) y luego se escogen a mano bajo un estereomicroscopio.

[0551] Los islotes se cultivaron durante toda la noche en medios Roswell Park Memorial Institute (RPMI) que contenían 10% de suero fetal bovino y 50 uM de beta-mercaptoetanol. Tras el cultivo durante toda la noche, los islotes se encubaron durante una hora en una modificación de Dulbecco del medio de Eagle (DMEM) que contenía 2.8 mM de glucosa.

[0552] Para determinar la secreción de insulina, los islotes se incubaron en DMEM que contenía 12.5 mM de glucosa y los compuestos de prueba por 1 hora. La insulina liberada en el medio de cultura de los islotes se midió utilizando el método ELISA insulina.

[0553] Todas las publicaciones y solicitudes de patentes citadas en esta especificación se incorporan por referencia, como que si se indicara de forma individual que cada publicación individual o solicitud de patente se incorpora por referencia. Aunque la invención anterior se ha descrito en cierto detalle a manera de ilustración y ejemplo con el fin de hacerla entendible y clara, será evidente para los que tengan conocimientos normales de la materia, que se pueden hacer modificaciones sin desviarse del espíritu o alcance de las reivindicaciones adjuntas.

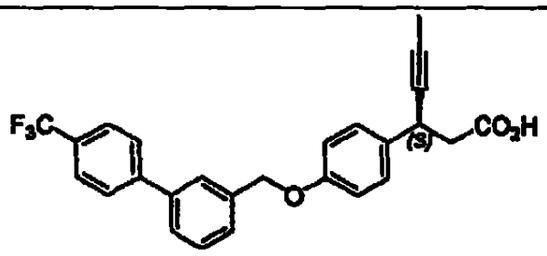
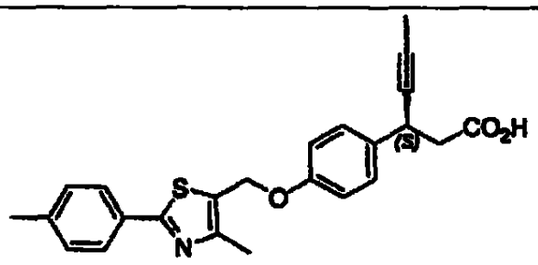
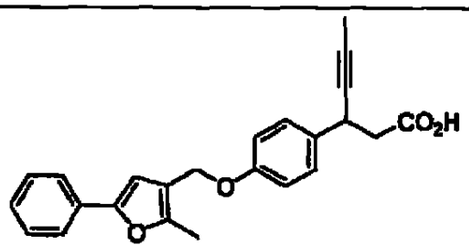
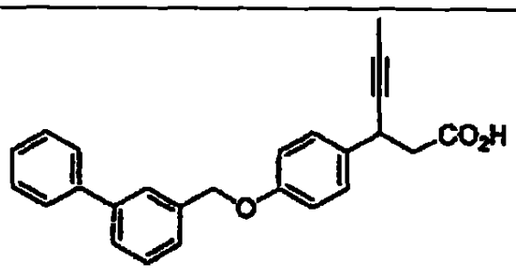
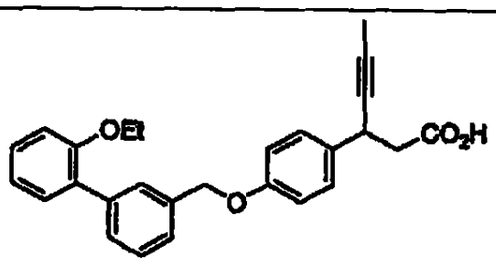
Tabla 21 Ensayo de Aequorina Utilizando GPR40 Humano		
No.	**Estructura**	**EC_{50} Relativo**
2		++++
3		+++++
5		++++
6.1		++++
6.2		++++

Tabla 21

Ensayo de Aeuorina Utilizando GPR40 Humano

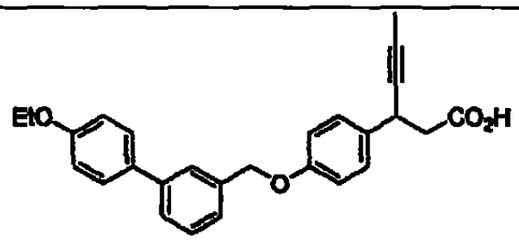
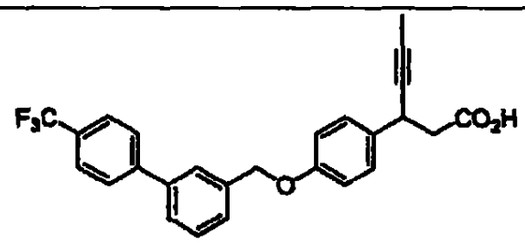
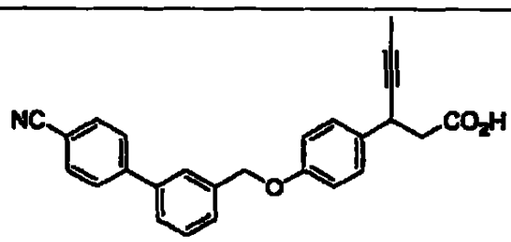
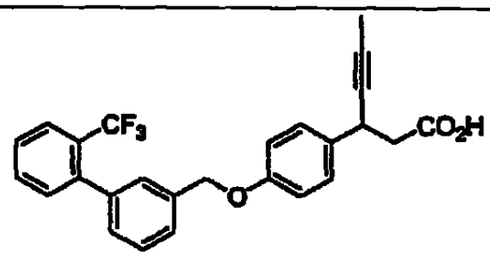
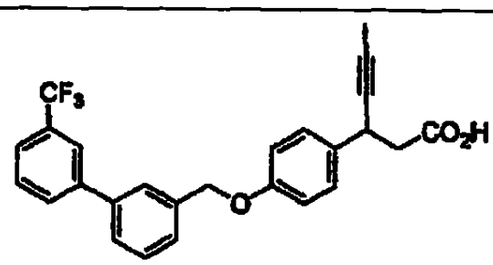
No.	Estructura	EC_{50}* Relativo
6.3		++++
6.5		++++
6.7		++++
6.8		++++
6.9		++++

Tabla 21

Ensayo de Aeuorina Utilizando GPR40 Humano

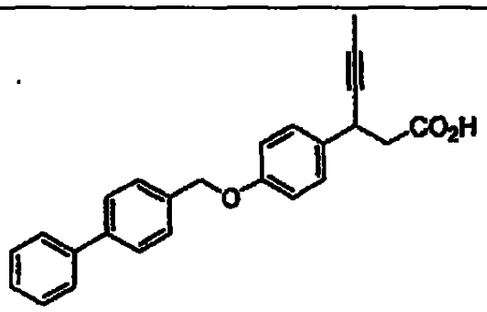
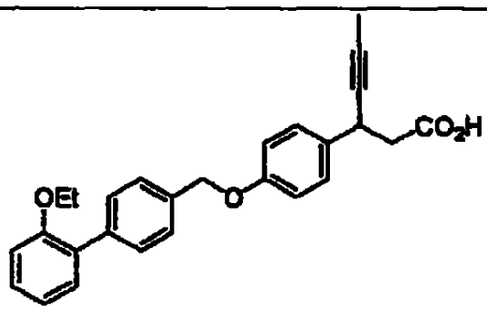
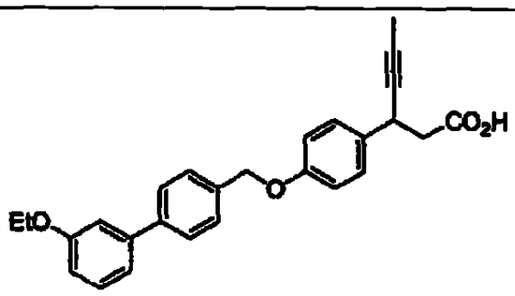
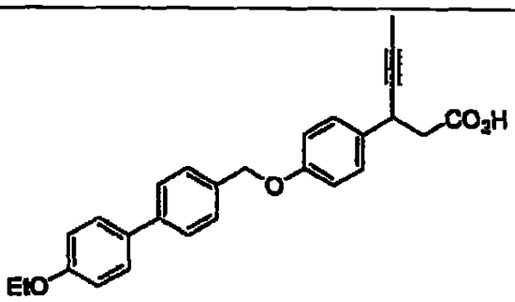
No.	Estructura	EC_{50}* Relativo
7.3		++
7.5		++++
7.8		+++
7.9		+++

Tabla 21

Ensayo de Aequorina Utilizando GPR40 Humano

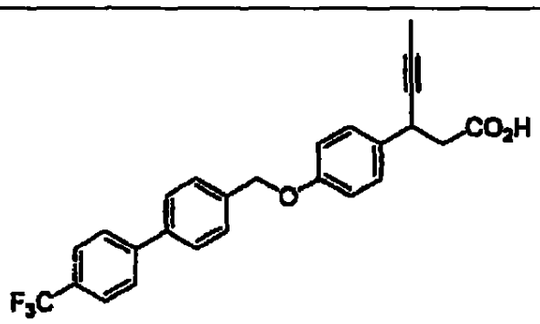
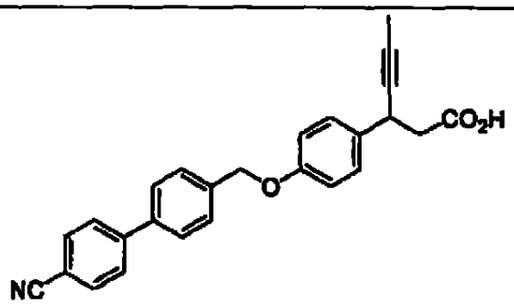
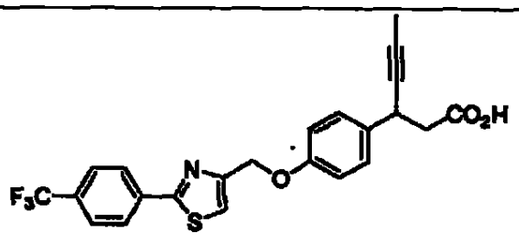
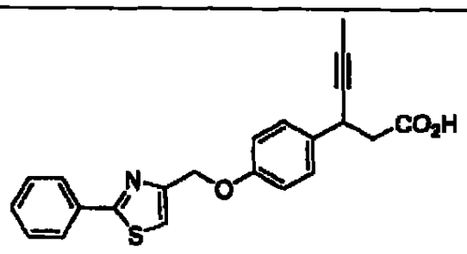
No.	Estructura	EC_{50}[a] Relativo
7.10		+++
7.15		++++
8.1		++++
8.2		++++

Tabla 21

Ensayo de Aequorina Utilizando GPR40 Humano

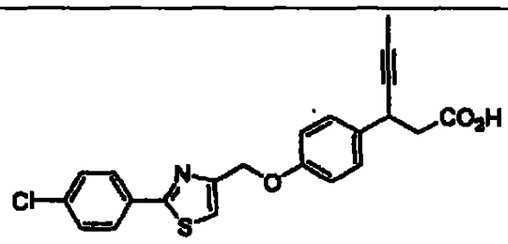
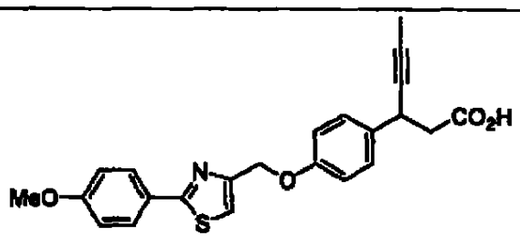
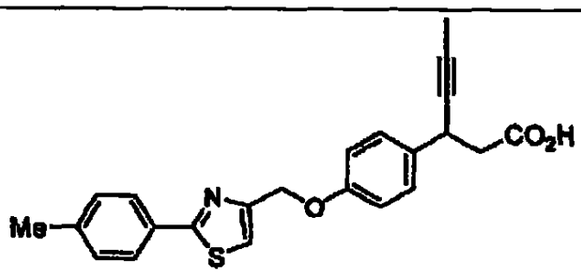
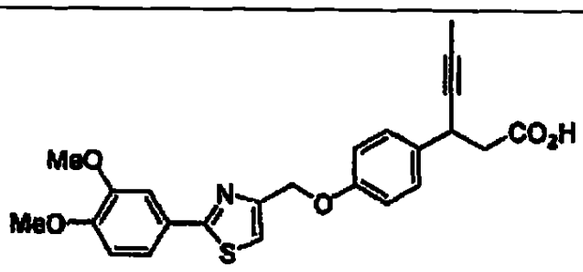
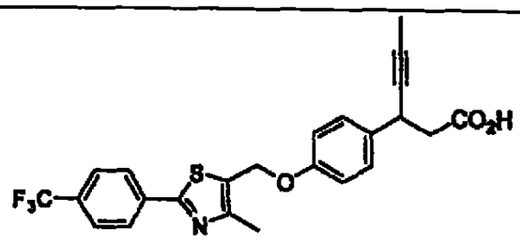
No.	Estructura	EC_{50}* Relativo
8.3		++++
8.4		++++
8.5		++++
8.6		+++
9.1		++++

Tabla 21

Ensayo de Aequorina Utilizando GPR40 Humano

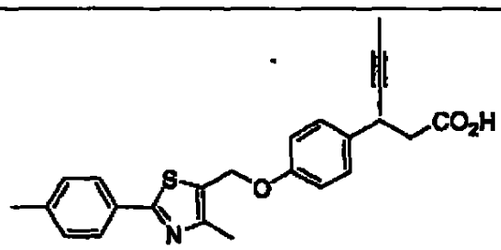
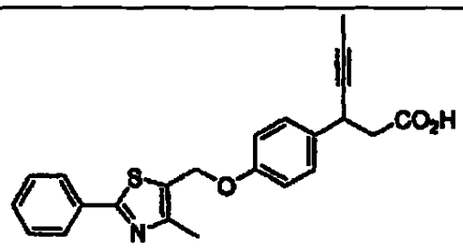
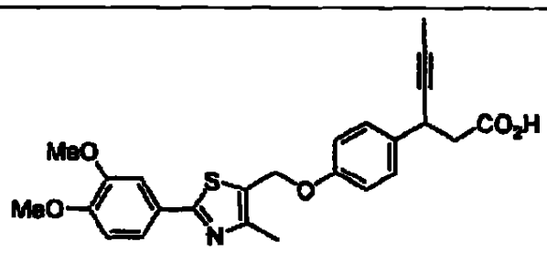
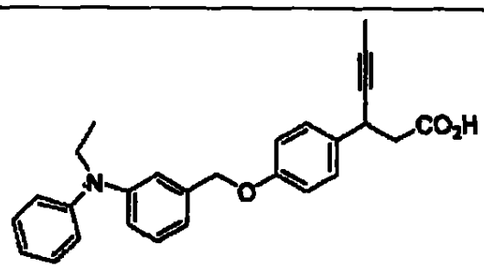
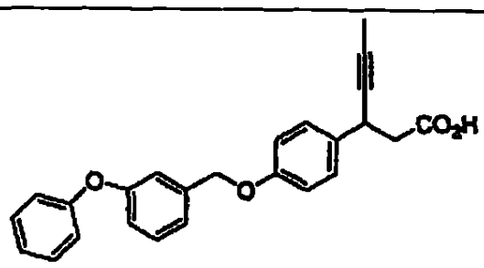
No.	Estructura	EC_{50}* Relativo
9.2		+++++
9.3		++++
9.4		++++
10.2		++++
10.3		++++

Tabla 21

Ensayo de Aequorina Utilizando GPR40 Humano

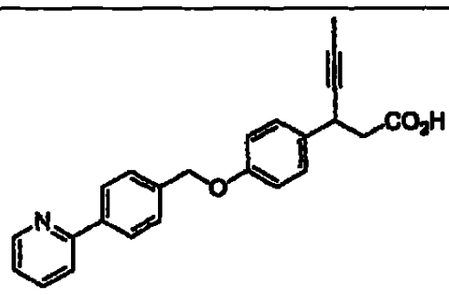
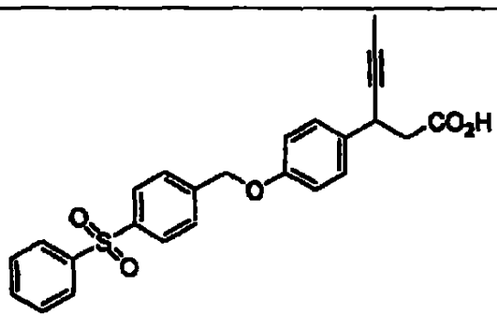
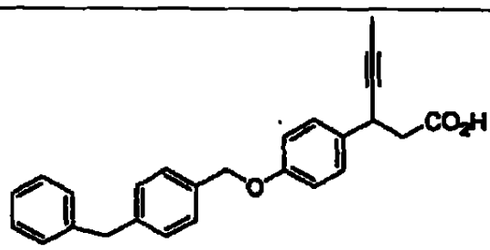
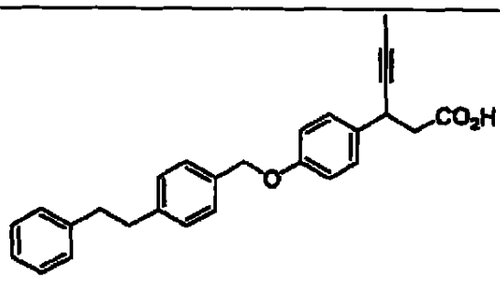
No.	Estructura	EC_{50}* Relativo
10.4		++++
10.5		+++
10.6		++++
10.7		+++

Tabla 21

Ensayo de Aeuorina Utilizando GPR40 Humano

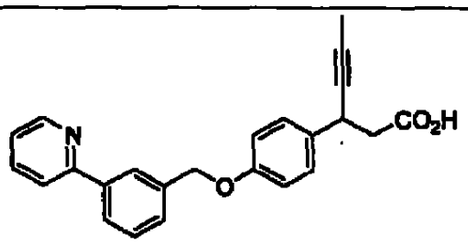
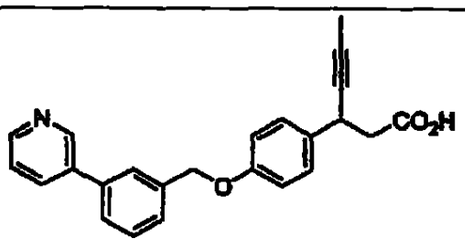
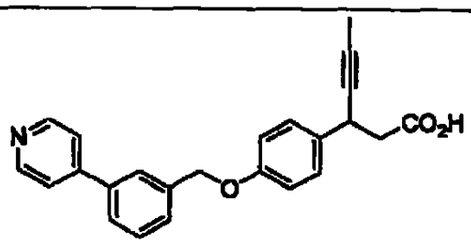
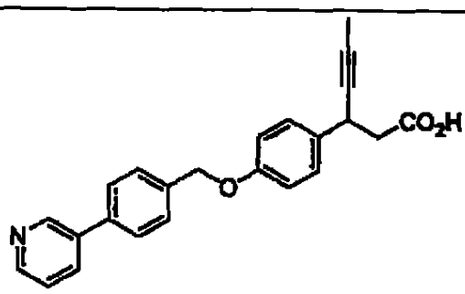
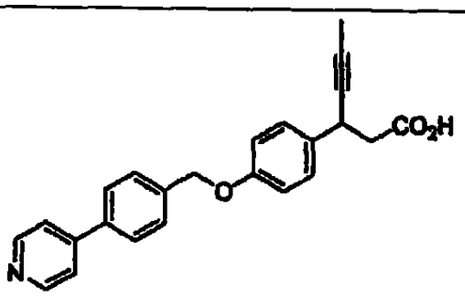
No.	Estructura	EC_{50}* Relativo
10.8		+++
10.9		+++
10.10		+++
10.12		++
10.13		+++

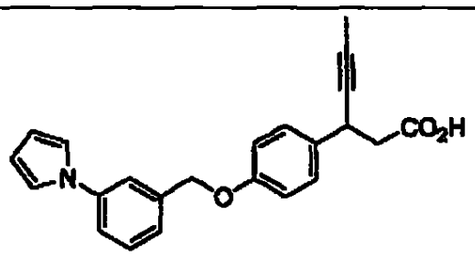
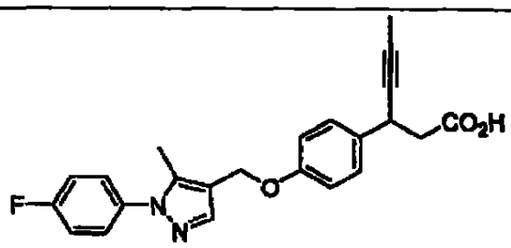
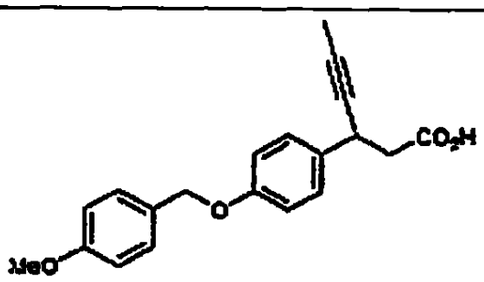
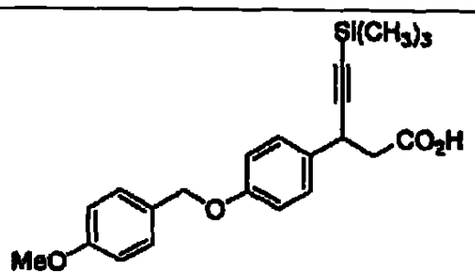
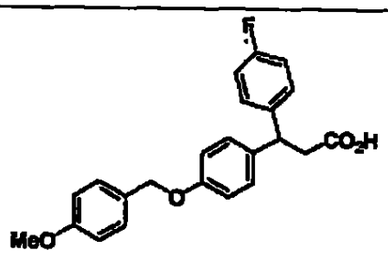
Tabla 21 Ensayo de Aeuorina Utilizando GPR40 Humano		
No.	**Estructura**	**EC_{50} Relativo**
10.14		++++
11.1		+++
12		+++
14.1		++
14.2		+++

Tabla 21

Ensayo de Aequorina Utilizando GPR40 Humano

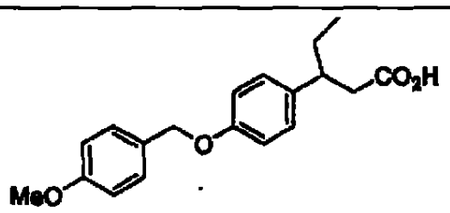
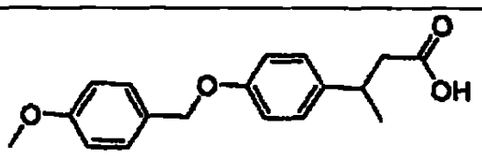
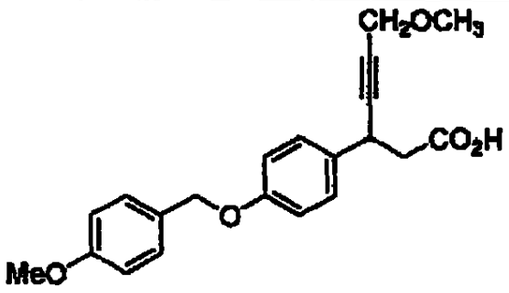
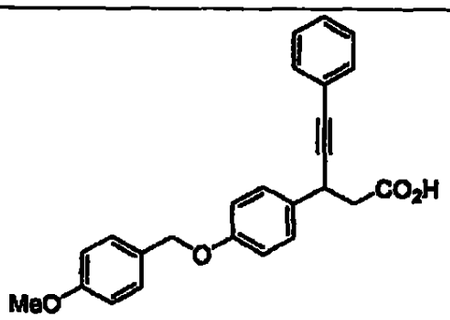
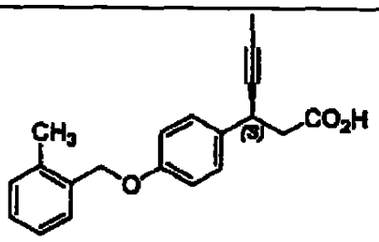
No.	Estructura	EC_{50} Relativo
14.3		++
14.4		+
14.5		++
14.6		++
15		++++

Tabla 21

Ensayo de Aeuorina Utilizando GPR40 Humano

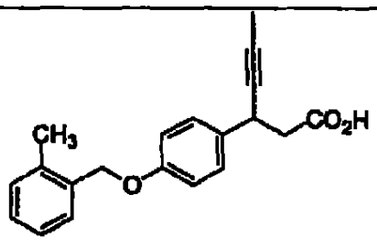
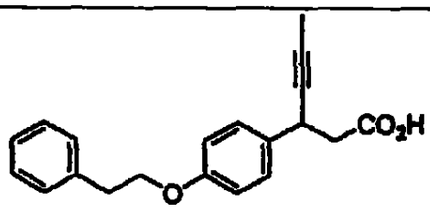
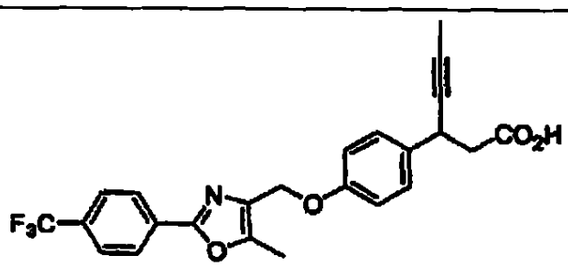
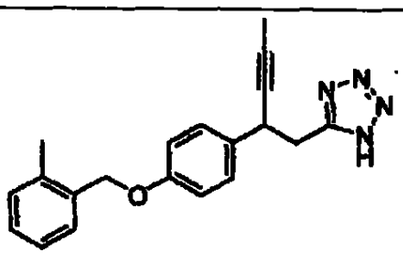
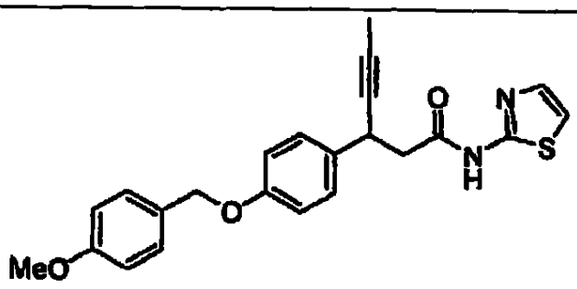
No.	Estructura	EC_{50}* Relativo
17.6		+++
17.8		++
18		++++
23		++
24		+++

Tabla 21

Ensayo de Aequorina Utilizando GPR40 Humano

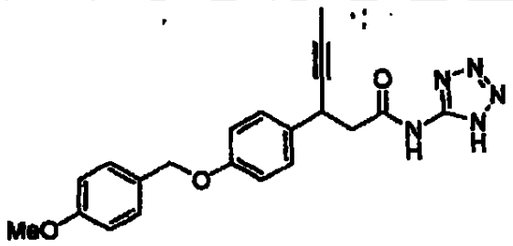
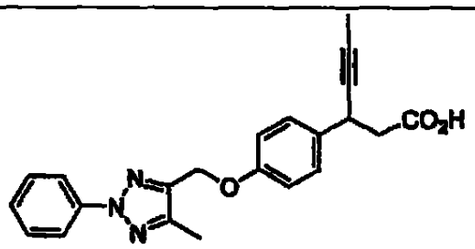
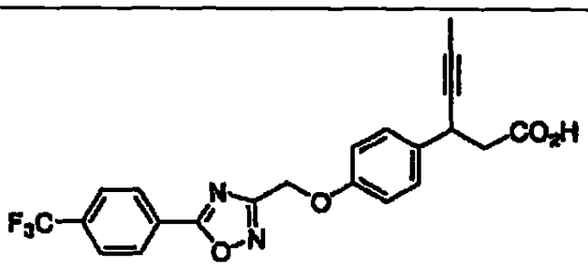
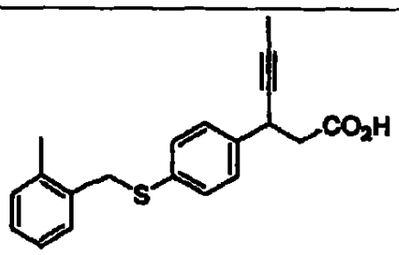
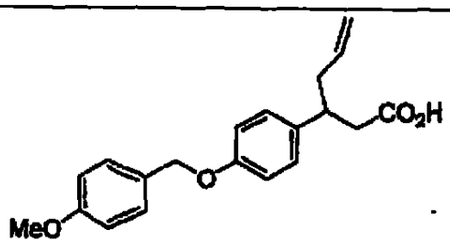
No.	Estructura	EC_{50}* Relativo
25.1		++
26		++++
27.1		+++
28		+++
34.4		++

Tabla 21

Ensayo de Aequorina Utilizando GPR40 Humano

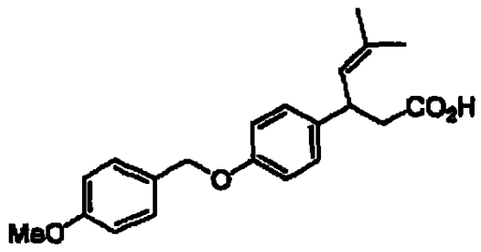
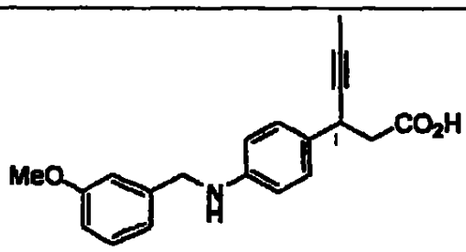
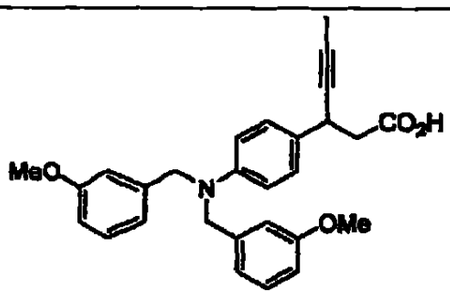
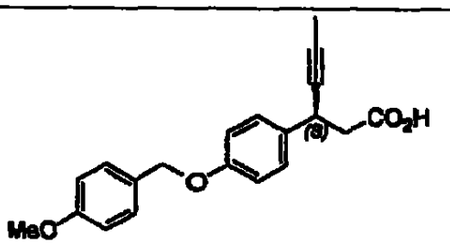
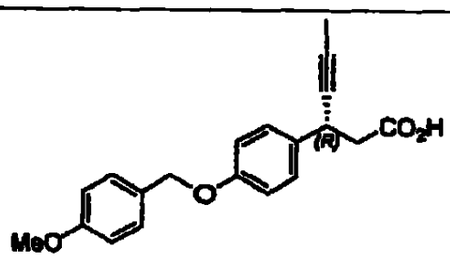
No.	Estructura	EC_{50}* Relativo
34.5		+++
36.1		+++
36.2		+++
39.7		++++
40.5		++

Tabla 21

Ensayo de Aequorina Utilizando GPR40 Humano

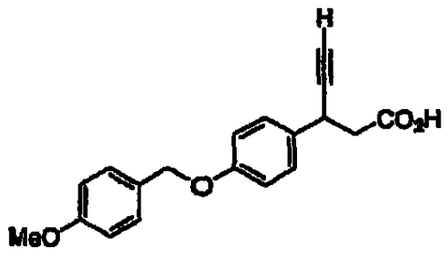
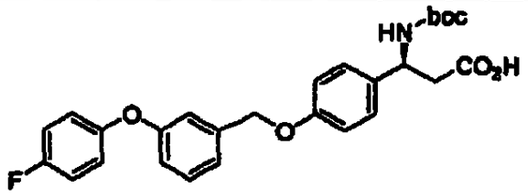
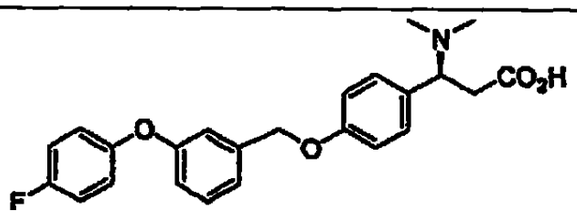
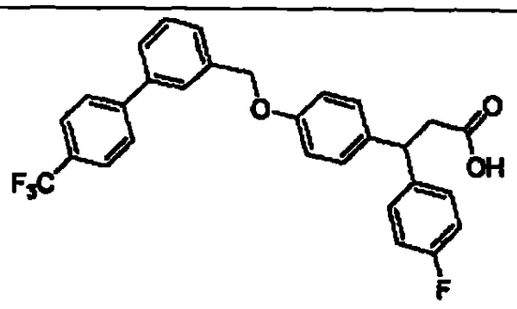
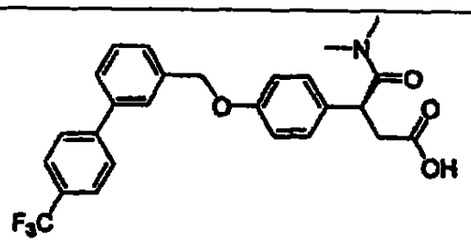
No.	Estructura	EC_{50} Relativo
41		+++
42.11		+++
42.14		+++
46.1		+++
53		++++

Tabla 21

Ensayo de Aequorina Utilizando GPR40 Humano

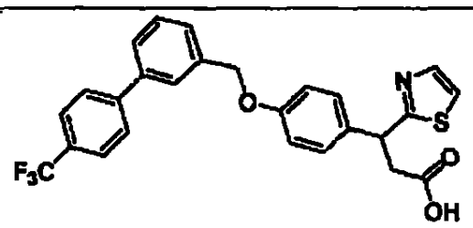
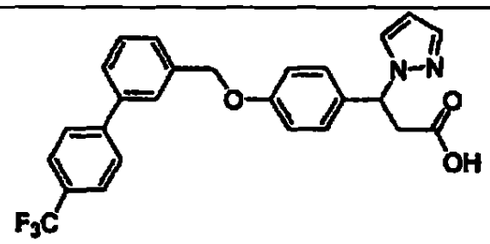
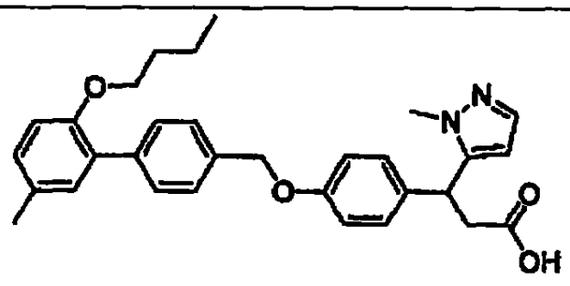
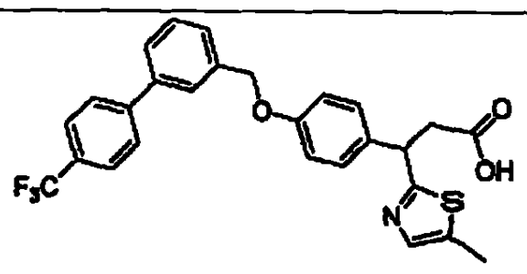
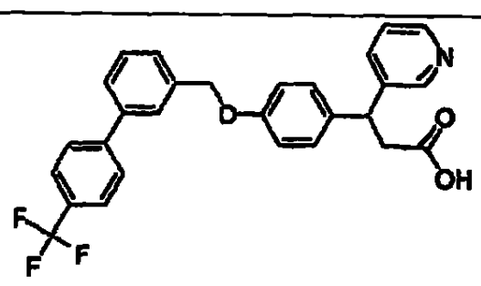
No.	Estructura	EC_{50}* Relativo
56		+++
62.3		++++
66.5		+++
70.1		++
70.2		+++

Tabla 21

Ensayo de Aequorina Utilizando GPR40 Humano

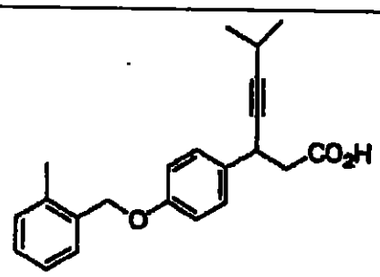
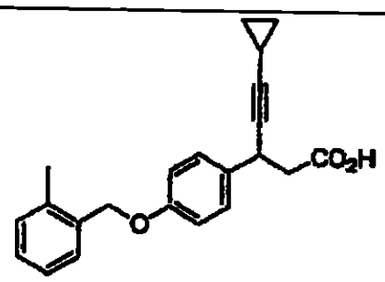
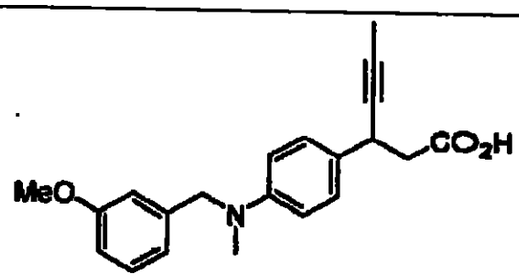
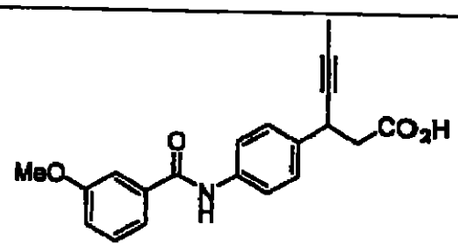
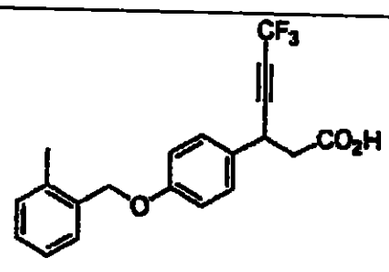
No.	Estructura	EC_{50}* Relativo
71		+++
72		+++
73		++
74		++
75		+

Tabla 21

Ensayo de Aequorina Utilizando GPR40 Humano

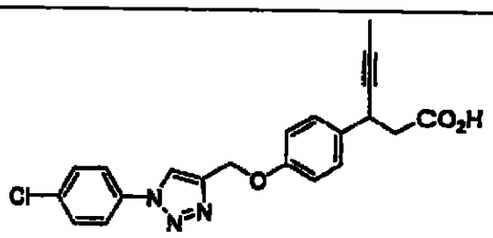
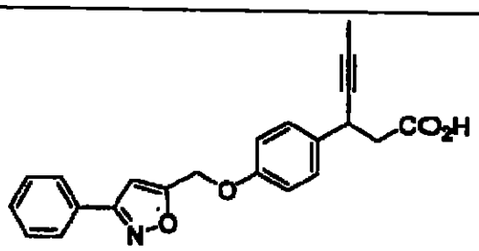
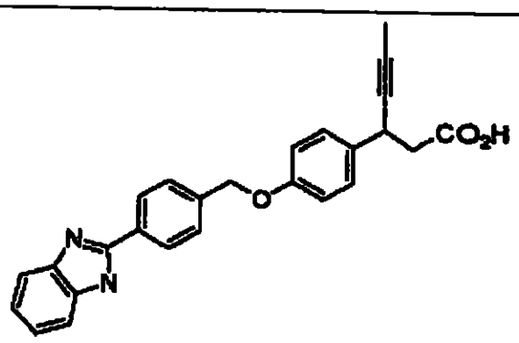
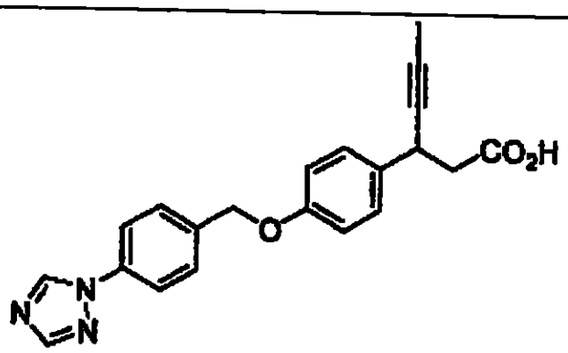
No.	Estructura	EC_{50}* Relativo
76		++
77		+++
78		++
79		++

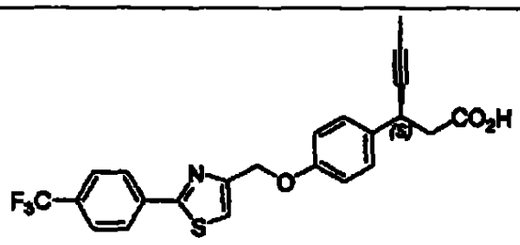
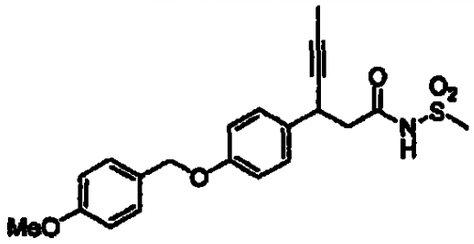
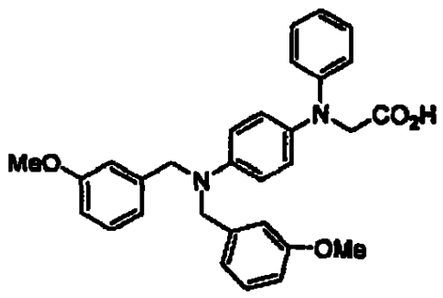
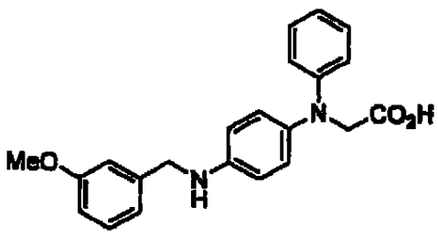
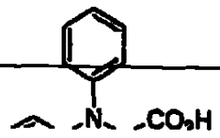
Tabla 21 Ensayo de Aeuorina Utilizando GPR40 Humano		
No.	**Estructura**	**EC_{50} Relativo**
80		+++++
81		++
82.1[b]		++++ +
82.2[b]		++++ +
82.3[b]		++++

Tabla 21

Ensayo de Aeuorina Utilizando GPR40 Humano

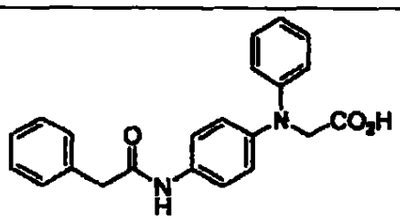
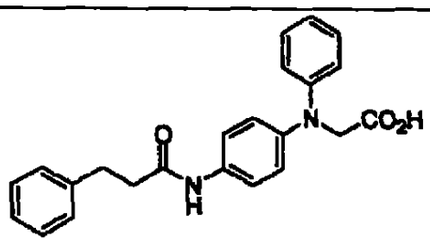
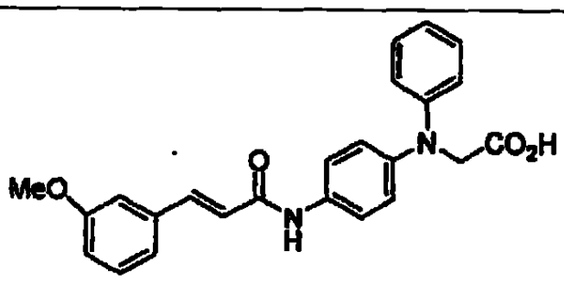
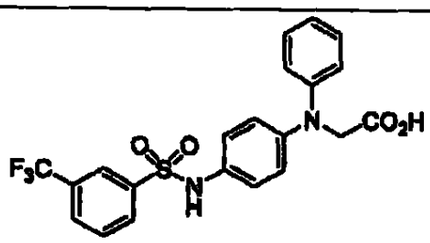
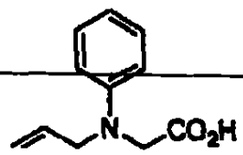
No.	Estructura	EC_{50}[a] Relativo
		+
82.4[b]		+++
		+
82.5[b]		++++
		+
82.6[b]		++++
		+
82.7[b]		+++++
		+
82.8[b]		+++++

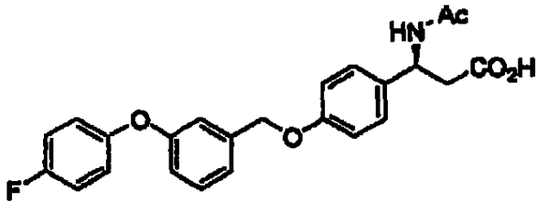
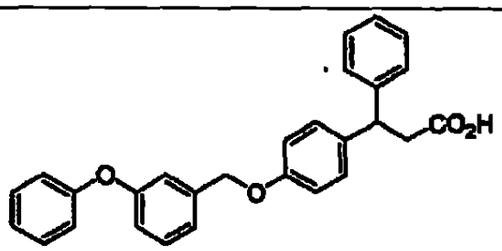
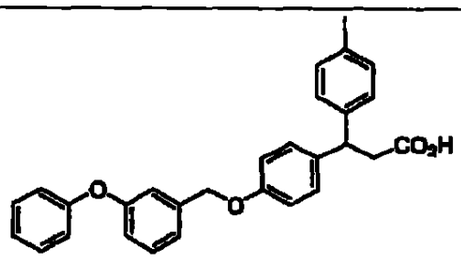
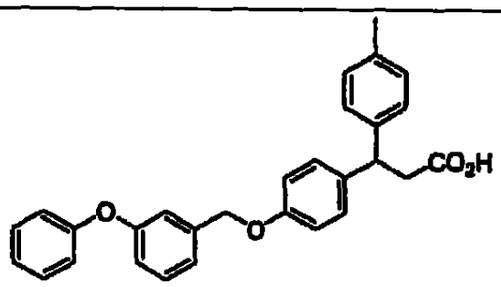
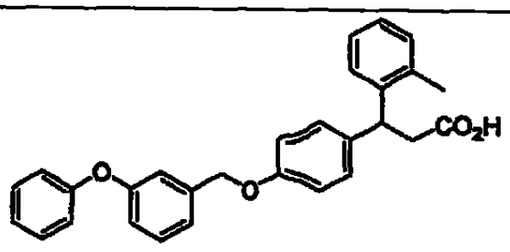
Tabla 21 Ensayo de Aeuorina Utilizando GPR40 Humano		
No.	**Estructura**	**EC_{50} Relativo**
		+
83		++
84.1		++++
84.2		++
84.3		+++
84.4		+++

Tabla 21

Ensayo de Aeuorina Utilizando GPR40 Humano

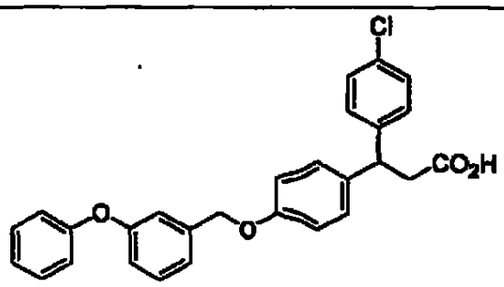
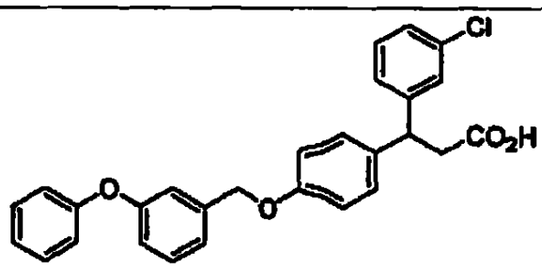
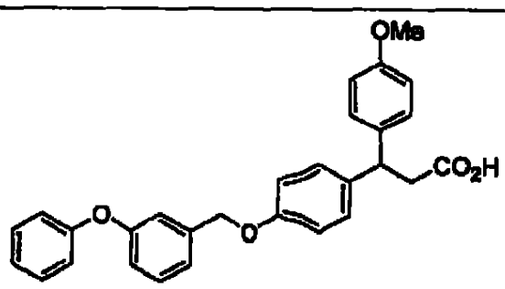
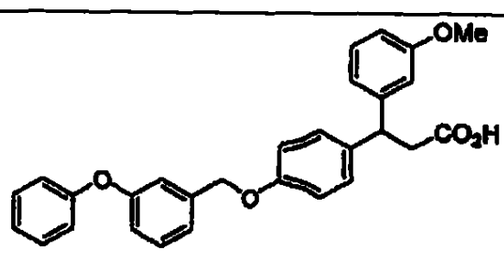
No.	Estructura	EC_{50}* Relativo
84.5		+++
84.6		+++
84.7		+++
84.8		+++

Tabla 21

Ensayo de Aeuorina Utilizando GPR40 Humano

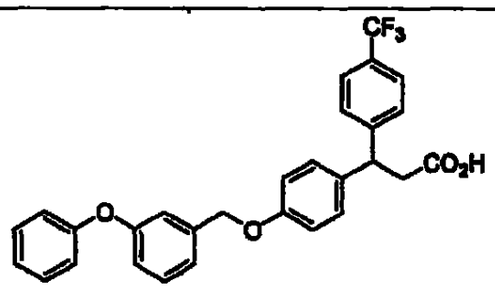
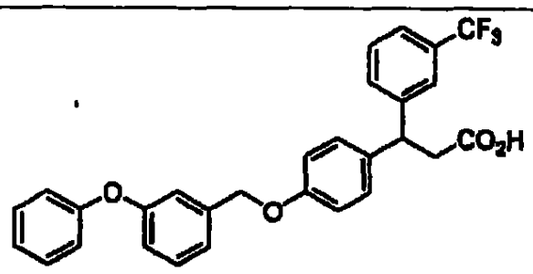
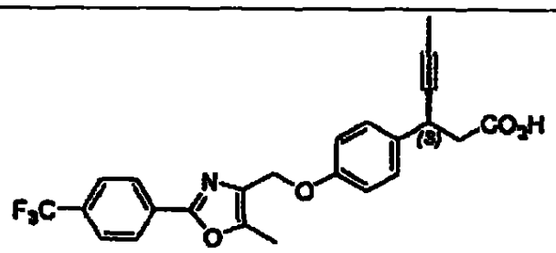
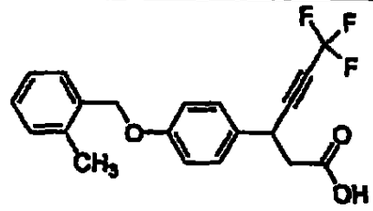
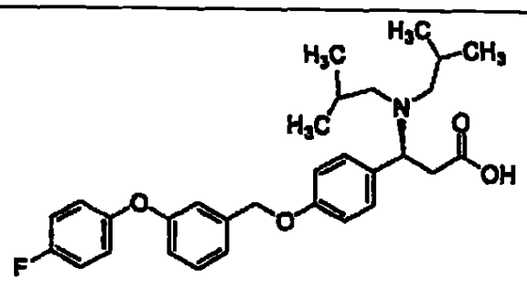
No.	Estructura	EC_{50} Relativo
85.1		++
85.2		+++
86		+++++
87		+
88.1		+

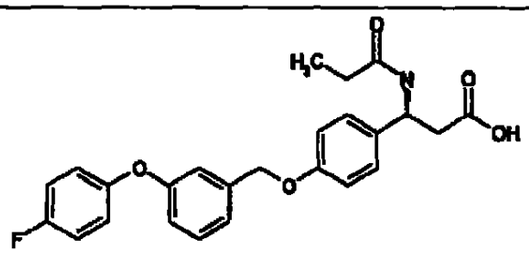
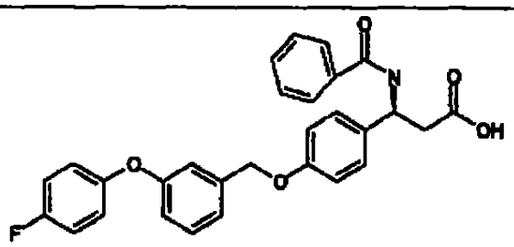
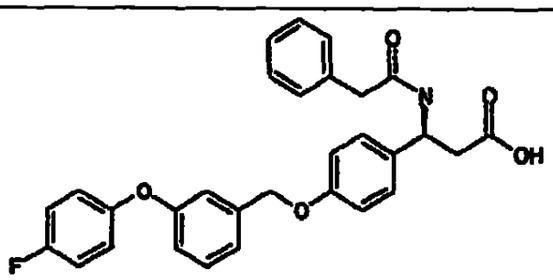
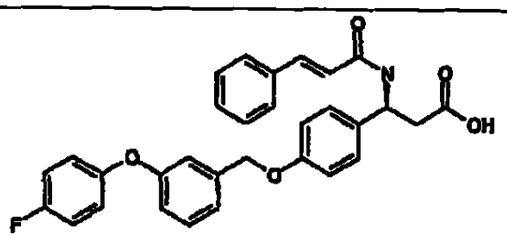
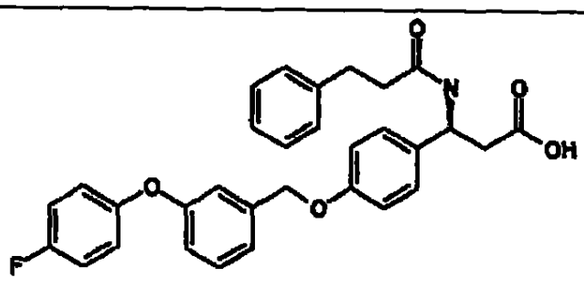
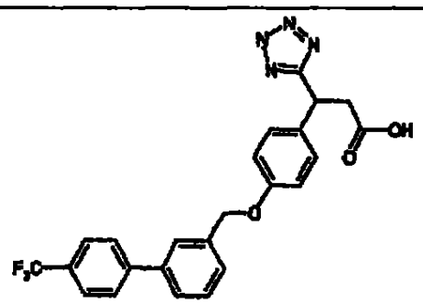
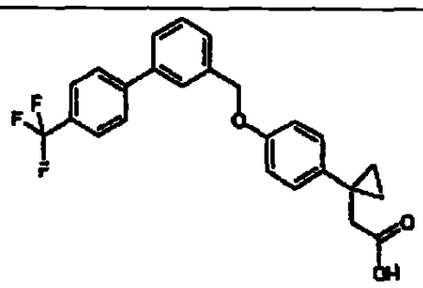
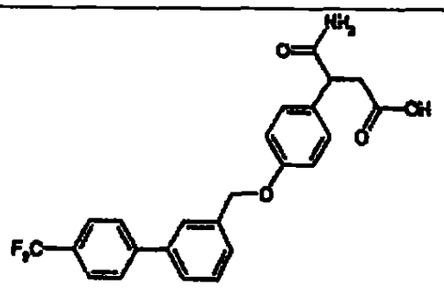
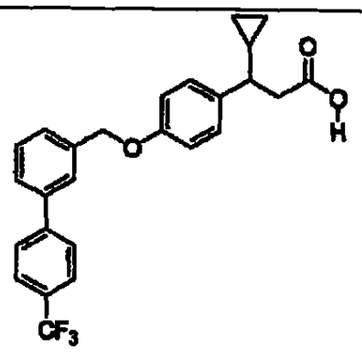
Tabla 21 Ensayo de Aequorina Utilizando GPR40 Humano		
No.	**Estructura**	**EC_{50} Relativo**
88.2		+
88.3		+
88.4		+
88.5		+
88.6		+

Tabla 21

Ensayo de Aeuorina Utilizando GPR40 Humano

No.	Estructura	EC_{50}[a] Relativo
88.7		++
89		++
90		++
91		++

[a] Rangos EC_{50} + $EC_{50} > 10\ \mu M$

++ $1\ \mu M \leq EC_{50} \leq 10\ \mu M$

Tabla 21

Ensayo de Aeuorina Utilizando GPR40 Humano

No.	Estructura	EC_{50}[a] Relativo
	+++ 0.1 μM ≤ EC_{50} < 1 μM	
	++++ 0.01 μM ≤ EC_{50} < 0.1 μM	
	+++++ EC_{50} < 0.01 μM	

[b] Cada rango EC_{50} relativo indicado para este compuesto refleja el rango para un EC_{50} observado para el compuesto cuando se determina en ensayos realizados separadamente.

LO QUE SE REIVINDICA:

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1. Un compuesto de la fórmula (I):

$$Q\text{-}L^1\text{-}P\text{-}L^2\text{-}M\text{-}X\text{-}L^3\text{-}A$$

I

o una sal farmacéuticamente aceptable, solvato o su prodroga, donde

Q es hidrógeno, arilo, heteroarilo, (C_1-C_6)alquilo o (C_2-C_6)heteroalquilo;

L^1 es un enlace, (C_1-C_4)alquileno, (C_2-C_4)heteroalquileno, O, $S(O)_m$, $N(R^1)$, C(O)-(C_5-C_7)heterocicloalquileno, (C_1-C_4)alquileno-$SO_2N(R_2)$, (C_1-C_4)alquileno-$N(R^2)SO_2$ o $C(O)N(R^2)$;

P es un anillo aromático, un anillo heteroaromático, (C_3-C_8)heterociclooalquileno o (C_3-C_8)cicloalquileno;

L^2 es un enlace, (C_1-C_6)alquileno, (C_2-C_6)heteroalquileno, oximetileno, O, $S(O)_m$, $N(R^1)$, $C(O)N(R^2)$, $SO_2N(R^2)$, (C_1-C_4)alquileno-$C(O)N(R^2)$, (C_1-C_4)alquileno-$N(R^2)C(O)$, (C_2-C_4)alquenileno-$C(O)N(R^2)$, (C_2-C_4)alquenileno-$N(R^2)C(O)$, (C_1-C_4)alquileno-$SO_2N(R^2)$, (C_1-C_4)alquileno-$N(R^2)SO_2$, (C_2-C_4)alquenileno-$SO_2N(R^2)$ o (C_2-C_4)alquenileno- $N(R^2)SO_2$;

M es un anillo aromático, un anillo heteroaromático, (C_5-C_8)cicloalquileno, arilo(C_1-C_4)alquileno o heteroarilo(C_1-C_4)alquileno;

X es CR^3R^4, $N(R^5)$, O o $S(O)_n$;

L^3 es un enlace, (C_1-C_5)alquileno o (C_2-C_5)heteroalquileno, siempre que L^3 no sea un enlace cuando L^2 es un enlace;

A es $-CO_2H$, tetrazol-5-il, $-SO_3H$, $-PO_3H_2$, $-SO_2NH_2$, $-C(O)NHSO_2CH_3$, -CHO, $-C(O)R^6$, $-C(O)NHR^6$, $-C(O)NHOR^7$, tiazolidindiona-il, hidroxifenil o piridil;

R^1 es (C_1-C_6)alquilo, arilo(C_1-C_3) alquilo o (C_2-C_6)heteroalquilo;

R2 es hidrógeno, (C_1-C_6)alquilo o (C_2-C_6)heteroalquilo;

R3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquilo, (C_2-C_8)alquenilo, (C_3-C_8)alquenilo, (C_2-C_8)alquinilo, (C_3-C_8)alquinilo, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$, $-NR^{12}C(O)R^{13}$ o $-NR^{12}S(O)_pR^{13}$;

R^4 es hidrógeno, ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo o (C_2-C_8)alquinilo;

opcionalmente, R^3 y R^4 se combinan para formar un anillo de 3, 4, 5, 6 o 7 miembros que contenga de cero a tres heteroátomos seleccionados de N, O y S;

R^5 es hidrógeno, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o (C_3-C_8)cicloalquilo;

R^6 es heteroarilo;

R^7 es hidrogeno o (C_1-C_5)alquilo;

R8 y R9 son independientemente hidrogeno, (C_1-C_5)alquilo, oxi(C_1-C_5)alquilo o carboxi(C_1-C_5)alquilo;

opcionalmente, R^8 y R^9 se combinan para formar un anillo de 4, 5, 6 ó 7 miembros que contengan el átomo de hidrogeno al cual están adheridos y de 0 a 2 heteroátomos adicionales seleccionados de N, O y S;

R^{10}, R^{11} y R^{12} se seleccionan independientemente de hidrógeno, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)heteroalquilo, (C_3-C_8)cicloalquilo y (C_3-C_8)heterocicloalquilo;

opcionalmente, R^{10} y R^{11} se combinan para formar un anillo de 4, 5, 6 o 7 miembros que contengan el átomo de nitrógeno al cual están adheridos y de 0 a 2 heteroátomos adicionales seleccionados de N, O y S;

R^{13} es arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)heteroalquilo, (C_3-C_8)cicloalquilo o (C_3-C_8)heterocicloalquilo;

los subíndices m y n son independientemente 0, 1 ó 2; y

el subíndice p es 1 ó 2; y

donde el compuesto es distinto a ácido 3-(4-(4-metoxibenciloxi)fenil)pentano-4-inóico; ácido β-etenil-4-fenilmetoxi-bencenopropanóico; ácido 4-(2-quinolinilmetoxi)-β-[4-(2-quinolinilmetoxi)fenil]-bencenopropanóico; N-[4-(benzoilamino)fenil]-N-fenil-glicina; 3-(4-(isopentiloxi)benzamido)-3-fenilpropanoato; 3-(4-isobutoxibenzamido)-3-fenilpropanoato; ácido (*R*)-2-((*1R,4R*)-4- isopropilciclohexanocarboxamido)-3-fenilpropanóico; ácido (*R*)-3-(4-(benciloxi)fenil)- 2-(tert-butoxicarbonil)propanóico; ácido 3-(4-clorofenil)-3-(furan-2-carboxamido)propanóico; ácido 3-(3,4-dimetoxifenil)-3-(furan-2-carboxamido)propanóico; ácido 3-(4-clorobenzamido)-3-(4-(dimetiamino)fenil)propanóico; ácido 3-(2-(2-(3,4-dimetilofenoxi)etitio)-1*H*-benzo[d]imidazol-1-il)propanóico; ácido { 2-Bromo-4-[(3,4-dicloro-fenil)-hidrazonometilo]-6-etoxi-fenoxi}-acético; ácido 2-(4-(2-(2-(4- clorofenil)furan-5-carboxamido)etilo)fenoxi)-2-metilopropanóico; ácido 5-(3-(3,4- dimetoxifenil)-5-(2-fluorofenil)-4,5-dihidropirazol-1-il)-5-oxopentanóico; ácido 2-(2- (3-(3,4-dihidro-2H-benzo[b][1,4] dioxepina-7-il)-2-metilo-4-oxo-4*H*-cromen-7- iloxi)acetamido)acético; ácido 3-(4'-Bromo-bifenil-4-il)-4-fenilo-butírico; ácido 3-(4'- Bromo-bifenil-4-il)-3-fenilsulfanil-propiónico; ácido 3-(5-(2-cloro-6-fluoro-4- (trifluorometilo)fenoxi)-2,4-

dinitrofenil)propanóico; ácido 3-(3-(2-cloro-4- (trifluorometilo)fenoxi)fenil)propanóico; ácido 3-(4-(4-metoxibenciloxi)fenil)pentano-4-inóico; ácido 3-(4-(4-metoxibenciloxi)fenil)-5-(trimetilsilil)pentano-4-inóico; ácido β,β-dimetilo-4-[[[4-metilo-2-[4-(trifluorometilo)fenilo]-5-tiazolil]metilo]tio]-bencenopropanóico; ácido β-amino-4-[(4-bromo-2,5-dihidro-2-metilo-5-oxo-1-fenil-1H- pirazol-3-il)metoxi]-3-metoxi-bencenopropanóico; o sus sales.

2. El compuesto de la Reivindicación 1, en qué cuando P y M son benceno, por lo menos dos de L^2, X y L^3 son distintos de CH_2.

3. El compuesto de la Reivindicación 1, en qué cuando Q es arilo o heteroarilo, L^1 es un enlace, M es un anillo aromático monocíclico, X es $N(R^5)$, O o $S(O)_n$, y A contiene un grupo carbonil, en tal caso P no es un anillo 1,2-azole.

4. El compuesto de la Reivindicación 1, donde cuando Q es arilo, L^1 es un enlace, M es un anillo aromático, X es CR^3R^4, O o $S(O)_n$ y A contiene un grupo carbonilo, en tal caso P es distinto de furano o tiofeno.

5. El compuesto de la Reivindicación 1, donde P se selecciona de un grupo de benceno, naftaleno, pirrol, pirazol, imidazol, pirazina, oxazol, isoxazol, tiazol, furano, tiofeno, piridina, pirimidina, piridazina, benzotiazol, purina, bencimidazol, benzoxazol, triazol, oxadiazol, tiadiazol, benzooxadiazol, dibenzofuran, indol, indazol, carbazol, carbolina, isoquinolina, quinoxalina y quinolina.

6. El compuesto de la Reivindicación 1, donde P se selecciona de un grupo de benceno, naftaleno, pirrol, pirazina, piridina, pirimidina, piridazina, purina, indol, carbolina, isoquinolina, quinoxalina y quinolina.

7. El compuesto de la Reivindicación 1.

8. El compuesto de la Reivindicación 1, donde A es $-CO_2H$, tetrazol-5-il, $-C(O)NHSO_2CH_3$ o $-C(O)NHR^6$.

9. El compuesto de la Reivindicación 1, donde R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o -NR^8R^9.

10. El compuesto de la Reivindicación 9, donde R^4 es hidrógeno.

11. El compuesto de la Reivindicación 1, donde M es un anillo aromático, un anillo heteroaromático o (C_5-C_8)cicloalquileno.

12. El compuesto de la Reivindicación 11, donde R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o -NR^8R^9.

13. El compuesto de la Reivindicación 12, donde A es -CO_2H o tetrazol-5-il.

14. El compuesto de la Reivindicación 12, donde A es -CO_2H.

15. El compuesto de la Reivindicación 14, donde X es CR^3R^4 o $N(R^5)$.

16. El compuesto de la Reivindicación 15, donde L^3 es (C_1-C_5)alquileno o (C_2-C_5)heteroalquileno.

17. El compuesto de la Reivindicación 16, donde P es un anillo aromático o un anillo heteroaromático.

18. El compuesto de la Reivindicación 1, donde P es un anillo aromático o un anillo heteroaromático.

19. El compuesto de la Reivindicación 18, donde X es CR^3R^4 o $N(R^5)$.

20. El compuesto de la Reivindicación 19, donde L^3 es (C_1-C_5)alquileno.

21. El compuesto de la Reivindicación 20, donde A es -CO_2H.

22. El compuesto de la Reivindicación 21, donde R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o -NR^8R^9.

23. El compuesto de la Reivindicación 22, donde M es benceno o un anillo heteroaromático.

24. El compuesto de la Reivindicación 23, donde R^4 es hidrógeno.

25. El compuesto de la Reivindicación 23, donde L^1 es un enlace, O o N(R^1) y L^2 es (C_2-C_6)heteroalquileno .

26. El compuesto de la Reivindicación 24, donde L^1 es un enlace y L^2 es (C_2-C_6)heteroalquileno.

27. El compuesto de la Reivindicación 19, donde M es benceno y X es *para* a L^2.

28. El compuesto de la Reivindicación 27, donde L^3 es metiloeno.

29. El compuesto de la Reivindicación 28, donde A es -CO_2H.

30. El compuesto de la Reivindicación 29, donde R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o -NR^8R^9.

31. El compuesto de la Reivindicación 30, donde L^1 es un enlace y L^2 es oximetileno o tiometileno.

32. El compuesto de la Reivindicación 31 , donde R^4 es hidrógeno.

33. El compuesto de la Reivindicación 1, donde Q es arilo.

34. El compuesto de la Reivindicación 1, donde L^1 es un enlace y L^2 es oximetileno o tiometileno.

35. El compuesto de la Reivindicación 1, donde P es un anillo aromático o un anillo heteroaromático y A es $-CO_2H$.

36. El compuesto de la Reivindicación 1, donde P es un anillo aromático o un anillo heteroaromático y X es CR^3R^4 o $N(R^5)$.

37. El compuesto de la Reivindicación 1, donde A es $-CO_2H$ y X es CR^3R^4 o $N(R^5)$.

38. El compuesto de la Reivindicación 36, donde X es CR^3R^4 y R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o $-NR^8R^9$.

39. El compuesto de la Reivindicación 37, donde X es CR^3R^4 y R^3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o $-NR^8R^9$.

40. Una composición farmacéutica que comprende un portador, un diluyente o un excipiente farmacéuticamente aceptables y el compuesto de la Reivindicación 1.

41. Un método para el tratamiento de una enfermedad o condición que se selecciona de un grupo que consiste en diabetes de tipo II, obesidad, hiperglicemia, intolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, hipercolesterolemia, hipertensión, hiperlipoproteinemia, hiperlipidemia, hipertrigliceridemia, dislipidemia, síndrome metabólico, síndrome X, enfermedades cardiovasculares, aterosclerosis, enfermedades renales, cetoacidosis, desordenes trombóticos, nefropatía, neuropatía diabética, retinopatia diabética, disfunción sexual, dermatopatía, dispepsia, hipoglicemia, cáncer y edema que comprenda la administración de una cantidad farmacéuticamente efectiva del compuesto de la reivindicación 1 a un sujeto que la necesite.

42. El método de la Reivindicación 41, donde dicha enfermedad o condición es diabetes de tipo II.

43. Un método para el tratamiento de una enfermedad o condición que responde a la modulación de GPR40 que comprenda la administración de una cantidad

farmacéuticamente efectiva del compuesto de la reivindicación 1 a un sujeto que la necesite.

44. El método de la Reivindicación 43 donde dicha enfermedad o condición se selecciona del grupo que consiste en diabetes de tipo II, obesidad, hiperglicemia, intolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, hipercolesterolemia, hipertensión, hiperlipoproteinemia, hiperlipidemia, hipertrigliceridemia, dislipidemia, síndrome metabólico, síndrome X, enfermedades cardiovasculares, aterosclerosis, enfermedades renales, cetoacidosis, desordenes trombóticos, nefropatía, neuropatía diabética, retinopatía diabética, disfunción sexual, dermatopatía, dispepsia, hipoglicemia, cáncer y edema.

45. El método de cualesquiera de las reivindicaciones 41-44 donde dicho compuesto se administra por vía oral, parenteral o tópica.

46. El método de la Reivindicación 41 donde dicho compuesto se administra en combinación con un segundo agente terapéutico.

47. El método de la Reivindicación 46 donde dicho segundo agente terapéutico es una metformina o una tiazolidindiona .

48. Un método para modular la función GPR40 en una célula, que comprende el poner en contacto a una célula con el compuesto de la Reivindicación 1.

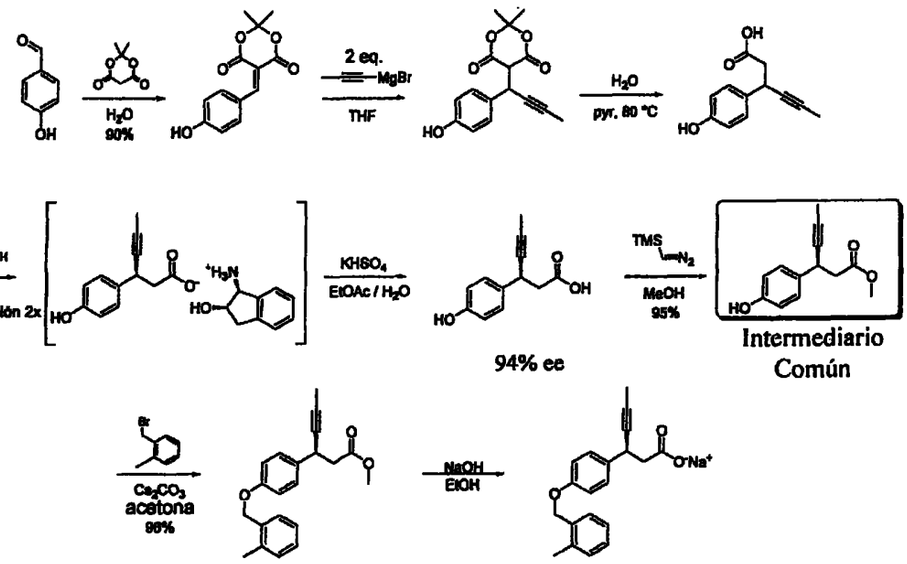
49. Un método para modular la función GPR40 que comprende el poner en contacto al GPR40 con el compuesto de la Reivindicación 1.

50. Un método para modular la concentración de insulina circulante en un sujeto, que comprende la administración al sujeto del compuesto de la Reivindicación 1.

51. El método de la Reivindicación 50 donde la concentración de insulina se incrementa.

52. El método de la Reivindicación 50 donde la concentración de insulina se disminuye.

Figura 1



PCT/US2005/005815

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 11134-36-228	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US05/05815	International filing date (*day/month/year*) 24 February 2005 (24.02.2005)	(Earliest) Priority Date (*day/month/year*) 27 February 2004 (27.02.2004)
Applicant AMGEN INC.		

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.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ANTHONY M. INSOGNA
JONES DAY
222 EAST 41ST STREET
NEW YORK, NY 10017-6702

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	14 SEP 2005
Applicant's or agent's file reference 11134-36-228	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/05815	24 February 2005 (24.02.2005)	27 February 2004 (27.02.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07C 53/132, 213/30, 277/24; A61K 31/19, 31/42/, 31/215 and US Cl.: 514/254.02, 340, 361, 365, 374, 557; 544/369; 546/271.4; 548/127, 204, 236; 562/465

Applicant

AMGEN INC.

1. This opinion contains indications relating to the following items:

- [X] Box No. I — Basis of the opinion
- [ ] Box No. II — Priority
- [ ] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [X] Box No. IV — Lack of unity of invention
- [X] Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [ ] Box No. VIII — Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Zinna Northington Davis Julia Jackson for
Facsimile No. (703) 305-3230	Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/05815

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/05815

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-52 (in part)

WRITTEN OPINION F THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/05815

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 9, 10, 22-26, 30-32, 38, and 39	YES
	Claims 1-8, 11, 18-21, 27-29, 33-37, and 40-52	NO
Inventive step (IS)	Claims 9, 10, 22-26, 30-32, 38 and 39	YES
	Claims 1-8, 11, 18-21, 27-29, 33-37, and 40-52	NO
Industrial applicability (IA)	Claims 1-52	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-8, 11, 18-21,27-29 33-37, and 40-52 lack novelty under PCT Article 33(2) as being anticipated byTajima et al.

The instant compound is disclosed. At page 79, lines 1-3, see example 3.

Claims 1-8, 11, 18-21,27-29 33-37, and 40-52 lack novelty under PCT Article 33(2) as being anticipated by Beecham Corporation.

The instant compounds are disclosed. At pages 15-20, see Table 1 and 2; pages 38-43, see Tables 9-10; pages 58-61 , see Table 17, respectively.

Claims 9, 10, 22-26, 30-32, and 38-39 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest structurally similar compounds as the instant invention.

Claims 1-52 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/05815

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.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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:
Please See Continuation Sheet

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.: 1-52 (in part)

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/US05/05815

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07C 53/132, 213/30, 277/24; A61K 31/19, 31/42/, 31/215
US CL : 514/254.02, 340, 361, 365, 374, 557; 544/369; 546/271.4; 548/127, 204, 236; 562/465
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. : 514/254.02, 340, 361, 365, 374, 557; 544/369; 546/271.4; 548/127, 204, 236; 562/465

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — A	US 6,506,757 B1 (TAJIMA et al) 14 January 2003 (14.01.2003), pages 15-20, pages 38-43, and pages 58-61.	1-8, 11, 18-21, 27-29, 33-37, and 40-52 — 9, 10, 22-26, 30-32, 38, and 39
X — A	WO 2004/000315 A1 (BEECHAM CORPORATION) 31 December 2003 (31.12.2003) page 79, example 3.	1-8, 11, 18-21, 27-29, 33-37, 40-52

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 August 2005 (05.08.2005)	14 SEP 2005
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 Zinna Northington Davis Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/05815

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-52, drawn to compounds, composition, and method of use wherein formula I is defined as Q is aryl, L^1 is a bond, P is an aromatic ring or a heteroaromatic ring, L^2 is $-CH_2O-$, M is an aromatic ring, X is -C, L^3 is AK , and A is C(O)OH.

Group II, claim(s) 1-52, drawn to compounds, composition, and method of use wherein formula I is not defined by Group I.

The inventions listed as Groups II and I do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

1) The radicals Q, L^1, P, L^2, M, X, L^3, and A are diverse in scope. A prior art reference which anticipates cyclobutanyl with respect to P would not render obvious another member such a pyridinyl.

2). The compounds have multiple uses. See claims 41-43.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

There is no common structural feature to which the utility is attributed. See the various radicals within the definition of formula I.

Industria y Comercio
SUPERINTENDENCIA

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

(21) N° de solicitud: 06096986

22) Fecha de solicitud: 25/09/2006

(30) Prioridad (31) 60/548,741 27/02/04 US
60/601,579 12/08/04 US

(51) Int Cl: A61K 31/19

(71) Solicitante(s) AMGEN INC.

(72) Inventor(es) MICHELLE AKERMAN
Y OTROS

(74) Apoderado: EMILIO FERRERO

(85) Fecha límite inicio fase nacional: 27/09/2006
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 24/02/2005
No. de solicitud PCT/US2005/005815

(87) Publicación Internacional
Fecha: 22/09/2005
N° publicación: WO 2005/086661 A2

(54) Título: **COMPUESTOS, COMPOSICIONES FARMACEUTICAS Y METODOS PARA EL USO EN EL TRATAMIENTO DE DESORDENES**

Reivindicación(es):

1. Un compuesto de la fórmula (I):

$$Q\text{-}L^1\text{-}P\text{-}L^2\text{-}M\text{-}X\text{-}L^3\text{-}A \qquad I$$

o una sal farmacéuticamente aceptable, solvato o su prodroga, donde

Q es hidrógeno, arilo, heteroarilo, (C_1-C_8)alquilo o (C_2-C_8)heteroalquilo;

L^1 es un enlace, (C_1-C_4)alquileno, (C_2-C_4)heteroalquileno, O, $S(O)_m$, $N(R^1)$, $C(O)$-(C_5-C_7)heterocicloalquileno, (C_1-C_4)alquileno-$SO_2N(R_2)$, (C_1-C_4)alquileno-$N(R^2)SO_2$ o $C(O)N(R^2)$;

P es un anillo aromático, un anillo heteroaromático, (C_3-C_8)heterocicloalquileno o (C_3-C_8)cicloalquileno;

L^2 es un enlace, (C_1-C_8)alquileno, (C_2-C_8)heteroalquileno, oximetileno, O, $S(O)_m$, $N(R^1)$, $C(O)N(R^2)$, $SO_2N(R^2)$, (C_1-C_4)alquileno-$C(O)N(R^2)$, (C_1-C_4)alquileno-$N(R^2)C(O)$, (C_2-C_4)alquenileno-$C(O)N(R^2)$, (C_2-C_4)alquenileno-$N(R^2)C(O)$, (C_1-C_4)alquileno-$SO_2N(R^2)$, (C_1-C_4)alquileno-$N(R^2)SO_2$, (C_2-C_4)alquenileno-$SO_2N(R^2)$ o (C_2-C_4)alquenileno-$N(R^2)SO_2$;

M es un anillo aromático, un anillo heteroaromático, (C_5-C_8)cicloalquileno, arilo(C_1-C_4)alquileno o heteroarilo(C_1-C_4)alquileno;

X es CR^3R^4, $N(R^5)$, O o $S(O)_n$;

L^3 es un enlace, (C_1-C_5)alquileno o (C_2-C_5)heteroalquileno, siempre que L^3 no sea un enlace cuando L^2 es un enlace;

A es $-CO_2H$, tetrazol-5-il, $-SO_3H$, $-PO_3H_2$, $-SO_2NH_2$, $-C(O)NHSO_2CH_3$, -CHO, $-C(O)R^6$, $-C(O)NHR^6$, $-C(O)NHOR^7$, tiazolidindiona-il, hidroxifenil o piridil;

R^1 es (C_1-C_8)alquilo, arilo(C_1-C_3) alquilo o (C_2-C_8)heteroalquilo;

R2 es hidrógeno, (C_1-C_8)alquilo o (C_2-C_8)heteroalquilo;

R3 es ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquilo, (C_2-C_8)alquenilo, (C_3-C_8)alquenilo, (C_2-C_8)alquinilo, (C_3-C_8)alquinilo, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$, $-NR^{12}C(O)R^{13}$ o $-NR^{12}S(O)_pR^{13}$;

R^4 es hidrógeno, ciano, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo o (C_2-C_8)alquinilo;

opcionalmente, R^3 y R^4 se combinan para formar un anillo de 3, 4, 5, 6 o 7 miembros que contenga de cero a tres heteroátomos seleccionados de N, O y S;

R^5 es hidrógeno, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)alquenilo, (C_2-C_8)alquinilo o (C_3-C_8)cicloalquilo;

R^6 es heteroarilo;

R^7 es hidrogeno o (C_1-C_8)alquilo;

R8 y R9 son independientemente hidrogeno, (C_1-C_8)alquilo, oxi(C_1-C_8)alquilo o carboxi(C_1-C_8)alquilo;

opcionalmente, R^8 y R^9 se combinan para formar un anillo de 4, 5, 6 ó 7 miembros que contengan el átomo de hidrogeno al cual están adheridos y de 0 a 2 heteroátomos adicionales seleccionados de N, O y S;

R^{10}, R^{11} y R^{12} se seleccionan independientemente de hidrógeno, arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)heteroalquilo, (C_3-C_8)cicloalquilo y (C_3-C_8)heterocicloalquilo;

opcionalmente, R^{10} y R^{11} se combinan para formar un anillo de 4, 5, 6 o 7 miembros que contengan el átomo de nitrógeno al cual están adheridos y de 0 a 2 heteroátomos adicionales seleccionados de N, O y S;

R^{13} es arilo, heteroarilo, (C_1-C_8)alquilo, (C_2-C_8)heteroalquilo, (C_3-C_8)cicloalquilo o (C_3-C_8)heterocicloalquilo;

los subíndices m y n son independientemente 0, 1 ó 2; y

el subíndice p es 1 ó 2; y

donde el compuesto es distinto a ácido 3-(4-(4-metoxibenciloxi)fenil)pentano-4-inóico; ácido β-etenil-4-fenilmetoxi-bencenopropanóico; ácido 4-(2-quinolinilmetoxi)-β-[4-(2-quinolinilmetoxi)fenil]-bencenopropanóico; N-[4-(benzoilamino)fenil]-N-fenil-glicina; 3-(4-(isopentiloxi)benzamido)-3-fenilpropanoato; 3-(4-isobutoxibenzamido)-3-fenilpropanoato; ácido (*R*)-2-((*IR,4R*)-4-isopropilciclohexanocarboxamido)-3-fenilpropanóico; ácido (*R*)-3-(4-(benciloxi)fenil)- 2-(tert-butoxicarbonil)propanóico; ácido 3-(4-clorofenil)-3-(furan-2- carboxamido)propanóico; ácido 3-(3,4-dimetoxifenil)-3-(furan-2-carboxamido)propanóico; ácido 3-(4-clorobenzamido)-3-(4-(dimetilamino)fenil)propanóico; ácido 3-(2-(2-(3,4-

FORMATO DE DIGITALIZACI N
RELACION DE ANEXOS

Royal Technologies S.A.

Item		Expediente No	06096986
		No de Unidades	No de Folio
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA	1	
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones: Sobre con Arte final

361

362

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-096986- -00000-0000
Fec: 2006-09-25 17:28:47 Dep: 2030 NUEVACREACION
Tra: 11 PATENTENU
Ent: 379 FASENACIONALI
Act: 411 PRESENTACION Folios: 362

RECIBO OFICIAL DE CAJA : 06 - 71,089
FECHA : SEPTIEMBRE 18 DE 2006

***** 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	49872310	18/09/2006	49,351,180.00

***** 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	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Clo 15193-841-004-1

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-096986- -00000-0000
Fec: 2006-09-25 17:23:47 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYII
Cla: 378 FASENACIONALI
Act:411 PRESENTACION Folios: 362

Industria y Comercio

SUPERINTENDENCIA

363

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (✓) MODELO DE UTILIDAD ( )	( )	( )
-Indicación de que se solicita la concesión de una patente.	(✓)	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	(✓)	( )
-Descripción de la invención.	(✓)	( )
-Dibujos de ser estos pertinentes.	(NO)	( )
-Comprobante de Pago de las tasas establecidas.	(✓)	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
ESQUEMA DE TRAZADO ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable: _____

Fecha: 26 SET. 2006

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

364

Bogotá,
2020

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
AMGEN INC.

REFERENCIA	Radicación No.	06 96986
	Solicitud internacional	PCT/US2005/005815
	Fecha inicio fase nacional	27/09/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	2330

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 16 FEB. 2007
lerazo

