



Industria y Comercio

SUPERINTENDENCIA

P.C.T.

Delegatura de propiedad Industrial

División de Nuevas Creaciones

040/6680

SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No. **040/6680**

54. TÍTULO **Agentes Antidiabeticos**

51. CLASIFICACIÓN INTERNACIONAL **A61K 31/140**

71. SOLICITANTE **Warner - Lambert. Company L.L.C.**

DOMICILIO **201 Tabor Road Morris Plains New Jersey
07950, Estados Unidos de América.**

74. APODERADO **Carlos R. Martic**

22. BOGOTÁ, D. C., **febrero, 25, 2004**

202099.

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

14 016880 00

SUPERINDUSTRIA Y COMERCIO

Radicación : 04016680 00000000

Folios: 832

Fecha (MD): 2004-02-25 16:15:10

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2820 DIVISION DE NUEVAS CREACIONES

ción

FÓRMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1

SOLICITUD DE :

☒ X

Patente de Invención

☐

Patente de Modelo de Utilidad

☐

Capítulo I.

☒ X

Capítulo II.

2

SOLICITANTE

(71)

Nombre: WARNER-LAMBERT COMPANY LLC

Dirección: 201 Tabor Road, Morris Plains, New Jersey 07950,
Estados Unidos de América.

Nacionalidad o Domicilio: ESTADOUNIDENSE

Lugar de Constitución: New Jersey

Teléfono:

Fax:

E-Mail

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

3

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre C, Calle 100 No. 8A-55 Piso 10.

Teléfono: 6386200

Fax: 6386201

E-Mail: filings@olarteraisbeck.com

IDENTIFICACION

C.C.

☒ X

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

79.782.747 Bta

TP 74.295

4

INVENTOR (ES)
(72)

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

5

PCT (85)

Solicitud Internacional No. PCT/IB02/02843

Fecha Julio 15, 2002

Publicación Internacional No. WO 03/018553

Fecha Marzo 6, 2003

6

Título (54)

AGENTES ANTIDIABETICOS

7

Clasificación Internacional (51)

A61K31140

8

Prioridad

SI

☒ X

NO

☐

(33) País de Origen

US

(32) Fecha

Agosto 29, 2001

(31) Número de Solicitud

60/315,728

9

Comprobante de pago No. 12,955

Fecha 19-02-04

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

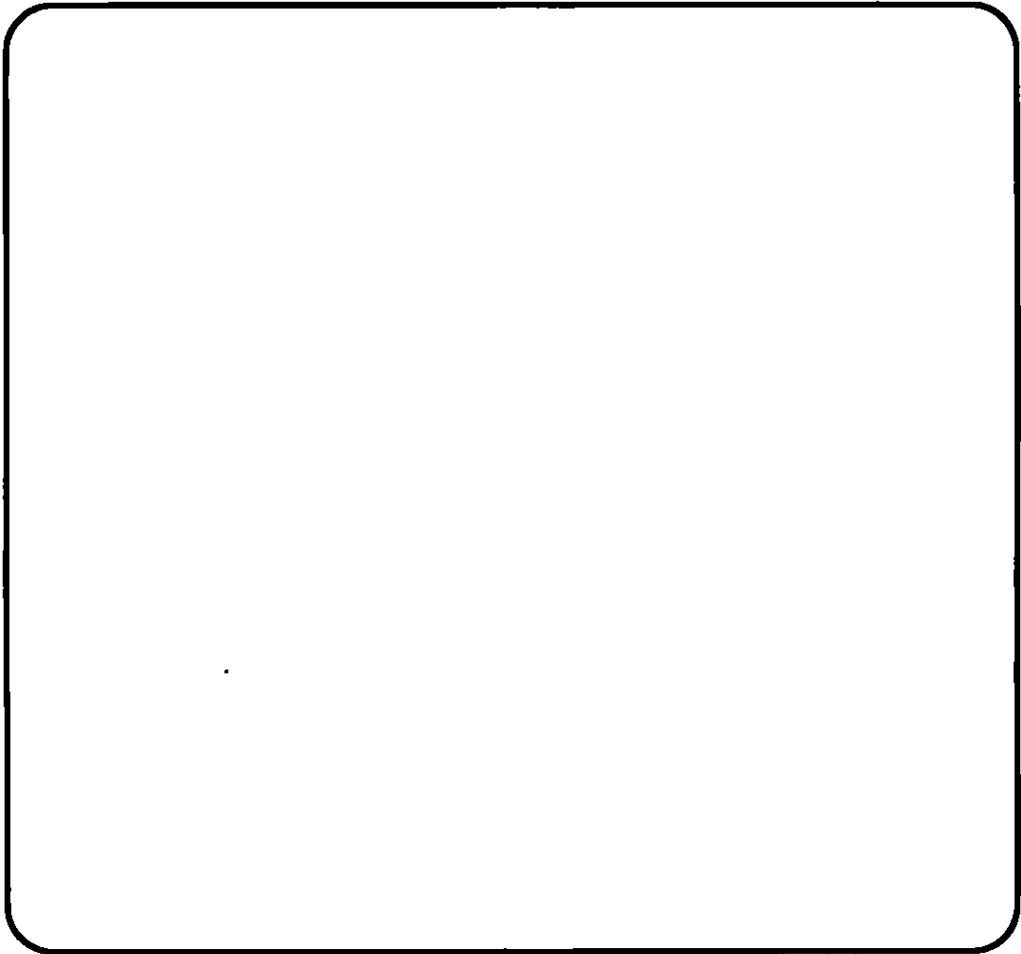
10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, al 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 internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: BUSQUEDA INTERNACIONAL

11

FIGURA CARATERISTICA



12

Solicito la concesión de la patente,

NOMBRE: CARLOS B. OLARTE

FIRMA:  C.C. 74.782.747 de Bta T.P. 74.295

CHRISTOPHER FRANKLIN BIGGE
2800 Plymouth Road,
Ann Arbor, Michigan 48105,
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

ALEXANDER JAMES BRIDGES
2800 Plymouth Road,
Ann Arbor, Michigan 48105,
Estados Unidos de América.
Nacionalidad: BRITANICA

AGUSTIN CASIMIRO-GARCIA
2800 Plymouth Road,
Ann Arbor, Michigan 48105,
Estados Unidos de América.
Nacionalidad: MEXICANA

STEPHEN ALAN FAKHOURY
2800 Plymouth Road,
Ann Arbor, Michigan 48105,
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

HELEN TSENWHEI LEE
2800 Plymouth Road,
Ann Arbor, Michigan 48105,
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

JESSICA ELIZABETH REED
2800 Plymouth Road,
Ann Arbor, Michigan 48105,
Estados Unidos de América.
Nacionalidad: BRITANICA

ROBERT PHILIPP SCHAUM
2800 Plymouth Road,
Ann Arbor, Michigan 48105,
Estados Unidos de América.
Nacionalidad: CANADIENSE

KEVIN MATTHEW SCHLOSSER
2800 Plymouth Road,
Ann Arbor, Michigan 48105,
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

KAREN ELAINE SEXTON
2800 Plymouth Road,
Ann Arbor, Michigan 48105,
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

HAIRONG ZHOU
2800 Plymouth Road,
Ann Arbor, Michigan 48105,
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

5

SUPERINDUSTRIA Y COMERCIO
Radicacion : 84016600 00000000 Folios: 832
Fecha (AMD): 2004-02-25 16:15:10
Tramite : 011 PCT-PATENT 379 FASE INCI 411 PRESENTAC
Dependencia: 8020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 12,953
FECHA : FEBRERO 19 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	090-00110-6	13594217	16/02/2004	3,302,000.00

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

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 30005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	422,000.00

SOM: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE :



RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

6
Traducción oficial del Inglés por Marlén Neira Castro, resolución
2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

WARNER- LAMBERT COMPANY LLC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio
de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

Sello: recibido el 21 julio de 2003 Departamento de Patentes NYD- Pfizer Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth
Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercía
funciones de Secretario Asistente de Warner-Lambert Company LLC, con sede en
Morris Plains, Nueva Jersey, Estados Unidos.

Firma del notario: Kenneth Greenwood

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham
en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman

Sello Notario Público en alto relieve rojo.

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)
REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento Público 2.ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADO 5. En Londres 6. El 17 de julio de 2003

7. Por el Secretario de Estado Principal de su Majestad para Asuntos
exteriores y de la mancomunidad.

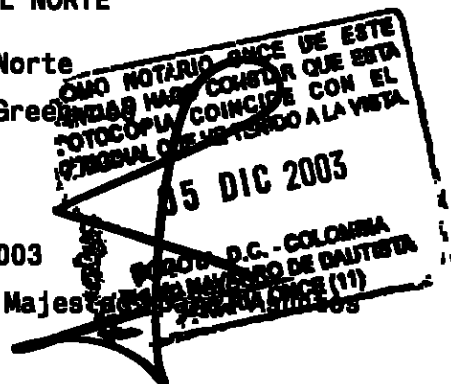
8. No. G210433

9. Sello del Secretario de Estado Principal de su Majestad para Asuntos
exteriores y de la mancomunidad

10. Firma de R. Bawden - Por Secretario de Estado

Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe
presentarse en sección consular de la misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlén Neira C



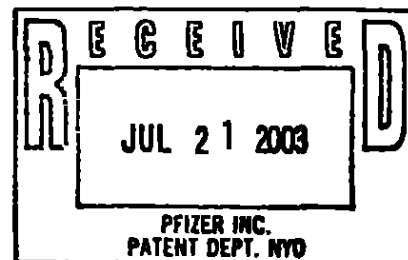
MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1999
Marlén Neira C.

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER — TORRE C
CALLE 100 No. 8A-55 PISO 10
BOGOTÁ, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com



Power of Attorney

The undersigned,

domiciled in

Warner-Lambert Company LLC

El suscrito,

domiciliado en

201 Tabor Road, Morris Plains, New Jersey 07950 USA

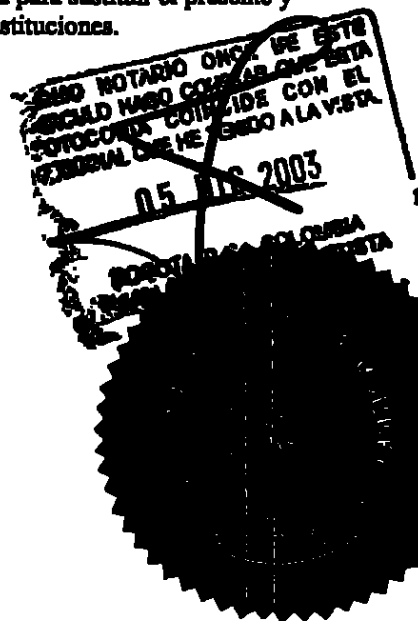
by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Ralsbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

por medio del presente otorga a **Carlos R. Olarte, J. Ian Ralsbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Date/Fecha: July 14, 2003

City/Country/Ciudad,País: New York, USA



1937

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
CALLE 100 No. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

On this date,
July 14, 2003

The undersigned Notary Public certifies:

1. That *J. Trevor Lamb*
of legal age and domiciled in
New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing
document as Assistant Secretary
of Warner-Lambert Company LLC

3. That Warner-Lambert Company LLC,
having its principal place of business located in
Morris Plains, New Jersey, U.S.A.
is duly incorporated, is currently in existence, and
that the purposes for which the Power of Attorney is
granted are within the scope of its corporate
purposes.

4. That the grantor has the authority to execute the
Power of Attorney and that his/her representation is
legal.

5. The foundation for my certifications contained in
points 2, 3 and 4 was the exhibition of the following
authentic document(s):

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
J. Trevor Lamb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido
documento en su carácter de
de

4. Que
con sede principal ubicada en

está legalmente constituida, que tiene existencia
legal vigente y que los propósitos para los cuales
se otorga el poder se encuentra dentro de los que
comprenden su objeto social.

4. Que el otorgante tiene la representación para
suscribir el poder, y que ésta es legítima.

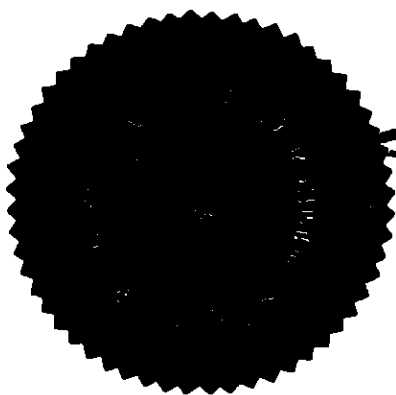
5. El fundamento de mis certificaciones
contenidas en los puntos 2, 3 y 4 fue la exhibición
de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Bellingham In Surrey

This *14th* Day Of *July*

Kenneth Greenwood
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN



APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by K Greenwood
a été signé par
3. Acting in the capacity of Notary Public
agissant en qualité de
4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de

5. at London/Londres
6. the/le 17 July 2003
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

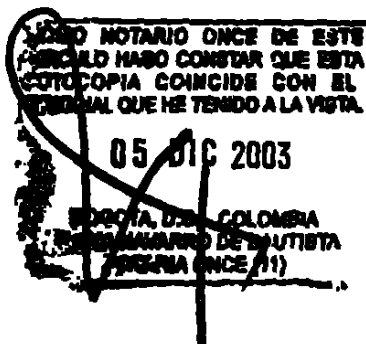
8. Number/sous No **G210433**

9. Stamp:
timbre:
10. Signature: R. Bowden



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.



TRADUCCIÓN FICIAL No. 04-011

Efectuada el día 28 de enero de 2004, de un documento escrito en Inglés, al cual para su identificación se le estampa el sello de María del Pilar Iglesias, Traductora e Intérprete Oficial por Resolución No. 819 de abril de 1971 expedida por el Ministerio de Justicia de la República de Colombia.

PC18324AHMB

-CO-1

CESIÓN

Por contraprestación onerosa recibida por nosotros de **WARNER-LAMBERT COMPANY LLC**, sociedad de responsabilidad limitada organizada y existente conforme a las leyes del Estado de Delaware, Estados Unidos de América, domiciliada en el 201 Tabor Road Morris Plains, Nueva Jersey 07950, Estados Unidos de América, por el presente vendemos y cedemos a la mencionada **WARNER-LAMBERT COMPANY LLC**, todo nuestro derecho, título e interés en nuestro invento para una nueva y útil Mejora en **AGENTES ANTIDIABÉTICOS ORALES** en cuanto respecta a la República de Colombia, tan ampliamente como se describe en las especificaciones, y por el presente autorizamos y solicitamos al Comisario de Patentes de Colombia que expida dicha patente a **WARNER-LAMBERT COMPANY LLC** de conformidad con esta Cesión.

M. P. Iglesias

María del Pilar Iglesias
TRADUCTORA E
INTÉRPRETE OFICIAL
Resolución No. 819 de 1971

En fe de lo cual firmamos este documento de nuestro puño y letra, así:

(Fdo) Christopher Franklin BIGGE en Ann Harbor, Michigan, el 12/17/03

(Fdo.) Alexander James BRIDGES en Ann Harbor, Michigan, el 1/5/2004

(Fdo.) Agustín CASMIRO-GARCIA en Ann Harbor, Michigan, el 12/12/2003

(Fdo.) Stephen Alan FAKHOURY en Ann Harbor, Michigan, el 12/11/2003

(Fdo.) Helen Tsenwhei LEE, en Ann Harbor, Michigan, el 12/17/2003

(Fdo.) Jessica Elizabeth REED, en Ann Harbor, Michigan, el 1/5/2004

(Fdo) Robert Philipp SCHAUM, en Ann Harbor, Michigan, el 12/17/2003

(Fdo.) Kevin Mathew SCHLOSSER, en Ann Harbor, Michigan, el 12/11/2003

(Fdo.) Karen Elaine SEXTON, en Ann Harbor, Michigan, el 12/11/2003

(Fdo.) Hairong ZHOU, en Ann Harbor, Michigan, el 1/05/04

Por el presente certifico que este es el documento original.

(Fdo.) Sami Swadek 1/12/04

M. J.
Escritura del Poder Judicial
TRANSACCIONES
Y DOCUMENTOS
JUDICIALES

22

Suscrito y jurado ante mi, Notario Público del Distrito de Columbia el 12 de enero de 2004.

(Fdo.) Melissa O. Jackson, Notario Público del Distrito de Columbia, cuyo cargo vence el 14 de diciembre de 2008, según consta en su correspondiente sello notarial.

APOSTILLA

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

1. País: Estados Unidos de América
El presente documento público
2. Fue firmado por Melissa O. Jackson
3. Que actuó en su calidad de Secretario de Notario Público del Distrito de Columbia
4. Lleva el sello de Melissa O. Jackson, Notario Público, D.C.

Se certificó:
5. En Washington, D.C.
6. El 13 de enero de 2004
7. Por parte del Secretario del Distrito de Columbia
8. Bajo el Número 120270
9. Aparece Sello del Distrito de Columbia

Maria del Pilar Iglesias

Maria del Pilar Iglesias
María del Pilar Iglesias
C. C. 41.337 '83 de Bogotá 3
Intérprete Oficial según Resolución
15 de Abril de 1971 C. C. 41.337 '83

10. Firmado por Cerril H. Newman, Secretario Distrito de
Columbia

Es traducción fiel y completa efectuada por:

Maria del Pilar Iglesias
María del Pilar Iglesias
C.C.41.339.183 de Bogotá

Maria del Pilar Iglesias
María del Pilar Iglesias
C. C. 41.339.183 de Bogotá
Intérprete Oficial según Resolución No. 819 de
15 de Abril de 1971 del Ministerio de Justicia

04/04.
13



APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *District of Columbia*
United States of America
2. This public document has been signed by MELISSA O. JACKSON
3. acting in the capacity of NOTARY PUBLIC IN AND FOR THE DISTRICT
OF COLUMBIA
4. bears the seal/stamp of MELISSA O. JACKSON, NOTARY PUBLIC, D.C.

CERTIFIED

5. at Washington, D. C.
6. the 13TH day of JANUARY 2004
7. by Secretary of the District of Columbia
8. No. 120270
9. Seal/Stamp

10. Signature


SHERRYL H. NEWMAN

ASSIGNMENT

For valuable consideration paid to me (us) by WARNER-LAMBERT COMPANY LLC a limited liability company organized and existing under the laws of the State of Delaware, United States of America whose full post office address is 201 Tabor Road, Morris Plains, New Jersey 07950, United States of America, I (we) do hereby sell and assign to the said WARNER-LAMBERT COMPANY LLC, all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in ORAL ANTIDIABETIC AGENTS so far as the Republic of Colombia is concerned, as fully set forth and described in the specification, and I (we) do hereby authorize and request the Commissioner of Patents of Colombia to issue said patent to the said WARNER-LAMBERT COMPANY LLC in accordance with this assignment.

In witness whereof I (we) have hereunto set my (our) hand(s) this

Ann Arbor MI 12/17/03 Christopher Franklin BIGGE
Place, date and signature - Christopher Franklin BIGGE

Ann Arbor MI 1/5/2004 Alexander James BRIDGES
Place, date and signature - Alexander James BRIDGES

Ann Arbor, MI 12/12/2003 Agustin Casimiro-Garcia
Place, date and signature - Agustin CASIMIRO-GARCIA

Ann Arbor, MI 12/17/2003 Stephen Alan FAKHOURY
Place, date and signature - Stephen Alan FAKHOURY

Ann Arbor, MI 12/17/2003 Helen Tsenwhei LEE
Place, date and signature - Helen Tsenwhei LEE

Ann Arbor, MI 1/5/2004 Jessica Elizabeth REED
Place, date and signature - Jessica Elizabeth REED

Ann Arbor MI 12/17/2003 Robert Philipp SCHAUM
Place, date and signature - Robert Philipp SCHAUM

Ann Arbor MI 12/17/2003 Kevin Matthew SCHLOSSER
Place, date and signature - Kevin Matthew SCHLOSSER

Ann Arbor MI 12-17-2003 Karen Elaine SEXTON
Place, date and signature - Karen Elaine SEXTON

Ann Arbor MI 1-05-04 Hairong ZHOU
Place, date and signature - Hairong ZHOU

I HEREBY CERTIFY THAT THIS
IS THE ORIGINAL DOCUMENT

SAMI SWADEK

1.12.04

Subscribed and sworn to before me, in my presence, this
12 day of Jan. 2004, a Notary Public
in and for the District of Columbia
Melissa O. Jackson
Notary Public
My commission expires Dec 14, 2006

MELISSA O. JACKSON
NOTARY PUBLIC DISTRICT OF COLUMBIA
My Commission Expires December 14, 2006

TRATADO DE COOPERACION DE PATENTES

De: OFICINA INTERNACIONAL

**Para: LUMB, J. Trevor
Pfizer Inc.
201 Tabor Road
Morris Plains, NJ 07950
Estados Unidos de América.**

**NOTIFICACION DE UN REGISTRO DE CAMBIO
(Regla PCT 92bis.1 e Instrucciones Administrativas, Sección 422)**

NOTIFICACION IMPORTANTE

Fecha de envío: 11 de Abril de 2003 (11.04.03)

Referencia de Solicitante o Agente: PC18324 AHMB

Solicitud Internacional: PCT/IB02/02843

Fecha de presentación internacional: 15 de julio de 2002 (15.07.02)

- 1. Las siguientes indicaciones aparecieron en archivo con respecto a:**
- ☒ **el solicitante**
 - ☐ **el inventor**
 - ☐ **el agente**
 - ☐ **representante común**

Nombre y Dirección:

**WARNER-LAMBERT COMPANY
201 Tabor Road
Morris Plains, NJ 07950
Estados Unidos de América.**

Nacionalidad: US

Residencia: US

- 2. Por medio de la presente, la Oficina Internacional notifica al solicitante que el siguiente cambio ha sido registrado con respecto a:**

- ☐ **la persona**
- ☒ **el nombre**
- ☐ **la dirección**
- ☐ **la nacionalidad**
- ☐ **la residencia**

Nombre y Dirección:

**WARNER-LAMBERT COMPANY LLC
201 Tabor Road
Morris Plains, NJ 07950**

Estados Unidos de América.

Nacionalidad: US

Residencia: US

3. Observaciones adicionales, si dan lugar:

4. Una copia de esta notificación ha sido enviado a:
- ☒ la Oficina receptora
 - ☐ la Autoridad de Búsqueda Internacional
 - ☐ la Autoridad Examinadora Preliminar Internacional
 - ☐ las Oficinas designadas involucradas
 - ☒ las Oficinas elegidas
 - ☐ otros: .

La Oficina Internacional de la OMPI
34, chemin des Colombettes
1211 Ginebra 20, Suiza
Fax No. : (41-22) 740.14.35

Funcionario:

Silvie STENDER

Teléfono: (41-22) 338-9926

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
6 March 2003 (06.03.2003)

PCT

(10) International Publication Number
WO 03/018553 A1

(51) International Patent Classification⁷: C07D 207/32,
263/32, 413/12, 403/12, 401/12

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(71) Applicant (for all designated States except US):
WARNER-LAMBERT COMPANY [US/US]; 201
Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BIGGE, Christo-
pher, Franklin [US/US]; Pfizer Global Research and
Development, Ann Arbor Laboratories, 2800 Plymouth
Road, Ann Arbor, MI 48105 (US). BRIDGES, Alexander,
James [GB/US]; Pfizer Global Research and Developpe-
ment, Ann Arbor Laboratories, 2800 Plymouth Road, Ann
Arbor, MI 48105 (US). CASIMIRO-GARCIA, Augustin
[MX/US]; Pfizer Global Research and Development,
Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor,
MI 48105 (US). FAKHOURY, Stephen, Alan [US/US];
Pfizer Global Research and Development, Ann Arbor
Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105
(US). LEE, Helen, Tseuwei [US/US]; Pfizer Global
Research and Development, Ann Arbor Laboratories,
2800 Plymouth Road, Ann Arbor, MI 48105 (US). REED,
Jessica, Elizabeth [GB/US]; Pfizer Global Research and

Development, Ann Arbor Laboratories, 2800 Plymouth
Road, Ann Arbor, MI 48105 (US). SCHAUM, Robert,
Phillipp [CA/US]; Pfizer Global Research and Developpe-
ment, Ann Arbor Laboratories, 2800 Plymouth Road, Ann
Arbor, MI 48105 (US). SCHLOSSER, Kevin, Matthew
[US/US]; Pfizer Global Research and Development, Ann
Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI
48105 (US). SEXTON, Karen, Elaine [US/US]; Pfizer
Global Research and Development, Ann Arbor Labora-
tories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US).
ZHOU, Hailong @ [US/US]; Pfizer Global Research and
Development, Ann Arbor Laboratories, 2800 Plymouth
Road, Ann Arbor, MI 48105 (US).

(74) Agents: LUMB, J., Trevor et al.; Pfizer Inc., 201 Tabor
Road, Morris Plains, NJ 07950 (US).

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(54) Title: ORAL ANTIDIABETIC AGENTS

(57) Abstract: The present invention provides compounds of Formula (I): f I wherein A, X, Q, Y, B, D, Z, and E have any of the
values defined in the specification, and pharmaceutically acceptable salt thereof, that are useful as antidiabetic agents. Also disclosed
are pharmaceutical compositions comprising one or more compounds of Formula I, process for preparing compounds of Formula I,
and intermediates useful for preparing compounds of Formula I.



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ORAL ANTIDIABETIC AGENTS

FIELD OF THE INVENTION

The present invention relates to compounds that are useful as antidiabetic agents.

5

BACKGROUND OF THE INVENTION

Type II diabetes, or non-insulin dependent diabetes (NIDDM) is a significant healthcare problem whose incidence is on the rise. Between 1990 and 1998, the prevalence of NIDDM in the United States increased by 33 percent, to about 13 million persons. An additional 5 million persons are presumed to have undiagnosed NIDDM, while another 14 million persons have impaired glucose tolerance. Direct medical costs associated with diabetes were \$44 billion in 1997, due mainly to hyperglycemia-related diabetic complications, including diabetic angiopathy, atherosclerosis, diabetic nephropathy, diabetic neuropathy, and diabetic ocular complications such as retinopathy, cataract formation, and glaucoma.

NIDDM is one of a number of disease states associated with the phenomenon of insulin resistance. Insulin resistance is defined as the reduced sensitivity to the actions of insulin in the whole body or individual tissues, such as skeletal muscle tissue, myocardial tissue, fat tissue or liver tissue. Insulin resistance occurs in many individuals with or without diabetes mellitus. Insulin resistance syndrome (hereinafter IRS) refers to the cluster of manifestations that include insulin resistance; hyperinsulinemia; non insulin dependent diabetes mellitus (NIDDM); arterial hypertension; central (visceral) obesity; and dyslipidemia.

The primary goal of IRS therapy and thus diabetes therapy is to lower blood glucose levels so as to prevent acute and long-term disease complications. For some persons, modified diet and increased exercise may be a successful

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therapeutic option for achieving the goal of glucose control. When modified diet and increased exercise are not successful, drug therapy using oral antidiabetic agents is initiated.

To date, a number of oral antidiabetic agents have been developed. For instance, sulfonylureas are generally used to stimulate insulin. The biguanide metformin is generally used to improve insulin sensitivity and to decrease hepatic glucose output. Acarbose is used to limit postprandial hyperglycemia, Thiazolidine 2,4 diones are used to enhance insulin action.

New drug therapies for the treatment of NIDDM have focused in part on the discovery of new Peroxisome Proliferator Activation Receptor (PPAR) agonists. PPARs are members of the nuclear receptor superfamily of transcription factors that includes steroid, thyroid, and vitamin D receptors. PPARs play a role in controlling expression of proteins that regulate lipid metabolism. There are three PPAR subtypes: PPAR α , PPAR δ , and PPAR γ .

Each PPAR receptor shows a different pattern of tissue expression, and differences in activation by structurally diverse compounds. PPAR γ , for instance, is expressed most abundantly in adipose tissue and at lower levels in skeletal muscle, heart, liver, intestine, kidney, vascular endothelial and smooth muscle cells as well as macrophages. Two isoforms of PPAR γ exist, identified as γ_1 and γ_2 , respectively. PPAR γ mediates adipocyte signalling, lipid storage, and fat metabolism. Evidence gathered to date support the conclusion that PPAR γ is the primary, and perhaps the only, molecular target mediating the insulin sensitizing action of one class of antidiabetic agents, the thiazolidine 2,4 diones.

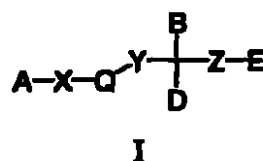
In a monotherapeutic or combination therapy context, new and established oral antidiabetic agents are still considered to have non-uniform and even limited effectiveness. The effectiveness of oral antidiabetic therapies may be limited, in part, because of poor or limited glycemic control, or poor patient compliance due to unacceptable side effects. These side effects include edema weight gain, or even more serious complications. For instance, hypoglycemia is observed in some patients taking sulfonylureas. Metformin, a substituted biguanide, can cause diarrhea and gastrointestinal discomfort. Finally, edema, weight gain, and in

some cases, hepatotoxicity, have been linked to the administration of some thiazolidine 2,4 dione antidiabetic agents. Combination therapy using two or more of the above agents is common, but generally only leads to incremental improvements in glycemic control.

- 5 As a result, there is a need for oral antidiabetic agents that can be used alone or in combination, and that do not give rise to side effects such as fluid retention, peripheral edema, weight gain, or more severe complications.

SUMMARY OF THE INVENTION

- 10 These and other needs are met by the current invention which is a compound of formula (I)



or a pharmaceutically acceptable salt thereof, wherein:

- 15 A is aryl and substituted aryl,
heteroaryl and substituted heteroaryl,
fused heteroaryl and substituted fused heteroaryl,
(C₃-C₇)cycloalkyl and substituted cycloalkyl, or
heterocycloalkyl and substituted heterocycloalkyl;

- 20 X is a tether 2 to 5 atoms in length selected from
~CH₂-O~, ~CH₂-CH₂-O~, ~CH₂-CH₂-CH₂~, ~CH₂-≡~, or
~CH₂-CH=CH~, wherein "~" indicates a point of attachment;

- Q is aryl or substituted aryl;
heteroaryl or substituted heteroaryl;
fused heteroaryl, or substituted fused heteroaryl; provided that when q is a
25 five-membered heteroaryl, the point of attachment from X to Q is
not at the heteroatom of the heteroaryl;

Y and Z are independently absent or are $(CR_1R_2)_n$ and $(CR_3R_4)_m$, wherein R_1 - R_4 are each independently H, halo, (C_1-C_6) alkyl, hydroxy, (C_1-C_6) alkoxy, and m and n are each independently 1, 2, or 3;

B is H, halo, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, or (C_1-C_6) alkoxy;

5 D is H, H, $—NH$ -aryl and $—NH$ -substituted aryl,

(C_1-C_6) alkanoyl and substituted alkanoyl,

benzoyl and substituted benzoyl,

aryl and substituted aryl,

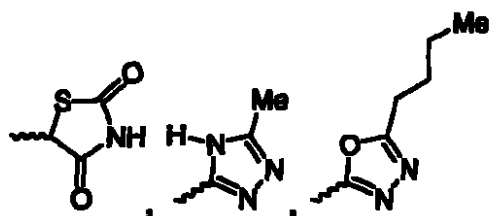
heteroaryl and substituted heteroaryl,

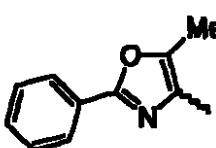
10 (C_3-C_7) cycloalkyl and substituted cycloalkyl, or

heterocycloalkyl and substituted heterocycloalkyl;

E is COR_5 , wherein R_5 is (C_1-C_6) alkyl, OH, (C_1-C_6) alkoxy, NR_6R_7 , wherein R_6 and R_7 are each independently H or (C_1-C_6) alkyl, or one of R_6 and R_7 is H or (C_1-C_6) alkyl and the other is SO_2R_8 , wherein R_8 is H or (C_1-C_6) alkyl, or

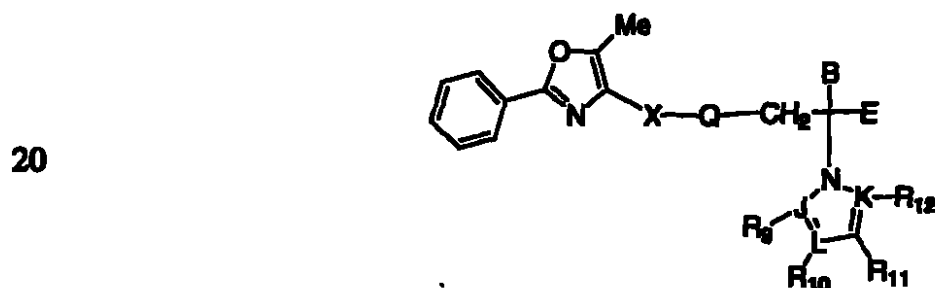
15 E is substituted heteroaryl or



provided that when A is , X is $—CH_2—CH_2—O—$ Q is

phenyl, Y and Z are CH_2 , B is H, and E is CO_2H , D is not pyrrolyl.

The invention also provides a compound of formula (II)



or a pharmaceutically acceptable salt thereof, wherein:

X is a tether 2 to 5 atoms in length selected from

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$\sim\text{CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\text{-}\equiv\sim$, or
 $\sim\text{CH}_2\text{-}\text{CH}=\text{CH}\sim$, wherein " $\sim$ " indicates a point of attachment;

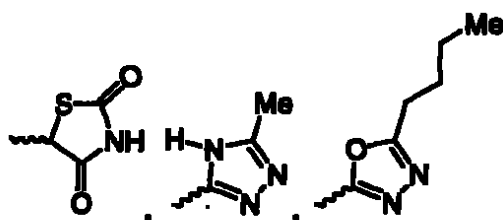
Q is aryl or substituted aryl;

heteroaryl or substituted heteroaryl;

5 fused heteroaryl, or substituted fused heteroaryl; provided that when q is a five-membered heteroaryl, the point of attachment from X to Q is not at the heteroatom of the heteroaryl;

B is H, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or (C₁-C₆)alkoxy;

E is COR₅, wherein R₅ is (C₁-C₆)alkyl, OH, (C₁-C₆)alkoxy, NR₆R₇, wherein R₆
 10 and R₇ are each independently H or (C₁-C₆)alkyl, or one of R₆ and R₇ is H or (C₁-C₆)alkyl and the other is SO₂R₈, wherein R₈ is H or (C₁-C₆)alkyl, or E is substituted heteroaryl or

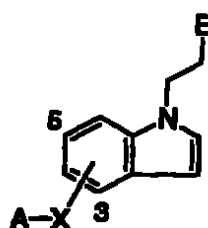


R₉-R₁₂ are each independently H, halo, aryl, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-
 15 C₆)alkanoyl, halo(C₁-C₆)alkanoyl, (C₃-C₇)cycloalkylcarbonyl, benzoyl, or halo(C₂-C₆)alkanoyl; and

one or two of J, K, and L are N,

provided that when J, K, or L are N, R₉, R₁₀, R₁₁, or R₁₂ is absent at that position.

20 The invention also provides a compound of formula (III):



III

or a pharmaceutically acceptable salt thereof, wherein:

A is aryl and substituted aryl,

25 heteroaryl and substituted heteroaryl,

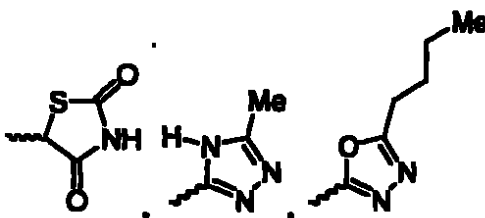
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fused heteroaryl and substituted fused heteroaryl,
 (C₃-C₇)cycloalkyl and substituted cycloalkyl, or
 heterocycloalkyl and substituted heterocycloalkyl;

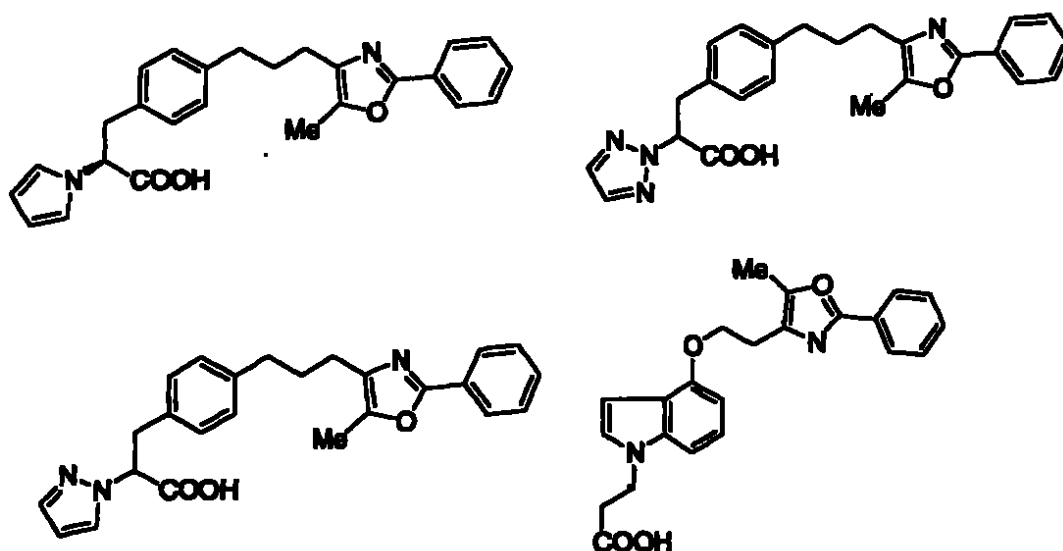
X is a tether 2 to 5 atoms in length selected from

5 $\sim\text{CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$,
 $\sim\text{CH}_2\text{-}\equiv\sim$, or $\sim\text{CH}_2\text{-CH=CH}\sim$, wherein " $\sim$ " indicates a point of
 attachment, and wherein $\sim\text{XA}$ can be attached to the 3, 4, 5, or 6 position
 of the indoliny core; and

10 E is COR₅, wherein R₅ is (C₁-C₆)alkyl, OH, (C₁-C₆)alkoxy, NR₆R₇, wherein R₆
 and R₇ are each independently H or (C₁-C₆)alkyl, or one of R₆ and R₇ is H
 or (C₁-C₆)alkyl and the other is SO₂R₈, wherein R₈ is H or (C₁-C₆)alkyl, or
 E is substituted heteroaryl or



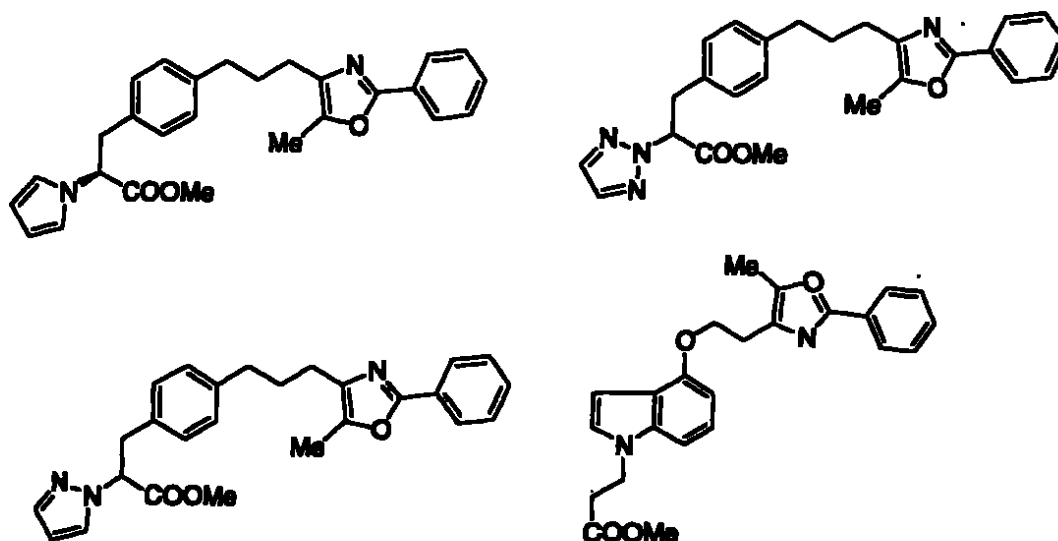
The invention also provides a compound which is:



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The invention also provides a compound which is:



The invention also provides a compound which is:

5 (R)-2-(2-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

(R)-2-Ethyl-5-(2-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

(R)-2-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

10 (R)-2-Methyl-3-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid;

(R)-3-Methyl-5-(2-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;

15 (R)-2-(3-Bromo-pyrrol-1-yl)-2-methyl-3-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-propionic acid;

(S)-3,3,3-Trifluoro-2-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl)-2-pyrrol-1-yl-propionic acid;

(R)-3,3,3-Trifluoro-2-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl)-2-pyrrol-1-yl-propionic acid;

20 (R)-2-ethyl-3-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid;

(S)-2-ethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(R)-2-propyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

5 (S)-2-propyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-3,3,3-Trifluoroethyl-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

10 (R)-3,3,3-Trifluoroethyl-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

(R)-2-Fluoromethyl-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-Fluoromethyl-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

15 (S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-fluoromethyl-2-pyrrol-1-yl-propionic acid;

(R)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-fluoromethyl-2-pyrrol-1-yl-propionic acid;

20 (S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

(R)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

(S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

25 (R)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

(S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

30 (R)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

- (R)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;
- (S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;
- 5 (R)-2-(3-Bromo-pyrrol-1-yl)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-propionic acid;
- (S)-2-(3-Bromo-pyrrol-1-yl)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-propionic acid;
- (S)-3,3,3-Trifluoro-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;
- 10 (R)-3,3,3-Trifluoro-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;
- (R)-2-ethyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;
- 15 (S)-2-ethyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;
- (R)-2-propyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;
- (S)-2-propyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;
- 20 (S)-3,3,3-Trifluoroethyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;
- (R)-3,3,3-Trifluoroethyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;
- 25 (S)-2-Pyrrol-1-yl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-propionic acid;
- (R)-2-Pyrrol-1-yl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-propionic acid;
- (R)-2-(2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl])-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;
- 30 (S)-2-(2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl])-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

(R)-2-Ethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

(S)-2-Ethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

5 (R)-2-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

(S)-2-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

10 (R)-2-Methyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;

(S)-2-Methyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;

(R)-3-Methyl-5-(3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;

15 (S)-3-Methyl-5-(3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;

(R)-2-(3-Bromo-pyrrol-1-yl)-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-propionic acid;

20 (R)-2-(3-Bromo-pyrrol-1-yl)-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-propionic acid;

(S)-3,3,3-Trifluoro-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;

(R)-3,3,3-Trifluoro-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;

25 (R)-2-ethyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;

(S)-2-ethyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;

30 (R)-2-propyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;

(S)-2-propyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;

- (S)-3,3,3-Trifluoroethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;
- (R)-3,3,3-Trifluoroethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;
- 5 (R)-2-Fluoromethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;
- (S)-2-Fluoromethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;
- 10 (S)-2-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;
- (R)-2-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;
- (S)-2-Ethyl-2-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;
- 15 (R)-2-Ethyl-2-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;
- (R)-2-2-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;
- (S)-2-2-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;
- 20 (R)-2-Methyl-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid;
- (S)-2-Methyl-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid;
- 25 (R)-3-Methyl-5-(3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;
- (S)-3-Methyl-5-(3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;
- (R)-2-(3-Bromo-pyrrol-1-yl)-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-propionic acid;
- 30 (S)-2-(3-Bromo-pyrrol-1-yl)-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-propionic acid;

(S)-3,3,3-Trifluoro-2-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

(R)-3,3,3-Trifluoro-2-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

5 (R)-2-ethyl-3-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-ethyl-3-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

10 (R)-2-propyl-3-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-propyl-3-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-3,3,3-Trifluoroethyl-2-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

15 (R)-3,3,3-Trifluoroethyl-2-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

(R)-2-Fluoromethyl-2-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid; or

20 (S)-2-Fluoromethyl-2-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid.

The invention also provides a compound which is:

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

25 (S)-2-(2-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

(S)-2-(3-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid;

30 (S)-3-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid;

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N-(S)-(3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionyl)-Benzenesulfonamide

N-(S)-(3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionyl)-methanesulfonamide;

5 (S)-2-(3-Isobutyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

(S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

10 (S)-3-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-cyclohexanecarbonyl-pyrrol-1-yl)-propionic acid;

(S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-(2-fluoro-benzoyloxy)-phenyl]-propionic acid;

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid;

15 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyridin-4-yl-propionic acid;

2-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-2H-tetrazole

20 2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-2-yl-propionic acid;

N-(2,2-Dimethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionyl)-methanesulfonamide

N-(2-Fluoro-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionyl)-methanesulfonamide

25 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid;

2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

30 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-phenyl-propionic acid;

(S)-2-(2-Acetyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

3-{4-[2-(Benzothiazol-2-ylsulfanyl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-Pyrrol-1-yl-3-{4-[2-(2-trifluoromethyl-phenyl)-ethoxy]-phenyl}-propionic acid;

5 (S)-3-{4-[2-(4-Phenyl-piperazin-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-3-{4-[2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

10 (S)-2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

(S)-3-(4-{2-[(7-Chloro-quinolin-4-yl)-methyl-amino]-ethoxy}-phenyl)-2-pyrrol-1-yl-propionic acid;

(S)-2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(4-methyl-2-phenyl-oxazol-5-yl)-ethoxy]-phenyl}-propionic acid;

15 (S)-2-[2,5-Dimethyl-3-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

3-{4-[2-(2-Phenyl-benzimidazol-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

20 2-(3-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

2-(2-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

2-(2-Chloro-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

25 (S)-2-(2-Butyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

(S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-[4-(2-fluoro-benzyloxy)-phenyl]-propionic acid;

30 (S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-methyl-5-phenyl-pyrrol-1-yl)-propionic acid;

(S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

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- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl}-2-pyrrol-1-yl-propionic acid;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-2-yl-propionic acid;
- 5 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyridin-3-yl-propionic acid;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid;
- 10 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-triflorophenyl)-propionic acid;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid; (R)
- 2-(4-Methoxy-phenyl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;
- 15 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-phenyl}-2-pyrrol-1-yl-propionic acid;
- 2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid;
- 2,2-Dimethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;
- 20 2-Fluoro-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-oxo-pyrrolidin-1-yl)-propionic acid;
- 25 2-Ethyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1,3,4-oxadiazole
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl}-2-pyrrol-1-yl-propionic acid;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyridin-3-yl-propionic acid;
- 30 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid;

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-triflorophenyl)-propionic acid;

(R)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid;

5 S)-2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid; methyl ester

3-{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-propionic acid;

10 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-propionic acid;

(S)-2-(2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole

(S)-2-Ethyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole

15 (S)-2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole

(S)-3-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole

20 2-(3-Bromo-pyrrol-1-yl)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

3,3,3-Trifluoro-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

2-(4-Benzylloxy-indol-1-yl)-propionic acid;

25 3-(1-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-benzyl}-1H-pyrrol-2-yl)-propionic acid;

(1-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl]-1H-indol-5-yloxy)-phenyl-acetic acid;

2-(1-Methyl-1H-indol-3-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

30 3-(4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propoxy]-indol-1-yl)-propionic acid;

- 2-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl)-propionic acid;
- 3-(4-[2-(2-Trifluoromethyl-phenyl)-ethoxy]-indol-1-yl)-propionic acid;
- (4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propoxy]-indol-1-yl)-acetic acid;
- 5 4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl)-acetic acid;
- 4-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-butyric acid;
- 3-(3-Fluoro-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-(S)-pyrrol-1-yl-propionic acid;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyridin-4-yl-propionic acid;
- 10 2-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-2H-tetrazole
- 1-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1H-tetrazole
- 15 2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-2-yl-propionic acid;
- 2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-3-yl-propionic acid;
- N-(2,2-Dimethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionyl)-methanesulfonamide
- 20 N-(2-Fluoro-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionyl)-methanesulfonamide
- 3-{3-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-isoxazol-5-yl}-2-pyrrol-1-yl-propionic acid;
- 25 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid;
- 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-phenyl-propionic acid;
- 30 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-phenylpropionic acid;

- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-pyrrol-1-yl-propionic acid;
- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-phenylpropionic acid;
- 5 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-phenylpropionic acid;
- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-thiophen-2-yl-propionic acid;
- 10 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-acrylic acid;
- {4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]benzylamino}phenylacetic acid
- Methyl-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid;
- 15 6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-naphthalene-2-carboxylic acid;
- 3-{5-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-naphthalen-1-yl}-2-pyrrol-1-yl-propionic acid;
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,3-triazol-1-yl-propionic acid; ethyl ester
- 20 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,3-triazol-1-yl-propionic acid;
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrazol-1-yl-propionic acid;
- 25 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,4-triazol-1-yl-propionic acid;
- 5-Methyl-2-phenyl-4-prop-2-enyloxazole
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-2-pyridin-3-yl-propionic acid;
- 30 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyridin-3-yl-propionic acid;

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyridin-3-yl-propionic acid;

2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid;

5 2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid;

2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid;

10 2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid;

2-(5-Methyl-isoxazol-3-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid;

2-(3-Methyl-isoxazol-5-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid;

15 (S)-3-(4-{[(5-Methyl-2-phenyl-oxazol-4-ylmethyl)-amino]-methyl}-phenyl)-2-pyrrol-1-yl-propionic acid;

(S)-3-(4-{[Acetyl-(5-methyl-2-phenyl-oxazol-4-ylmethyl)-amino]-methyl}-phenyl)-2-pyrrol-1-yl-propionic acid;

20 (S)-3-(4-{[Methyl-(5-methyl-2-phenyl-oxazol-4-ylmethyl)-amino]-methyl}-phenyl)-2-pyrrol-1-yl-propionic acid;

(S)-3-(4-{[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-methyl}-phenyl)-2-pyrrol-1-yl-propionic acid;

(S)-3-[4-({Benzyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino)-methyl]-phenyl]-2-pyrrol-1-yl-propionic acid;

25 (S)-3-[4-({Benzoyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino)-methyl]-phenyl]-2-pyrrol-1-yl-propionic acid;

(S)-3-[4-({Acetyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino)-methyl]-phenyl]-2-pyrrol-1-yl-propionic acid;

30 4-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-butyric acid;

3-{1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-2-pyrrol-1-yl-propionic acid;

3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid;

5 3-{3-Methoxy-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

Butane-1-sulfonic acid; (3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-amide

10 N-(3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-methanesulfonamide

3-{3-Iodo-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-phenyl}-2-pyrrol-1-yl-propionic acid;

15 3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-biphenyl-3-yl}-2-pyrrol-1-yl-propionic acid;

20 4-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-butyric acid;

2-Pyrrol-1-yl-4-(4-trifluoromethanesulfonyl-phenyl)-butyric acid; methyl ester

3-{1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-2-pyrrol-1-yl-propionic acid;

25 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid;

30 3-{3-Methoxy-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

Butane-1-sulfonic acid; (3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-amide;

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N-(3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-methanesulfonamide;

3-{3-Iodo-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

5 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

10 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-biphenyl-3-yl}-2-pyrrol-1-yl-propionic acid;

The invention also provides a compound which is:

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

15 (S)-2-(2-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

(S)-2-(3-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester;

20 (S)-3-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester;

N-(S)-(3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionyl)-Benzenesulfonamide

25 N-(S)-(3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionyl)-Methanesulfonamide

(S)-2-(3-Isobutyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

(S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

30 (S)-3-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-cyclohexanecarbonyl-pyrrol-1-yl)-propionic acid methyl ester;

(S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-(2-fluoro-benzyloxy)-phenyl]-propionic acid methyl ester;

(S)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid methyl ester;

5 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyridin-4-yl-propionic acid methyl ester;

2-Methyl-5-(2-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-1-phenyl-ethyl)-2H-tetrazole;

10 2-Methyl-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-thiophen-2-yl-propionic acid methyl ester;

N-(2,2-Dimethyl-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionyl)-methanesulfonamide;

N-(2-Fluoro-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-propionyl)-methanesulfonamide

15 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-[4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-propionic acid methyl ester;

2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester;

20 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-phenyl-propionic acid methyl ester;

(S)-2-(2-Acetyl-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester;

3-[4-[2-(Benzothiazol-2-ylsulfanyl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester;

25 (S)-2-Pyrrol-1-yl-3-[4-[2-(2-trifluoromethyl-phenyl)-ethoxy]-phenyl]-propionic acid methyl ester;

(S)-3-[4-[2-(4-Phenyl-piperazin-1-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester;

30 (S)-3-[4-[2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester;

(S)-3-(4-[2-[(7-Chloro-quinolin-4-yl)-methyl-amino]-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-[4-[2-(4-methyl-2-phenyl-oxazol-5-yl)-ethoxy]-phenyl]-propionic acid methyl ester;

5 (S)-2-[2,5-Dimethyl-3-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester;

3-[4-[2-(2-Phenyl-benzimidazol-1-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester;

10 2-(3-Bromo-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester;

2-(2-Bromo-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester;

2-(2-Chloro-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester;

15 (S)-2-(2-Butyryl-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester;

(S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-[4-(2-fluoro-benzyloxy)-phenyl]-propionic acid methyl ester;

20 (S)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-(2-methyl-5-phenyl-pyrrol-1-yl)-propionic acid methyl ester;

(S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester;

3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester;

25 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-thiophen-2-yl-propionic acid methyl ester;

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyridin-3-yl-propionic acid methyl ester;

30 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-propionic acid methyl ester;

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-(3-triflorophenyl)-propionic acid methyl ester;

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid methyl ester, (R)

2-(4-Methoxy-phenyl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

5 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid methyl ester;

10 2,2-Dimethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

2-Fluoro-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid methyl ester;

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-oxo-pyrrolidin-1-yl)-propionic acid methyl ester;

15 2-Ethyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1,3,4-oxadiazole

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

20 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyridin-3-yl-propionic acid methyl ester;

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid methyl ester;

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-triflorophenyl)-propionic acid methyl ester;

25 (R)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid methyl ester;

S)-2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester; methyl ester

30 3-{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester;

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester;

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(S)-2-(2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl})-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

(S)-2-Ethyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl})-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

5 (S)-2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

(S)-3-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl})-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;

10 2-(3-Bromo-pyrrol-1-yl)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

3,3,3-Trifluoro-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid methyl ester;

2-(4-Benzoyloxy-indol-1-yl)-propionic acid methyl ester;

15 3-(1-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-benzyl})-1H-pyrrol-2-yl)-propionic acid methyl ester;

(1-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl]-1H-indol-5-yloxy)-phenyl-acetic acid methyl ester;

2-(1-Methyl-1H-indol-3-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

20 3-(4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propoxy]-indol-1-yl)-propionic acid methyl ester;

2-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl)-propionic acid methyl ester;

25 3-(4-[2-(2-Trifluoromethyl-phenyl)-ethoxy]-indol-1-yl)-propionic acid methyl ester;

(4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propoxy]-indol-1-yl)-acetic acid methyl ester;

4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl)-acetic acid methyl ester;

30 4-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-butyric acid methyl ester;

- 3-(3-Fluoro-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-(S)-pyrrol-1-yl-propionic acid methyl ester;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyridin-4-yl-propionic acid methyl ester;
- 5 2-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-2H-tetrazole
- 1-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1H-tetrazole
- 2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-
- 10 thiophen-2-yl-propionic acid methyl ester;
- 2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-3-yl-propionic acid methyl ester;
- N-(2,2-Dimethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionyl)-methanesulfonamide
- 15 N-(2-Fluoro-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionyl)-methanesulfonamide
- 3-{3-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-isoxazol-5-yl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester;
- 20 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-phenyl-propionic acid methyl ester;
- 25 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-phenylpropionic acid methyl ester;
- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-
- 30 phenylpropionic acid methyl ester;
- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-phenylpropionic acid methyl ester;

- 3-[6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl]-2-thiophen-2-yl-propionic acid methyl ester;
- 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-acrylic acid methyl ester;
- 5 4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino)-phenylacetic acid methyl ester;
- 4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino)-phenylacetic acid methyl ester; methyl ester
- 10 Methyl-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino)-phenylacetic acid methyl ester;
- 6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-naphthalene-2-carboxylic acid methyl ester;
- 3-[5-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-naphthalen-1-yl]-2-pyrrol-1-yl-propionic acid methyl ester;
- 15 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-1,2,3-triazol-1-yl-propionic acid methyl ester; ethyl ester
- 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-1,2,3-triazol-1-yl-propionic acid methyl ester;
- 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-pyrazol-1-yl-propionic acid methyl ester;
- 20 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-1,2,4-triazol-1-yl-propionic acid methyl ester;
- 5-Methyl-2-phenyl-4-prop-2-enyloxazole
- 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl]-2-pyridin-3-yl-propionic acid methyl ester;
- 25 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-pyridin-3-yl-propionic acid methyl ester;
- 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-pyridin-3-yl-propionic acid methyl ester;
- 30 2-Biphenyl-4-yl-3-[4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-propionic acid methyl ester;

2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid methyl ester;

2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid methyl ester;

5 2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester;

2-(5-Methyl-isoxazol-3-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester;

10 2-(3-Methyl-isoxazol-5-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester;

(S)-3-(4-{[(5-Methyl-2-phenyl-oxazol-4-yl)methyl]-amino}-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-3-(4-{[Acetyl-(5-methyl-2-phenyl-oxazol-4-yl)methyl]-amino}-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester;

15 (S)-3-(4-{[Methyl-(5-methyl-2-phenyl-oxazol-4-yl)methyl]-amino}-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-3-(4-{[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-methyl}-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester;

20 (S)-3-[4-({Benzyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino}-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-3-[4-({Benzoyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino}-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-3-[4-({Acetyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino}-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester;

25 4-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-butyric acid methyl ester;

3-{1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-2-pyrrol-1-yl-propionic acid methyl ester;

30 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

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- 3-{3-Methoxy-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- Butane-1-sulfonic acid methyl ester; (3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-amide
- 5 N-(3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-methanesulfonamide
- 3-{3-Iodo-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 10 2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-biphenyl-3-yl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 15 4-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-butyric acid methyl ester;
- 2-Pyrrol-1-yl-4-(4-trifluoromethanesulfonyl-phenyl)-butyric acid methyl ester; methyl ester
- 3-{1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 20 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 25 3-{3-Methoxy-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- Butane-1-sulfonic acid methyl ester; (3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-amide
- N-(3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-methanesulfonamide
- 30 3-{3-Iodo-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

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3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-phenyl}-
2-pyrrol-1-yl-propionic acid methyl ester;

3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-
pyrrol-1-yl-propionic acid methyl ester;

5 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-biphenyl-3-yl}-2-pyrrol-
1-yl-propionic acid methyl ester;

The invention also provides a pharmaceutical composition comprising a
compound of formula I, II, or III admixed with a carrier, diluent, or excipient.

10 The invention also provides a method of treating, preventing or controlling
non-insulin dependent diabetes mellitus in a mammal comprising administering to
the mammal in need thereof an effective amount of a compound of formula I, II,
or III.

The invention also provides a method of treating, preventing or controlling
15 obesity in a mammal comprising administering to the mammal in need thereof an
effective amount of a compound of formula I, II, or III.

The invention also provides a method of reducing body weight in an obese
mammal comprising administering to the mammal in need thereof an effective
amount of a compound of formula I, II, or III.

20 The invention also provides a method of treating, preventing or controlling
hyperglycemia in a mammal comprising administering to the mammal in need
thereof an effective amount of a compound of formula I, II, or III.

The invention also provides a method of treating, preventing or controlling
hyperlipidemia in a mammal comprising administering to the mammal in need
25 thereof an effective amount of a compound of formula I, II, or III.

The invention also provides a method of treating, preventing or controlling
hypercholesteremia in a mammal comprising administering to the mammal in
need thereof an effective amount of a compound of formula I, II, or III.

30 The invention also provides a method of treating, preventing or controlling
atherosclerosis in a mammal comprising administering to the mammal in need
thereof an effective amount of a compound of formula I, II, or III.

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The invention also provides a method of treating, preventing or controlling hypertriglyceridemia in a mammal comprising administering to the mammal in need thereof an effective amount of a compound of formula I, II, or III.

5 The invention also provides a method of treating, preventing or controlling hyperinsulinemia in a mammal comprising administering to the mammal in need thereof an effective amount of a compound of formula I, II, or III.

10 The invention also provides a method of treating a patient suffering from abnormal insulin and/or evidence of glucose disorders associated with circulating glucocorticoids, growth hormone, catecholamines, glucagon, or parathyroid hormone, comprising administering to the patient a therapeutically effective amount of a compound of formula I, II, or III.

The invention also provides a method of treating insulin resistance syndrome in humans comprising administering to a patient in need of treatment a composition of formula I, II, or III.

15 The invention also provides a method of modulating PPAR activity in a mammal, comprising administering to a mammal an effective amount of a PPAR modulator of formula I, II, or III.

20 The invention also provides a method of lowering blood glucose in a mammal, comprising administering to a mammal an effective amount of a compound of formula I, II, or III.

The invention also provides a method of modulating fat cell differentiation in a mammal, comprising administering to a mammal an effective amount of a compound of formula I, II, or III.

25 The invention also provides a process for preparing a compound of formula I, wherein:

A is aryl and substituted aryl,

heteroaryl and substituted heteroaryl,

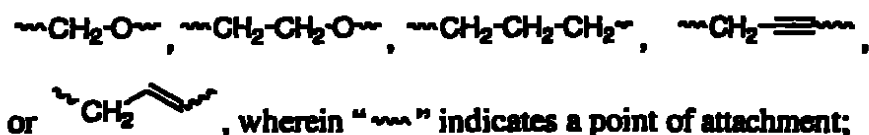
fused heteroaryl and substituted fused heteroaryl,

(C₃-C₇)cycloalkyl and substituted cycloalkyl, or

30 heterocycloalkyl and substituted heterocycloalkyl;

X is a tether 2 to 5 atoms in length selected from

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Q is aryl or substituted aryl;

heteroaryl or substituted heteroaryl;

5

fused heteroaryl, or substituted fused heteroaryl; provided that

when q is a five-membered heteroaryl, the point of attachment

from X to Q is not at the heteroatom of the heteroaryl;

Y and Z are independently absent or are $(\text{CR}_1\text{R}_2)_n$ and $(\text{CR}_3\text{R}_4)_m$, wherein

$\text{R}_1\text{-R}_4$ are each independently H, halo, $(\text{C}_1\text{-C}_6)$ alkyl, hydroxy, $(\text{C}_1\text{-}$

10

$\text{C}_6)$ alkoxy, and m and n are each independently 1, 2, or 3;

B is H, halo, $(\text{C}_1\text{-C}_6)$ alkyl, halo $(\text{C}_1\text{-C}_6)$ alkyl, or $(\text{C}_1\text{-C}_6)$ alkoxy;

D is H, H, -NH-aryl and $\text{-NH-substituted aryl}$,

$(\text{C}_1\text{-C}_6)$ alkanoyl and substituted alkanoyl,

benzoyl and substituted benzoyl,

15

aryl and substituted aryl,

heteroaryl and substituted heteroaryl,

$(\text{C}_3\text{-C}_7)$ cycloalkyl and substituted cycloalkyl, or

heterocycloalkyl and substituted heterocycloalkyl;

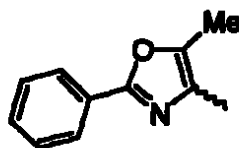
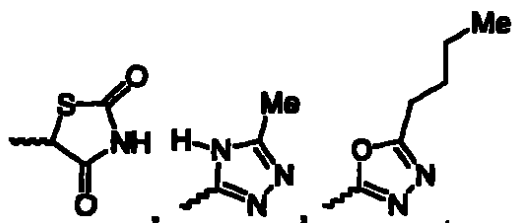
E is COR_5 , wherein R_5 is $(\text{C}_1\text{-C}_6)$ alkyl, OH, $(\text{C}_1\text{-C}_6)$ alkoxy, NR_6R_7 ,

20

wherein R_6 and R_7 are each independently H or $(\text{C}_1\text{-C}_6)$ alkyl, or

one of R_6 and R_7 is H or $(\text{C}_1\text{-C}_6)$ alkyl and the other is SO_2R_8 ,

wherein R_8 is H or $(\text{C}_1\text{-C}_6)$ alkyl, or E is substituted heteroaryl or



provided that when A is $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$ Q is

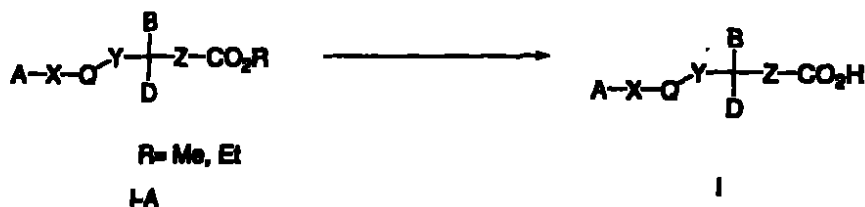
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phenyl, Y and Z are CH_2 , B is H, and E is CO_2H , D is not pyrrolyl;

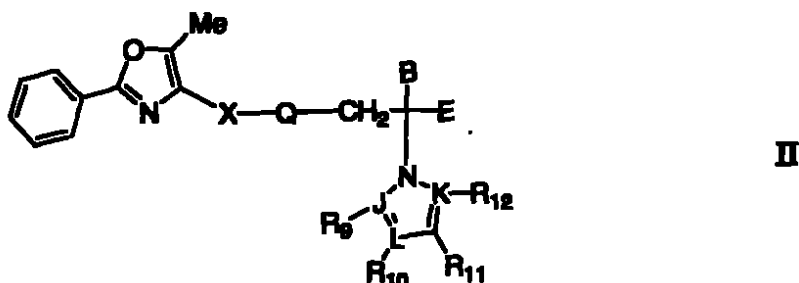
comprising:

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- (a) hydrolyzing the ester moiety in the compound of formula I-A to an acid moiety under basic conditions.



5 The invention also provides a process for preparing a compound of formula II,



wherein:

X is a tether 2 to 5 atoms in length selected from

10

~CH₂-O~, ~CH₂-CH₂-O~, ~CH₂-CH₂-CH₂~, ~CH₂-CH₂-O~,

~CH₂-≡~, or ~CH₂-CH=CH~, wherein "~" indicates a point of attachment;

Q is aryl or substituted aryl;

heteroaryl or substituted heteroaryl;

15

fused heteroaryl, or substituted fused heteroaryl; provided that when q is a five-membered heteroaryl, the point of attachment from X to Q is not at the heteroatom of the heteroaryl;

B is H, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or (C₁-C₆)alkoxy;

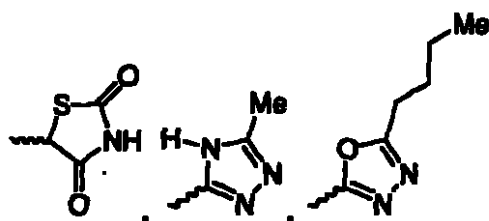
E is COR₃, wherein R₃ is (C₁-C₆)alkyl, OH, (C₁-C₆)alkoxy, NR₆R₇,

20

wherein R₆ and R₇ are each independently H or (C₁-C₆)alkyl, or one of R₆ and R₇ is H or (C₁-C₆)alkyl and the other is SO₂R₈,

wherein R₈ is H or (C₁-C₆)alkyl, or E is substituted heteroaryl or

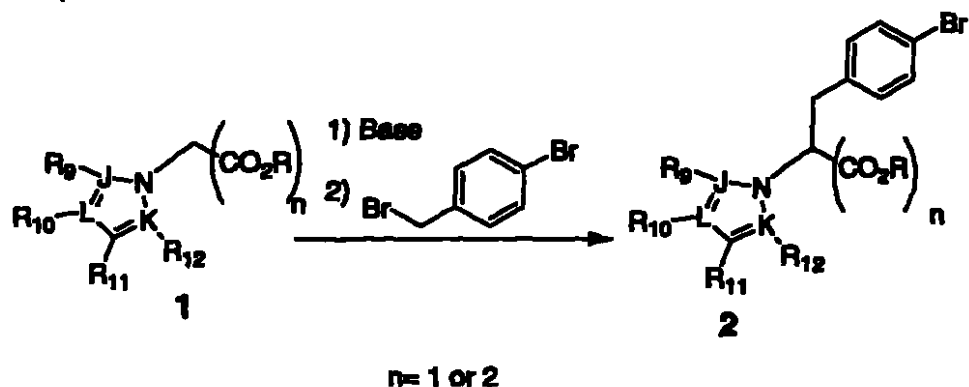
-34-



R_9 - R_{12} are each independently H, halo, aryl, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, (C_1-C_6) alkanoyl, halo (C_1-C_6) alkanoyl, (C_3-C_7) cycloalkylcarbonyl, benzoyl, or halo (C_2-C_6) alkanoyl; and

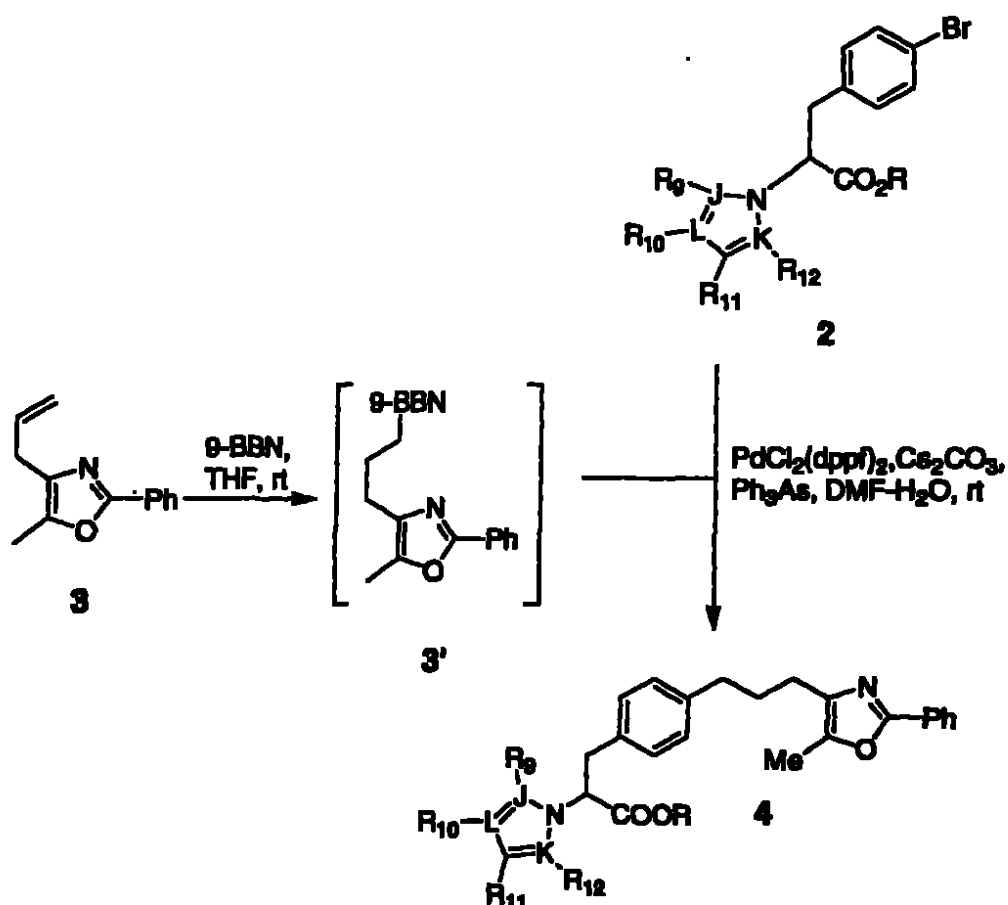
5 one or two of J, K, and L are N,
provided that when J, K, or L are N, R_9 , R_{10} , R_{11} , or R_{12} is absent at that position;
comprising:

(a) alkylating 1 with 2 and decarboxylating 2 when $n=2$;

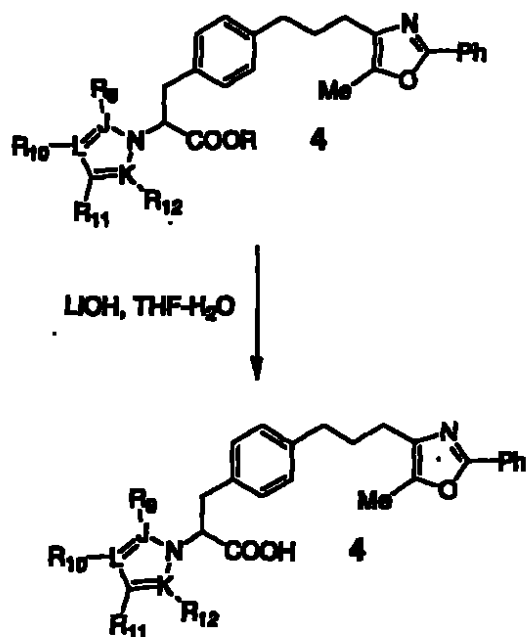


10 (b) coupling 2 with 3' to form 4;

-35-

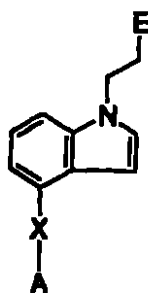


(c) hydrolyzing the ester moiety in 4 to form a compound of the invention.



5 The invention also provides a process for preparing a compound of formula (III)

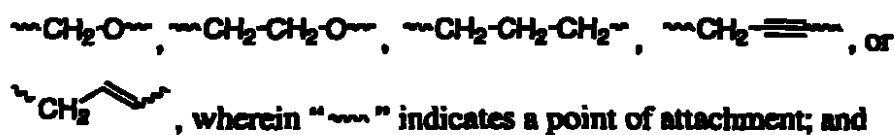
-36-



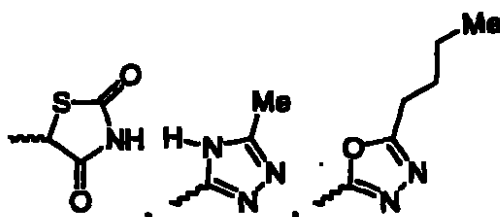
III

wherein A is aryl and substituted aryl,
heteroaryl and substituted heteroaryl,
fused heteroaryl and substituted fused heteroaryl,
(C₃-C₇)cycloalkyl and substituted cycloalkyl, or
heterocycloalkyl and substituted heterocycloalkyl;

X is a tether 2 to 5 atoms in length selected from



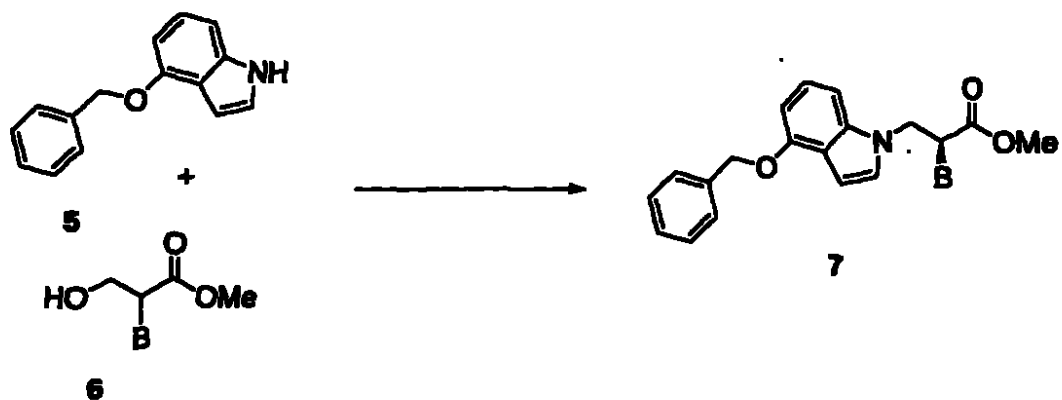
E is COR₅, wherein R₅ is (C₁-C₆)alkyl, OH, (C₁-C₆)alkoxy, NR₆R₇,
wherein R₆ and R₇ are each independently H or (C₁-C₆)alkyl, or
one of R₆ and R₇ is H or (C₁-C₆)alkyl and the other is SO₂R₈,
wherein R₈ is H or (C₁-C₆)alkyl, or E is substituted heteroaryl or



comprising:

- (a) preparing compound 6 by coupling beta hydroxy ester 6 with
indole derivative 5:

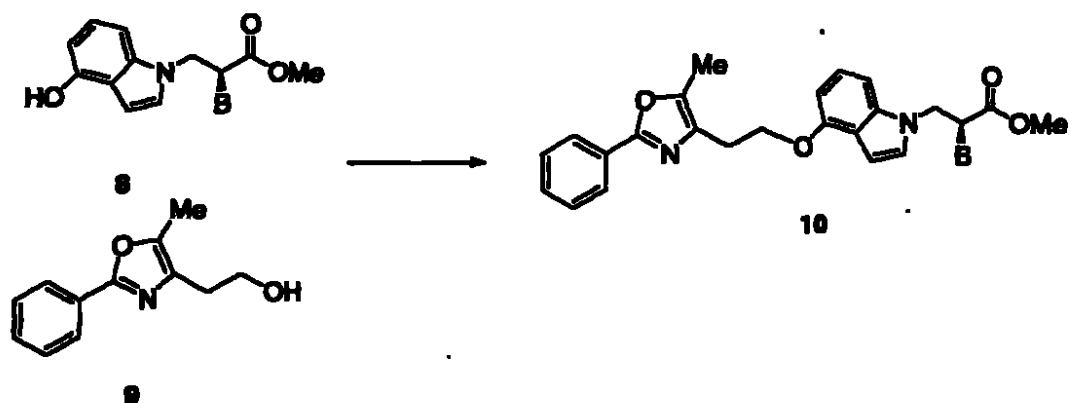
-37-



(b) removing the benzyl group in 7 to provide 8;



(c) coupling 8 with 9 to provide 10;



(d) hydrolyzing the ester moiety in 10 to form a compound of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, alkenyl, alkynyl, etc. denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to.

The term "(C₁-C₆)alkyl" means a straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, and n-hexyl.

5 The term "heterocycloalkyl" means a monocyclic, fused, bridged, or spiro bicyclic heterocyclic ring system. Monocyclic heterocyclic rings contain from about 3 to 12 ring atoms, with from 1 to 5 heteroatoms selected from N, O, and S, and preferably from 3 to 7 member atoms, in the ring. Bicyclic heterocyclics contain from 7 to 17 member atoms, preferably 7 to 12 member atoms, in the ring. Bicyclic heterocyclics contain from about 7 to about 17 ring atoms, preferably
10 from 7 to 12 ring atoms. Bicyclic heterocyclics rings may be fused, spiro, or bridged ring systems. Examples of heterocyclic groups include cyclic ethers (oxiranes) such as ethyleneoxide, tetrahydrofuran, dioxane, and substituted cyclic ethers, wherein the substituents are those described above for the alkyl and cycloalkyl groups. Typical substituted cyclic ethers include propyleneoxide,
15 phenyloxirane (styrene oxide), cis-2-butene-oxide (2,3-dimethyloxirane), 3-chlorotetrahydrofuran, 2,6-dimethyl-1,4-dioxane, and the like. Heterocycloalkyl groups containing nitrogen are groups such as pyrrolidine, piperidine, piperazine, tetrahydrotriazine, tetrahydropyrazole, and substituted groups such as 3-aminopyrrolidine, 4-methylpiperazin-1-yl, and the like. Typical sulfur containing
20 heterocycles include tetrahydrothiophene, dihydro-1,3-dithiol-2-yl, and hexahydrothiepin-4-yl. Other commonly employed heterocycles include dihydro-oxathiol-4-yl, tetrahydro-oxazolyl, tetrahydro-oxadiazolyl, tetrahydro-dioxazolyl, tetrahydro-oxathiazolyl, hexahydrotriazinyl, tetrahydro-oxazinyl, morpholinyl, thiomorpholinyl, tetrahydropyrimidinyl, dioxolinyl, octahydrobenzofuranyl, octahydrobenzimidazolyl, and octahydrobenzothiazolyl. For heterocycles
25 containing sulfur, the oxidized sulfur heterocycles containing SO or SO₂ groups are also included. Examples include the sulfoxide and sulfone forms of tetrahydrothiophene.

30 The term "aryl" means a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms, and being unsubstituted or substituted with up to 3 of the substituent groups recited above for alkyl, alkenyl, and alkynyl. Examples of aryl groups include phenyl, 2,6-dichlorophenyl, 3-methoxyphenyl, naphthyl,

4-thionaphthyl, tetralinyl, anthracinyl, phenanthrenyl, benzonaphthenyl, fluorenyl, 2-acetamidofluoren-9-yl, and 4'-bromobiphenyl.

The term "heteroaryl" means an aromatic cyclic or fused polycyclic ring system having from 1 to 8 heteroatoms selected from N, O, and S. The heteroaryl groups or fused heteroaryl groups may be unsubstituted or substituted by 1 to 3 substituents selected from those described above for alkyl, alkenyl, and alkynyl, for example, cyanothienyl and formylpyrrolyl.

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

Aromatic fused heteroaryl groups of from 8 to 20 atoms include but are not limited to 1-, 2-, 3-, 5-, 6-, 7-, or 8-indoliziny, 1-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-indazolyl, 2-, 4-, 5-, 6-, 7-, or 8-puriny, 1-, 2-, 3-, 4-, 6-, 7-, 8-, or 9-quinoliziny, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinoliyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinoliyl, 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl, 2-, 3-, 4-, 5-, or 6-naphthyridiny, 2-, 3-, 5-, 6-, 7-, or 8-quinazolinyl, 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl, 2-, 4-, 6-, or 7-pteridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-4aH carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-carbzaolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-carboliny, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenanthridiny, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-acridiny, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-perimidiny, 2-, 3-, 4-, 5-, 6-, 8-, 9-, or 10-phenathroliny, 1-, 2-, 3-, 4-, 6-, 7-, 8-, or 9-phenazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenothiaziny, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenoxazinyl, 2-, 3-, 4-, 5-, 6-, or 1-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-benzisoquinolinyl, 2-, 3-, 4-, or thieno[2,3-b]furanyl, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-7H-pyrazino[2,3-c]carbazolyl, 2-, 3-, 5-, 6-, or 7-2H-furo[3,2-b]pyranyl, 2-, 3-, 4-, 5-, 7-, or 8-5H-pyrido[2,3-d]-o-oxazinyl, 1-, 3-, or 5-1H-pyrazolo[4,3-d]-oxazolyl, 2-, 4-, or 5-4H-imidazo[4,5-d]thiazolyl, 3-, 5-, or 8-pyrazino[2,3-d]pyridazinyl, 2-, 3-, 5-, or 6-imidazo[2,1-b]thiazolyl, 1-, 3-, 6-, 7-, 8-, or 9-furo[3,4-c]cinnolinyl, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 9-, 10-, or 11-4H-pyrido[2,3-c]carbazolyl, 2-, 3-, 6-, or 7-imidazo[1,2-b][1,2,4]triaziny, 7-benzo[b]thienyl, 2-,

4-, 5-, 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 5-, 6-, or 7-benzothiazolyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-benzoxapinyl, 2-, 4-, 5-, 6-, 7-, or 8-benzoxazinyl, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-1*H*-pyrrolo[1,2-*b*][2]benzazapinyl. Typical fused heteroaryl groups include, but are not limited to

2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[*b*]thienyl, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 5-, 6-, or 7-benzothiazolyl.

Other heteroaryl groups include the following groups wherein “~” indicates the point of attachment.



The alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl can be substituted with 1 to 4 groups selected from halo, hydroxy, cyano, C₁-C₆ alkoxy, nitro, nitroso, amino, C₁-C₆ alkylamino, di-C₁-C₆ alkylamino, carboxy, C₁-C₆ C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, aminocarbonyl, halomethyl, dihalomethyl, trihalomethyl, haloethyl, dihaloethyl, trihaloethyl, tetrahaloethyl, pentahaloethyl, thiol, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfinyl, and aminosulfonyl. Examples of substituted alkyl groups include fluoromethyl, tribromomethyl, hydroxymethyl, 3-methoxypropyl, 3-carboxypentyl, 3,5-dibromo-6-aminocarbonyldecyl, and 4-ethylsulfinyloctyl.

The term “prodrug” denotes a compound that is converted in vivo to an active compound. The term “prodrug group” denotes a moiety that is converted in vivo into the active compound of formula I wherein E is substituted heteroaryl or —CO₂H. Such groups are generally known in the art and include ester forming groups, that form an ester prodrug, such as benzyloxy, di(C₁-C₆)alkylaminoethyloxy; acetoxymethyl, pivaloyloxymethyl, phthalidoyl, ethoxycarbonyloxyethyl, 5-methyl-2-oxo-1,3-dioxol-4-yl methyl, and (C₁-C₆)alkoxy optionally substituted by N-morpholino and amide-forming groups such as di(C₁-C₆)alkylamino. Other prodrug groups include C₁-C₆ alkoxy, and O⁻M⁺ where M⁺ represents a cation. Preferred cations include sodium, potassium,

and ammonium. Other cations include magnesium and calcium. Further prodrug groups include O^-M^{++} , where M^{++} is a divalent cation such as magnesium or calcium.

5 The term "diabetes" refers to a metabolic disorder in which there is impaired glucose utilization inducing hyperglycemia. An overview of the pathogenesis and morphology of diabetes and its late complications, particularly NIDDM, is available to practitioners of the art, for instance, in Robins' Pathologic Basis of Disease (5th Ed., pp. 910-922). Other metabolic disorders associated with impaired glucose utilization and insulin resistance include IRS, described
10 previously. In addition to the major late-stage complications of NIDDM (diabetic angiopathy, atherosclerosis, diabetic nephropathy, diabetic neuropathy, and diabetic ocular complications such as retinopathy, cataract formation and glaucoma), many other conditions are linked to NIDDM, including dyslipidemia glucocorticoid induced insulin resistance, dyslipidemia, polycystic ovarian
15 syndrome, obesity, hyperglycemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hyperinsulinemia, and hypertension. Brief definitions of these conditions are available in any medical dictionary, for instance, Stedman's Medical Dictionary (Xth Ed.).

20 As used herein, the term "modulate" means to change (something such as an action or a process); to make it more suitable for its situation. Cambridge Dictionaries Online ([http:// dictionary. cambridge. org/define. asp?key=modulate*2+0](http://dictionary.cambridge.org/define.asp?key=modulate*2+0) last visited June 20, 2002).

25 It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution
30 of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine activity or cytotoxicity

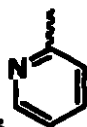
-42-

using the standard tests described herein, or using other similar tests which are well known in the art.

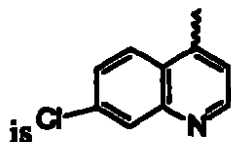
Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents

Specifically, (C₁–C₆)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; (C₁–C₆)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy; halo(C₁–C₆)alkyl can be iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trichloromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl; (C₃–C₇)heterocycloalkyl can be pyrrolidinyl, piperidinyl, furanyl, pyranyl, thiofuranyl, and thiopyranyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

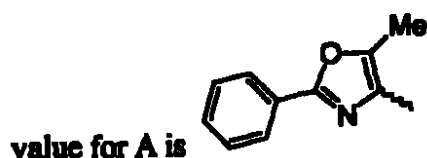
A specific value for A is



. Another specific value for A

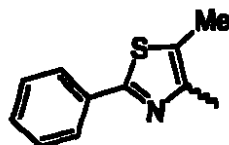


is Cl-wherein "wavy" indicates a point of attachment. Another specific

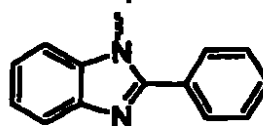


value for A is

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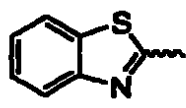
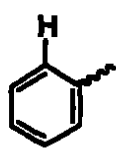
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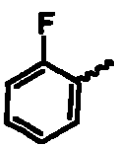
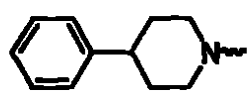


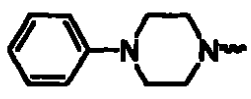
specific value for A is

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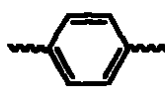
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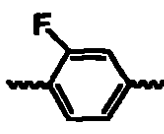
 . Another specific value for A is  . Another specific value

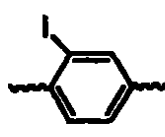
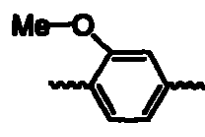
for A is  . Another specific value for A is ,  . Still

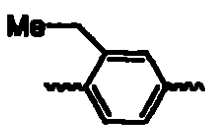
another specific value for A is  .

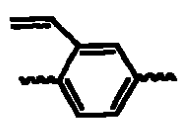
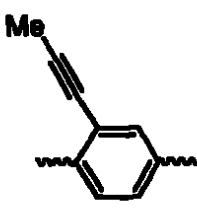
5 A specific value for X is $\sim\text{CH}_2\text{O}\sim$ wherein " $\sim$ " indicates a point of attachment. Another specific value for X is $\sim\text{CH}_2\text{CH}_2\text{O}\sim$. Another specific value for X is $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$. Another specific value for X is $\sim\text{CH}_2\text{CH}_2\text{O}\sim$. Another specific value for X is $\sim\text{CH}_2\equiv\sim$. Still another specific value for X is  .

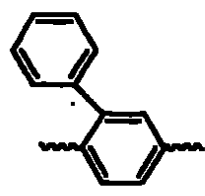
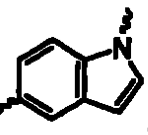
A specific value for Q is  wherein " $\sim$ " indicates a point of

10 attachment. Another specific value for Q is  . Another specific value

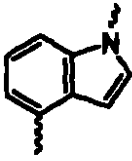
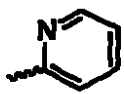
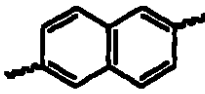
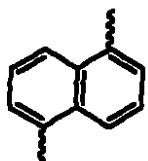
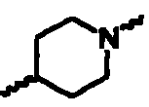
for Q is  . Another specific value for Q is  . Another

specific value for Q is  . Another specific value for Q is

 . Another specific value for Q is  . Another specific

value for Q is  . Another specific value for Q is  .

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Another specific value for Q is . Another specific value for Q is . Another specific value for Q is . Another specific value for Q is . Still another specific value for Q is .

A specific value for X is CH₂.

5

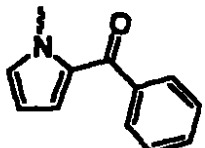
A specific value for Y is CH₂.

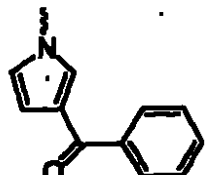
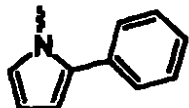
A specific value for B is H. Another specific value for B is F. Another specific value for B is methyl. Another specific value for B is methoxy.

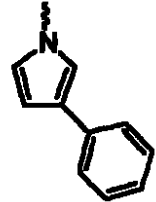
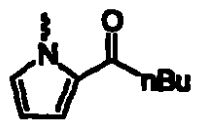
A specific value for D is H. Another specific value for D is Me. Another

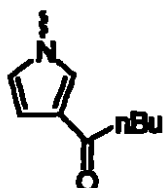
specific value for D is  wherein "~~~~" indicates a point of attachment.

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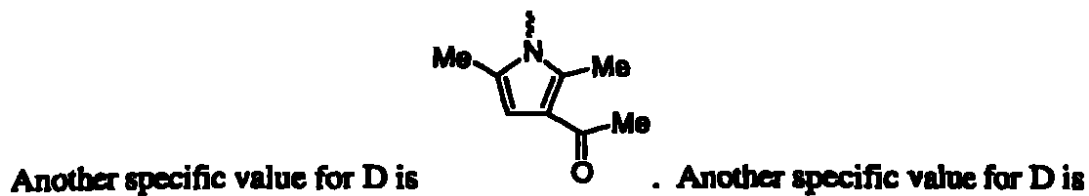
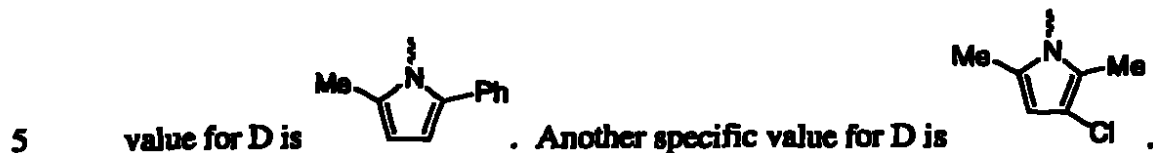
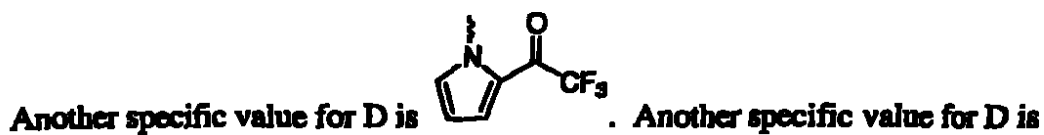
Another specific value for D is . Another specific value for D is

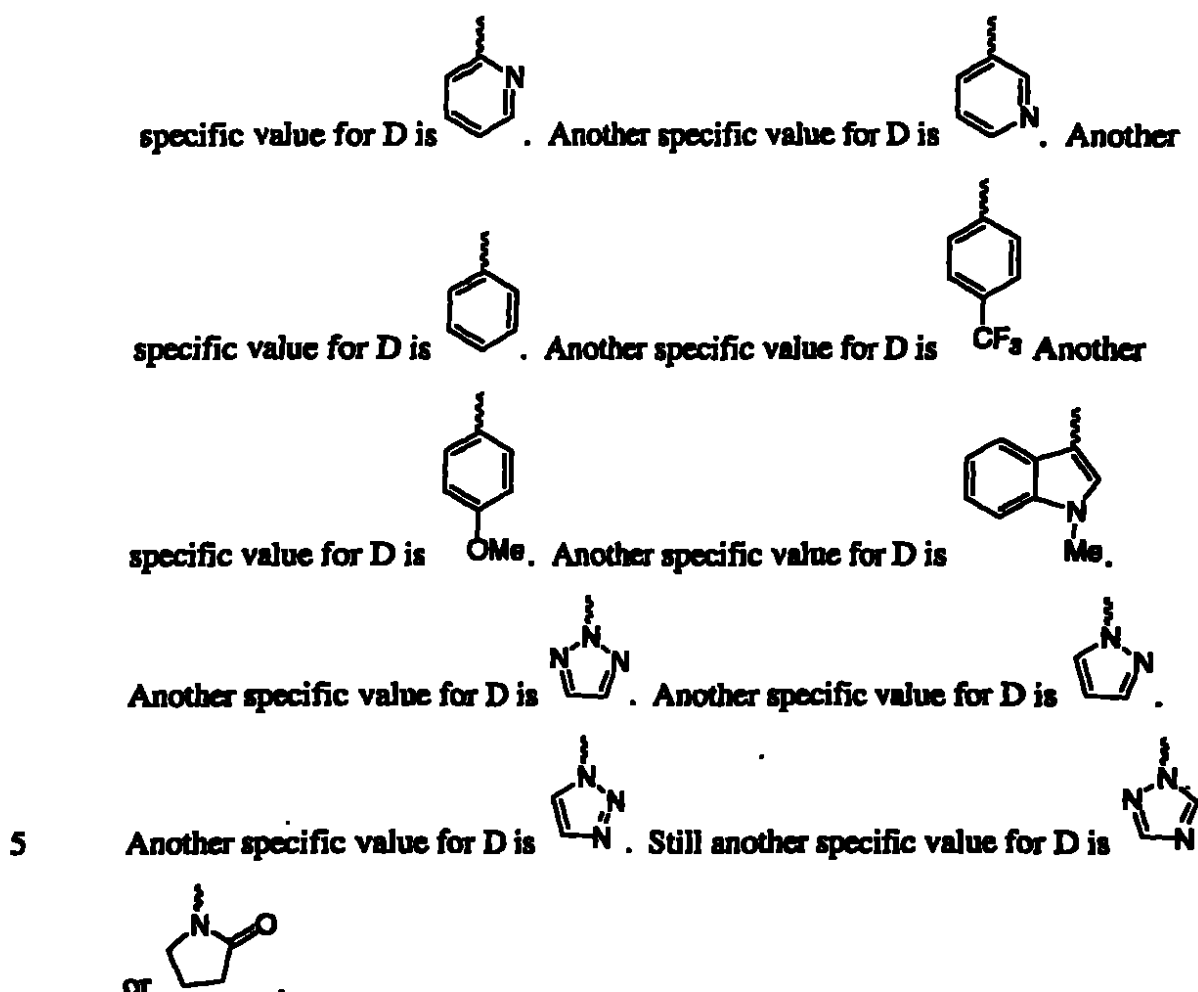
. Another specific value for D is . Another specific

value for D is . Another specific value for D is .

Another specific value for D is . Another specific value for D is

-45-

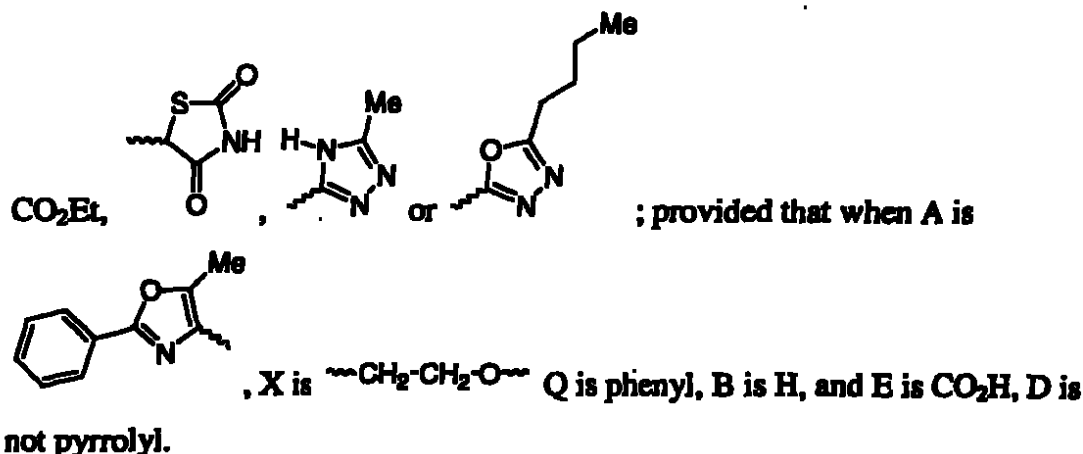




A group of compounds of the invention are compounds of formula I wherein A is aryl or substituted aryl, heteroaryl or substituted heteroaryl, fused heteroaryl or substituted fused heteroaryl, or heterocycloalkyl and substituted heterocycloalkyl; X is a tether 2 to 5 atoms in length selected from $\sim\text{CH}_2\text{O}\sim$, $\sim\text{CH}_2\text{CH}_2\text{O}\sim$, $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$, $\sim\text{CH}_2\text{C}\equiv\text{C}\sim$, or $\sim\text{CH}_2\text{CH}=\text{CH}\sim$, wherein "∼" indicates a point of attachment; Q is aryl or substituted aryl; heteroaryl or substituted heteroaryl; fused heteroaryl, or substituted fused heteroaryl; provided that when Q is a five-membered heteroaryl, the point of attachment from X to Q is not at the heteroatom of the heteroaryl; Y and Z are independently absent or are $(\text{CR}_1\text{R}_2)_n$ and $(\text{CR}_3\text{R}_4)_m$ wherein $\text{R}_1\text{-R}_4$ are each independently H, halo, $(\text{C}_1\text{-C}_6)$ alkyl, hydroxy, $(\text{C}_1\text{-C}_6)$ alkoxy, and m and n are each independently 1, 2, or 3; B is H, halo, $(\text{C}_1\text{-C}_6)$ alkyl, halo $(\text{C}_1\text{-C}_6)$ alkyl, or $(\text{C}_1\text{-C}_6)$ alkoxy; D is H, aryl and

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substituted aryl, or heteroaryl and substituted heteroaryl; E is CO₂H, CO₂Me,

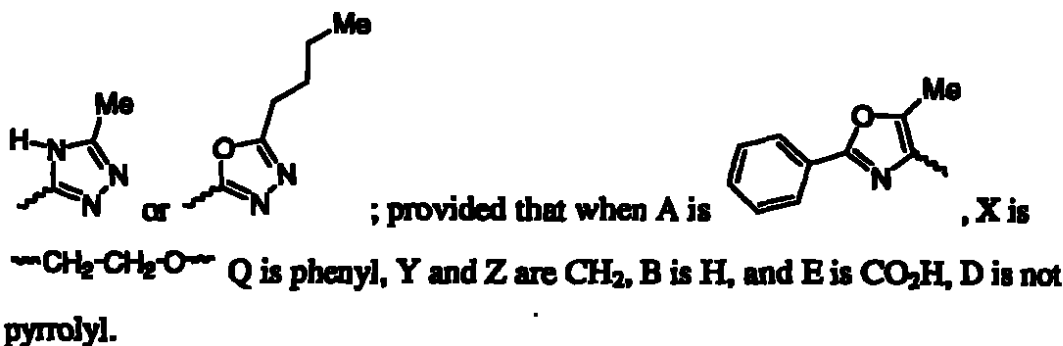
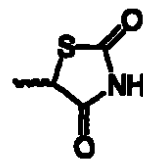


5 Another group of compounds of the invention are compounds of formula I wherein A is aryl or substituted aryl, heteroaryl or substituted heteroaryl, fused heteroaryl or substituted fused heteroaryl, or heterocycloalkyl and substituted heterocycloalkyl; X is a tether 2 to 5 atoms in length selected from



10 “ $\sim$ ” indicates a point of attachment; Q is aryl or substituted aryl; heteroaryl or substituted heteroaryl; fused heteroaryl, or substituted fused heteroaryl; provided that when Q is a five-membered heteroaryl, the point of attachment from X to Q is not at the heteroatom of the heteroaryl; Y and Z are independently absent or are CH₂; B is H, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or (C₁-C₆)alkoxy; D is H,

15 heteroaryl or substituted heteroaryl; and E is CO₂H, CO₂Me, CO₂Et,

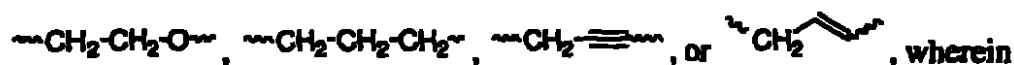


20 Another group of compounds of the invention are compounds of formula I wherein A is aryl or substituted aryl, heteroaryl or substituted heteroaryl, fused heteroaryl or substituted fused heteroaryl, or heterocycloalkyl and substituted

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heterocycloalkyl; X is a tether 2 to 5 atoms in length selected from



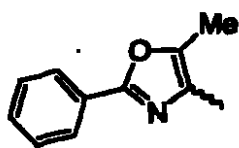
" $\sim$ " indicates a point of attachment; Q is phenyl or substituted phenyl, naphthyl or substituted naphthyl, indolyl or substituted indolyl, pyridyl or substituted pyridyl, or piperidinyll or substituted piperidinyll; Y and Z are independently absent or are CH₃; B is H, F, methyl, or methoxy. D is H, substituted pyrrolyl, pyridyl, substituted phenyl, diazoyl, or triazoyl; and E is CO₂H, CO₂Me, or CO₂Et.

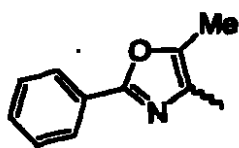
Another group of compounds of the invention are compounds of formula I wherein A is aryl or substituted aryl, heteroaryl or substituted heteroaryl, fused heteroaryl or substituted fused heteroaryl, or heterocycloalkyl and substituted heterocycloalkyl; X is a tether 2 to 5 atoms in length selected from



" $\sim$ " indicates a point of attachment; Q is phenyl or substituted phenyl, naphthyl or substituted naphthyl, indolyl or substituted indolyl, pyridyl or substituted pyridyl, or piperidinyll or substituted piperidinyll; Y and Z are independently absent or are CH₃; B is H, F, methyl, or methoxy. D is H, substituted pyrrolyl, pyridyl, substituted phenyl, diazoyl, or triazoyl; and E is CO₂H, CO₂Me, or CO₂Et.

Another group of compounds of the invention are compounds of formula I

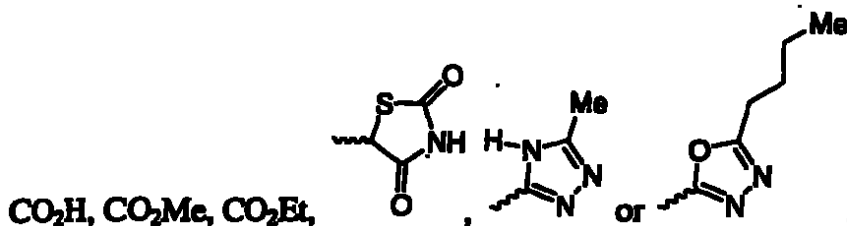


wherein A is , wherein " $\sim$ " indicates the point of attachment; X is $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-}\equiv\sim$, or

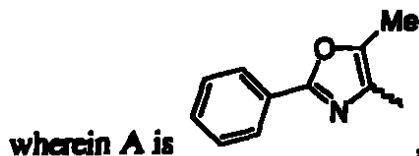
$\sim\text{CH}_2\text{-}\text{CH}=\text{CH}\sim$; Q is aryl or substituted aryl, heteroaryl or substituted heteroaryl, or fused heteroaryl, or substituted fused heteroaryl; provided that when Q is a five-membered heteroaryl, the point of attachment from X to Q is not at the heteroatom of the heteroaryl; B is H, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or (C₁-C₆)alkoxy;

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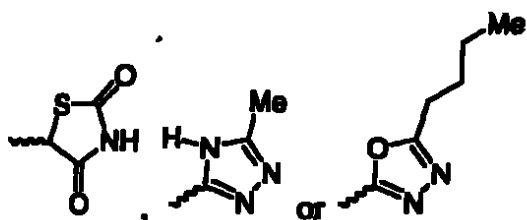
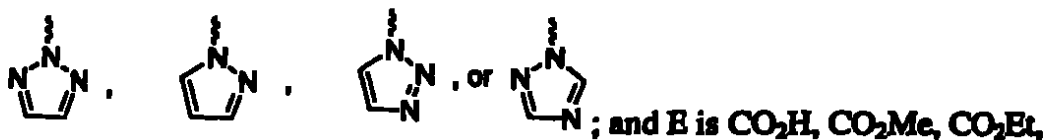
D is heteroaryl or substituted heteroaryl; Y is CH₂; Z is CH₂ or is absent; E is



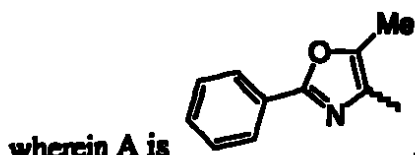
Another group of compounds of the invention are compounds of formula I



- 5 wherein "~~~~" indicates the point of attachment; X is ~CH₂-CH₂-CH₂~, or ~CH₂-CH₂-O~; Q is aryl or substituted aryl, heteroaryl or substituted heteroaryl, or fused heteroaryl, or substituted fused heteroaryl; provided that when Q is a five-membered heteroaryl, the point of attachment from X to Q is not at the heteroatom of the heteroaryl; B is H; Y is CH₂; Z is CH₂ or is absent; D is phenyl or unsubstituted pyrrolyl or pyrrolyl substituted with 1, 2, 3, or 4 groups selected from methyl, bromo, chloro, acetyl, trifluoroacetyl, benzoyl, cyclohexanecarbonyl, and propionyl; or
- 10

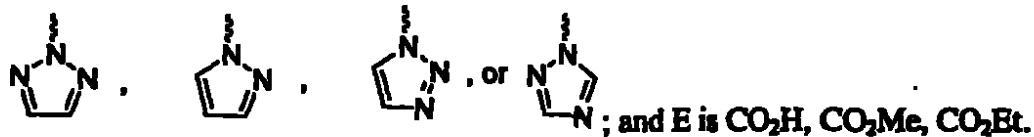


Another group of compounds of the invention are compounds of formula I

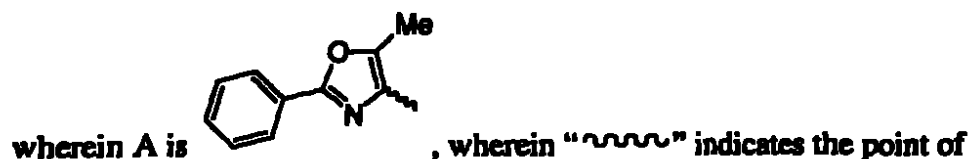


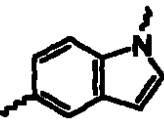
- wherein "~~~~" indicates the point of attachment; X is ~CH₂-CH₂-CH₂~ or -(CH₂)₂-O-; Q is phenyl, indolyl, pyrrolyl or pyridinyl, any of which may be substituted or unsubstituted; Y is —

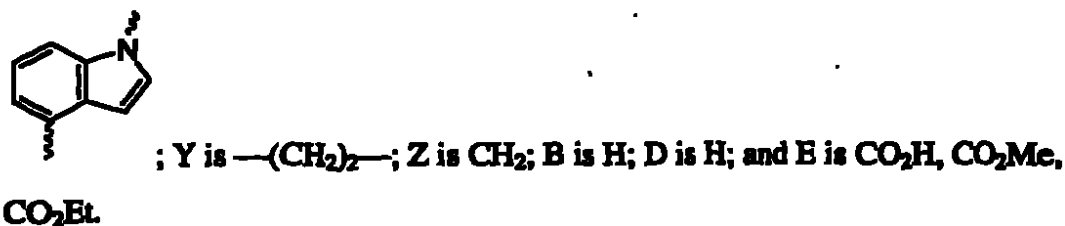
$(\text{CH}_2)_2$; Z is CH_2 or is absent; B is H; D is H,



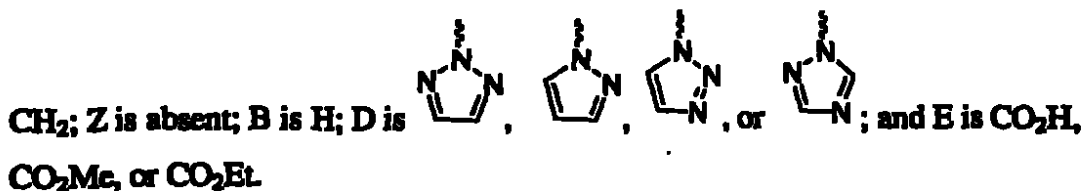
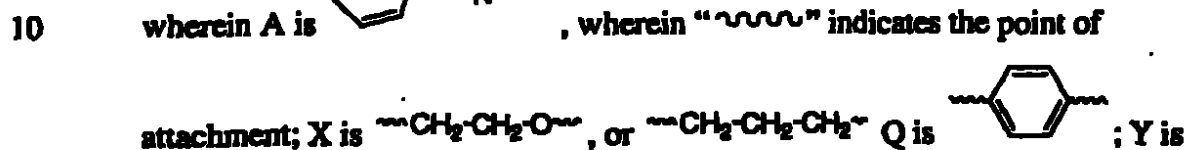
Another group of compounds of the invention are compounds of formula I



5 attachment; X is $\text{---CH}_2\text{---CH}_2\text{---CH}_2\text{---}$ or $\text{---(CH}_2)_2\text{---O---}$; Q is  or



Another group of compounds of the invention are compounds of formula I

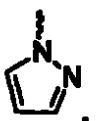
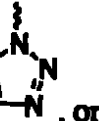
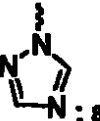


Another group of compounds of the invention are compounds of formula I

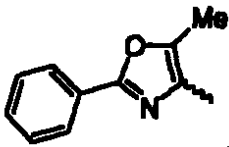


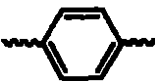
-51-

attachment; X is $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$ Q is ; Y is CH_2 ; Z is absent; B is

H; D is , , , or ; and E is CO_2H .

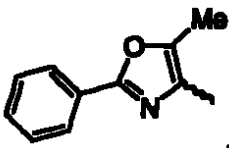
Another group of compounds of the invention are compounds of formula I

wherein A is , wherein "~~~~" indicates the point of

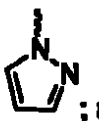
5 attachment; X is $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$ Q is ; Y is CH_2 ; Z is absent; B is

H; D is , or ; and E is CO_2H , CO_2Me , or CO_2Et .

Another group of compounds of the invention are compounds of formula I

wherein A is , wherein "~~~~" indicates the point of

attachment; X is $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$ Q is ; Y is CH_2 ; B is H; D is ,

10  or ; and E is CO_2H .

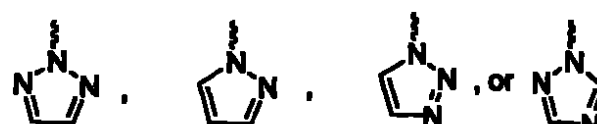
A group of compounds of the invention are compounds of formula II

wherein X is a tether 2 to 5 atoms in length selected from $\sim\text{CH}_2\text{O}\sim$,

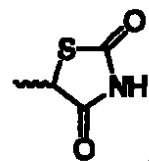
$\sim\text{CH}_2\text{CH}_2\text{O}\sim$, $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$, $\sim\text{CH}_2\equiv\sim$, or $\sim\text{CH}_2\text{CH}=\sim$, wherein

15 "~~~~" indicates a point of attachment; Q is aryl or substituted aryl; heteroaryl or substituted heteroaryl; fused heteroaryl, or substituted fused heteroaryl; provided that when Q is a five-membered heteroaryl, the point of attachment from X to Q is not at the heteroatom of the heteroaryl; B is H, halo, $(\text{C}_1\text{-C}_6)\text{alkyl}$, halo $(\text{C}_1\text{-C}_6)\text{alkyl}$, or $(\text{C}_1\text{-C}_6)\text{alkoxy}$; and one or two of three of J, K and L, are N to form

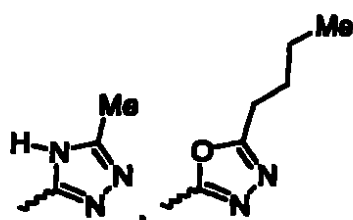
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 ; and E is COR₅, wherein R₅ is (C₁-C₆)alkyl, OH, (C₁-C₆)alkoxy, NR₆R₇, wherein R₆ and R₇ are each independently H or (C₁-C₆)alkyl, or one of R₆ and R₇ is H or (C₁-C₆)alkyl and the other is SO₂R₈,

wherein R₈ is H or (C₁-C₆)alkyl, or E is substituted heteroaryl or

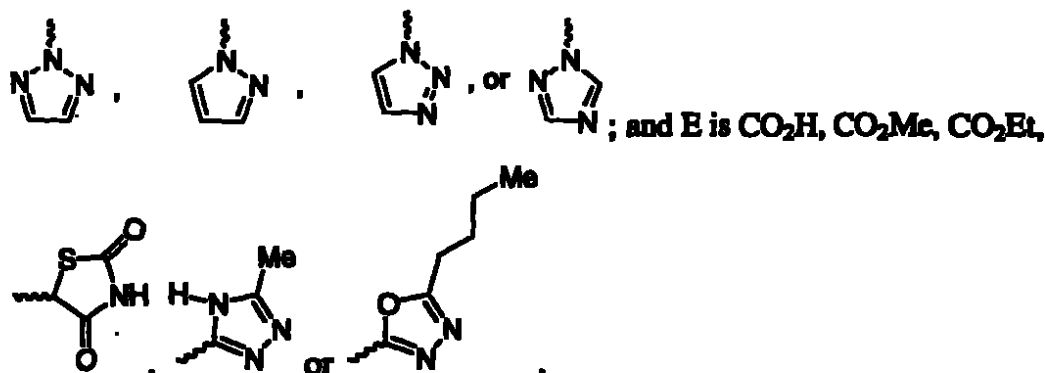


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Another group of compounds of the invention are compounds of formula II wherein X is a tether 2 to 5 atoms in length selected from $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\text{-}\equiv\sim$, or $\sim\text{CH}_2\text{-CH=CH}\sim$, wherein " $\sim$ " indicates a point of attachment; Q is aryl or substituted aryl; heteroaryl or substituted heteroaryl; fused heteroaryl, or substituted fused heteroaryl; provided that when Q is a five-membered heteroaryl, the point of attachment from X to Q is not at the heteroatom of the heteroaryl; B is H, fluoro, methyl, trifluoromethyl, or methoxy; one or two of three of J, K and L, are N to form

15

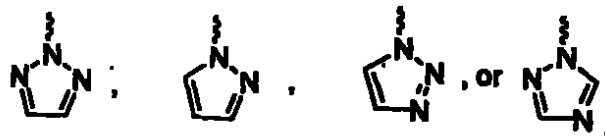


Another group of compounds of the invention are compounds of formula II wherein X is a tether 2 to 5 atoms in length selected from $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-}\equiv\sim$, or $\sim\text{CH}_2\text{-CH=CH}\sim$, wherein " $\sim$ " indicates a point

-53-

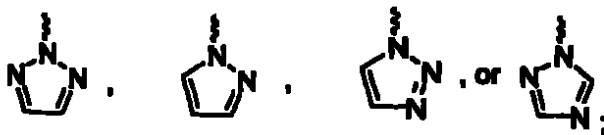
of attachment; Q is aryl or substituted aryl; heteroaryl or substituted heteroaryl; fused heteroaryl or substituted fused heteroaryl; provided that when Q is a five-membered heteroaryl, the point of attachment from X to Q is not at the heteroatom of the heteroaryl; B is H, fluoro, methyl, trifluoromethyl, or methoxy; one or two

5 of three of J, K and L, are N to form and E is CO₂H, CO₂Me, or CO₂Et.



Another group of compounds of the invention are compounds of formula II wherein X is a tether 2 to 5 atoms in length selected from $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$ or $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, wherein " $\sim$ " indicates a point of attachment; Q is aryl or substituted aryl; B is H, fluoro, methyl, trifluoromethyl, or methoxy; one or two of

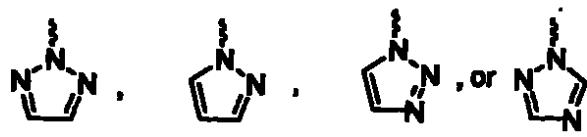
10 three of J, K and L, are N to form and E is CO₂H, CO₂Me, or CO₂Et.



Another group of compounds of the invention are compounds of formula II wherein X is a tether 2 to 5 atoms in length selected from $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$ or $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, wherein " $\sim$ " indicates a point of attachment; Q is aryl or substituted aryl; B is H; one or two of three of J, K and L, are N to form

15

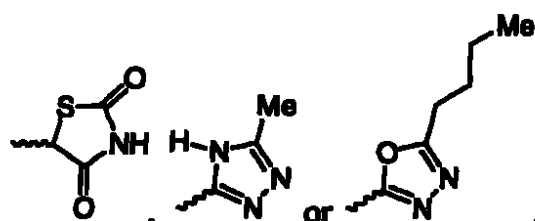
three of J, K and L, are N to form and E is CO₂H.



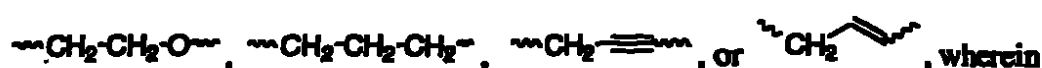
20 A group of compounds of the invention are compounds of formula III wherein A is aryl or substituted aryl; heteroaryl or substituted heteroaryl, fused heteroaryl or substituted fused heteroaryl, or heterocycloalkyl and substituted heterocycloalkyl; X is a tether 2 to 5 atoms in length selected from $\sim\text{CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\text{-}\equiv\sim$, or $\sim\text{CH}_2\text{-CH=CH}\sim$, wherein

-54-

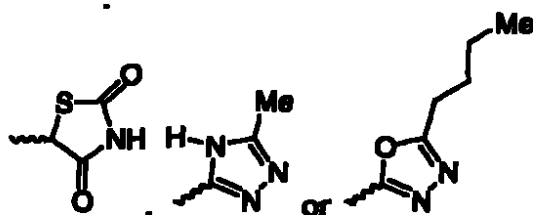
"~" indicates a point of attachment; and E is CO₂H, CO₂Me, CO₂Et,



Another group of compounds of the invention are compounds of formula III wherein A is aryl or substituted aryl; heteroaryl or substituted heteroaryl, fused heteroaryl or substituted fused heteroaryl, or heterocycloalkyl and substituted heterocycloalkyl; X is a tether 2 to 5 atoms in length selected from



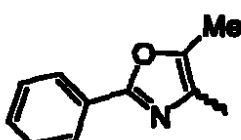
"~" indicates a point of attachment; and E is CO₂H, CO₂Me, CO₂Et,



Another group of compounds of the invention are compounds of formula III wherein A is aryl or substituted aryl; heteroaryl or substituted heteroaryl, fused heteroaryl or substituted fused heteroaryl, or heterocycloalkyl and substituted heterocycloalkyl; X is a tether 2 to 5 atoms in length selected from -CH₂-CH₂-O- or -CH₂-CH₂-CH₂-, wherein "~" indicates a point of attachment; and E is CO₂H, CO₂Me, or CO₂Et.

Another group of compounds of the invention are compounds of formula III wherein A is heteroaryl or substituted heteroaryl, X is a tether 2 to 5 atoms in length selected from -CH₂-CH₂-O- or -CH₂-CH₂-CH₂-, wherein "~" indicates a point of attachment; and E is CO₂H, CO₂Me, or CO₂Et.

Another group of compounds of the invention are compounds of formula

III wherein A is , wherein "~~~~" indicates the point of attachment; X is -CH₂-CH₂-CH₂- or -CH₂-CH₂-O- and E is CO₂H.

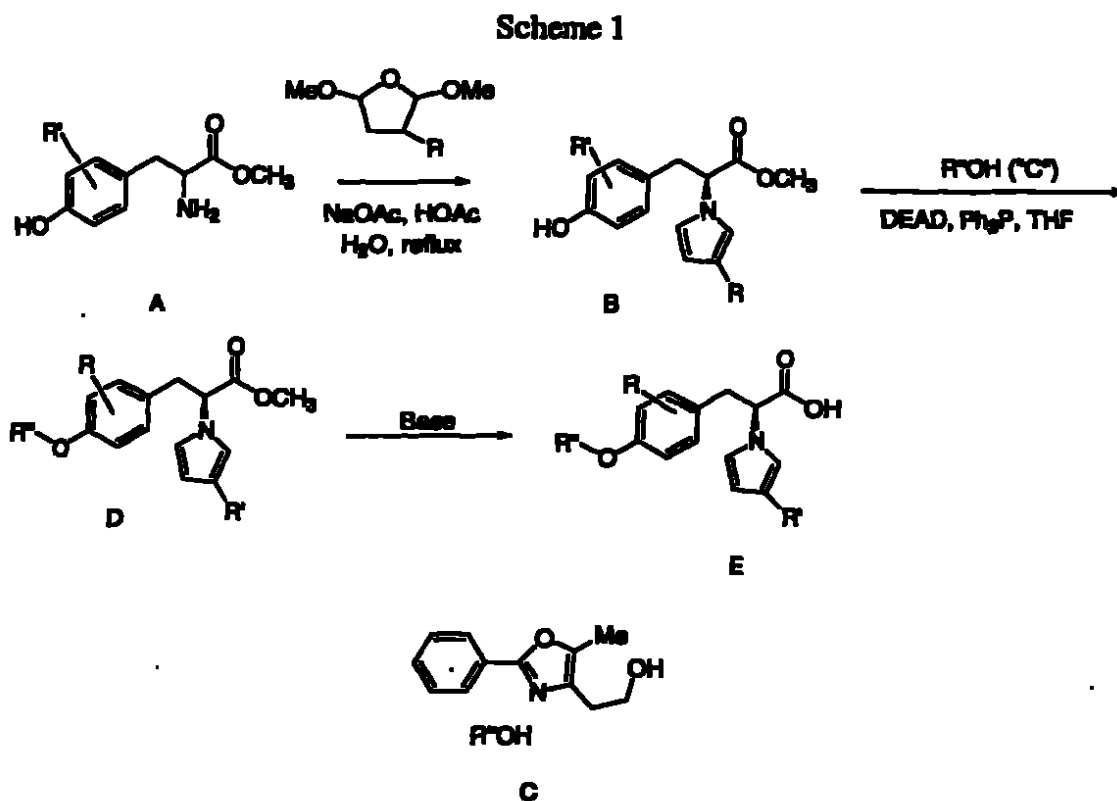
Processes and novel intermediates for preparing compounds of formula I are provided as further embodiments of the invention and are illustrated by the following procedures in which the meanings of the generic radicals are as given above unless otherwise qualified. Certain compounds of formula I are useful as intermediates for preparing other compounds of formula I.

It is also noted that compounds of formula I can be prepared using protecting groups. It is to be noted that the appropriate use and choice of protecting groups is well-known by one skilled in the art, and is not limited to the specific examples below. It is also to be understood that such groups not only serve to protect chemically reactive sites, but also to enhance solubility or otherwise change physical properties. A good general reference for protecting group preparation and deprotection is "Protecting Groups in Organic Synthesis" by T.W. Green and P.G. Wuts. A number of general reactions such as oxidations and reductions etc. are not shown in detail but can be done by methods understood by one skilled in the art. General transformations are well-reviewed in "Comprehensive Organic Transformation" by Richard Larock, and the series "Compendium of Organic Synthetic Methods" published by Wiley-Interscience. In general, the starting materials are obtained from commercial sources unless otherwise indicated.

It will be appreciated by those skilled in the art that compounds of the invention having one or more chiral centers may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, geometric, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine activity or cytotoxicity using the standard tests described herein, or using other similar tests which are well known in the art.

It will be further appreciated by the skilled artisan that the following schemes depict the synthesis of compounds wherein A, X, Q, Y, B, D, Z, or E are defined. It is to be understood however, that compounds of the invention other than those specifically disclosed can be prepared using the strategies depicted in the schemes.

Scheme 1 depicts a general approach to the preparation of compounds of Formula I wherein the pyrrolyl group is unsubstituted.



In Scheme 1, the pyrrolotirosine ester B is first prepared by allowing tyrosine ester A to undergo reaction with 2,5 dimethoxy tetrahydrofuran in the presence of base. The methyl ester is depicted in Scheme 1, but it is possible that other esters may be used. Coupling of pyrrolotirosine ester analogue with a compound bearing a primary or secondary alcohol under Mitsunobu-type or similar conditions provides pyrrolotirosine methyl ester derivative D. Hydrolysis of pyrrolotirosine methyl ester derivative D under basic conditions provides compound of the invention E.

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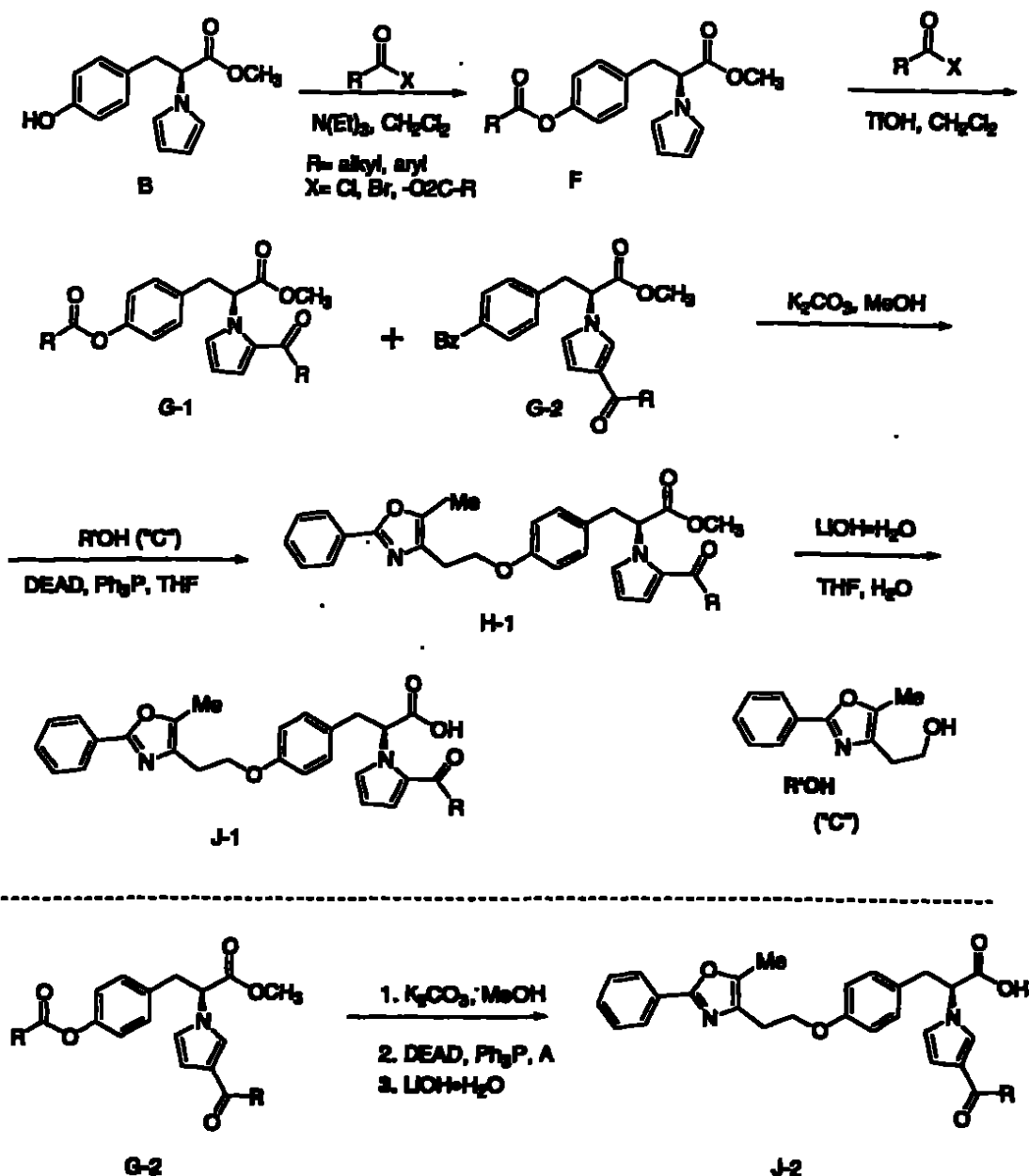
-57-

Scheme 2 depicts the preparation of compounds of Formula I wherein the pyrrolyl group bears an alkyl or aryl carbonyl substituent.

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Scheme 2

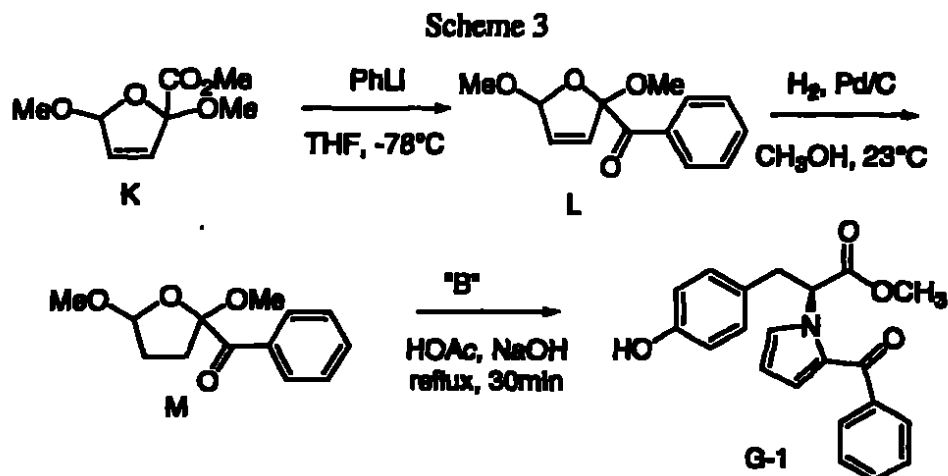


According to Scheme 2, the phenol group in pyrrolotyrosine ester B is first protected using an acid halide or anhydride using procedures known to the skilled artisan. Protected pyrrolotyrosine methyl ester E is then allowed to undergo reaction with an acid halide such as benzoyl chloride, although other acid halides or anhydrides may be used. Acylation occurs at the 2- or 3-position of the pyrrole ring to provide a mixture of the 2- and 3- substituted benzoyl derivatives G-1 and G-2, which can be separated using conventional techniques. Deprotection of the benzoyl group of pyrrolotyrosine derivative G-1 or G-2, and subsequent

Mitsunobu coupling provides penultimate methyl ester H-1 or H-2. Hydrolysis of the methyl ester provides compound of the invention J-1 or J-2.

An alternative approach to the preparation of substituted pyrrolotyrosine derivative G-1 is depicted in Scheme 3.

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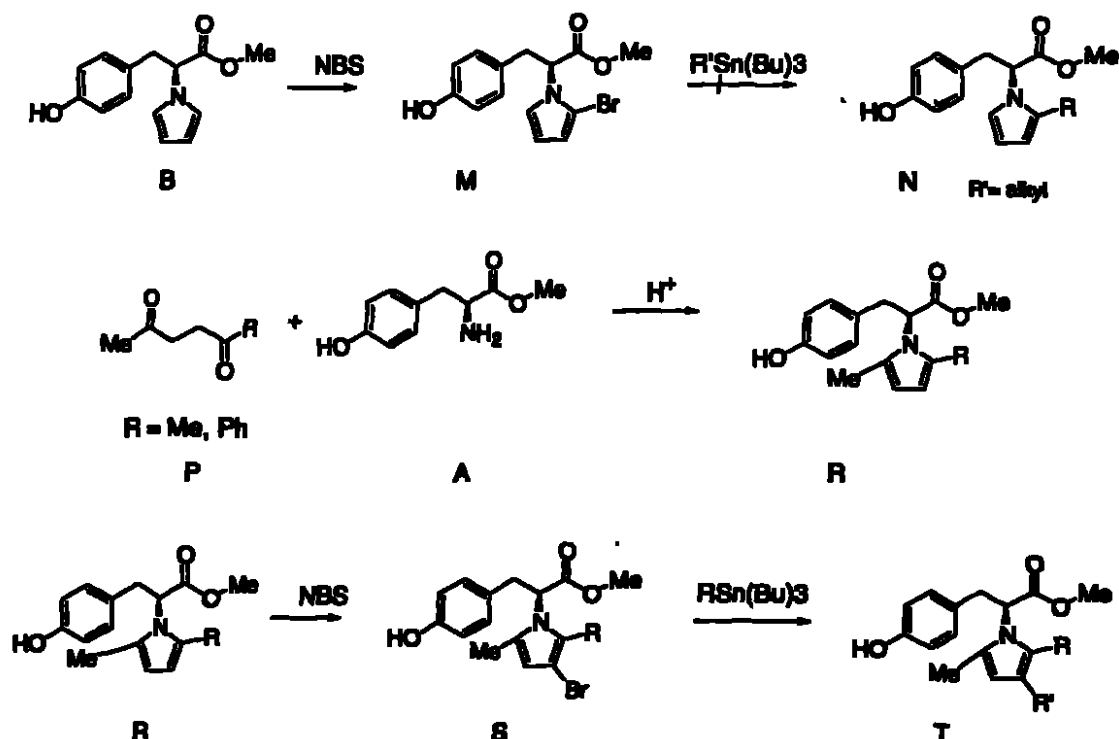
Accordingly, methyl 2,5 dihydro 2,5-dimethoxy-2-furan carboxylate K undergoes reaction with phenyl lithium to provide benzoyl derivative L. Benzoyl derivative L then undergoes reaction with tyrosine methyl ester B to provide compound G-1. Compound G-1 can be converted to the invention compound according to the steps provided above.

Scheme 4 provides another route to compounds of the invention wherein the pyrrolyl group bears more than one substituent.

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Scheme 4



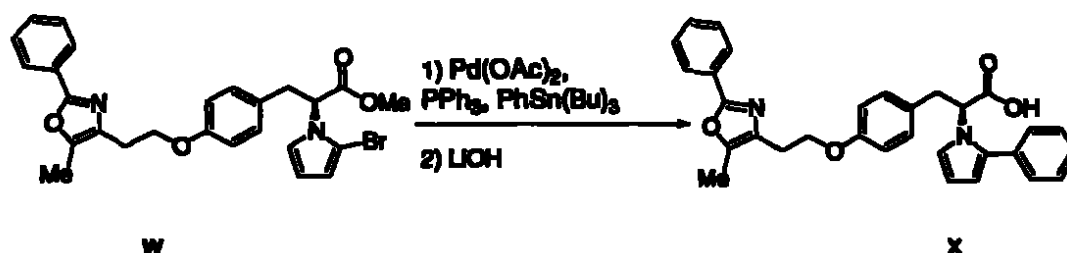
Thus, Row 1 of Scheme 4 depicts the synthesis of pyrrolotyrosine methyl ester derivatives bearing a substituent at the pyrrolyl 2- position. Pyrrolotyrosine methyl ester **B** undergoes reaction with N-bromosuccinimide or a similar agent to provide the 2-bromo pyrrolotyrosine methyl ester derivative **M**. The 2-bromo pyrrolotyrosine methyl ester derivative **M** may undergo coupling with alcohol **C** and hydrolysis to provide a compound of the invention. Alternatively, the 2-bromo pyrrolotyrosine methyl ester derivative **M** may undergo reaction with an alkyl tin reagent under conditions known in the art to provide 2-alkyl pyrrolotyrosine methyl ester derivative **N**, which may undergo coupling and hydrolysis to provide other compounds of the invention.

Row 2 of Scheme 4 depicts the synthesis of disubstituted pyrrolotyrosine methyl ester derivatives. Thus, diketone **P** undergoes reaction with tyrosine methyl ester **A** in the presence of acid to provide pyrrolotyrosine methyl ester derivative **P**, wherein the 2- and 5- positions of the pyrrolyl ring bear alkyl or aryl substituents. Pyrrolotyrosine methyl ester derivative **P** can be coupled with alcohol **C** or an alternative alcohol under Mitsunobu-type conditions, followed by ester hydrolysis, to provide a compound of the invention **R**.

Alternatively, pyrrolotyrosine methyl ester derivative R can be used to provide other compounds of the invention wherein the pyrrolyl ring is trisubstituted. Thus, as depicted in Row 3 of Scheme 4, bromination of pyrrolotyrosine methyl ester derivative R using N-bromosuccinimide or a similar agent provides the brominated compound S. Brominated compound S may undergo coupling and hydrolysis as described above to provide a compound of the invention. Brominated compound S may also undergo reaction with an alkyl tin reagent to provide trisubstituted derivatives such as V.

Scheme 5 depicts an alternative synthesis of compounds of the invention wherein the pyrrolyl ring is substituted at the 2-position.

Scheme 5

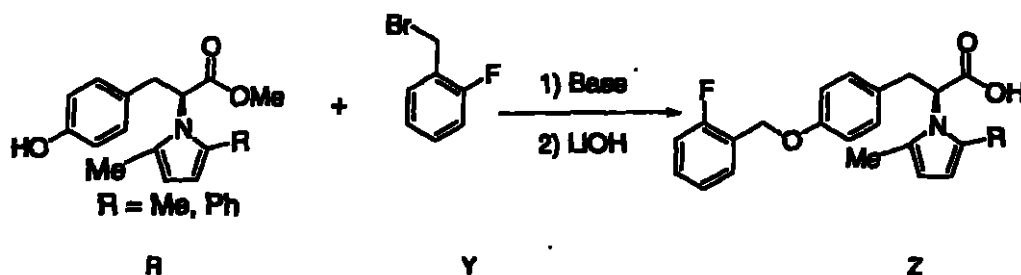


As Scheme 5 provides, methyl ester W, prepared by coupling 2-bromopyrrolotyrosine methyl ester derivative M with alcohol C, can undergo palladium catalyzed alkyl or aryl coupling to provide the 2-aryl substituted pyrrolotyrosine methyl derivative X. 2-alkyl or aryl substituted pyrrolotyrosine methyl derivative (aryl derivative X depicted). Upon hydrolysis, aryl derivative X gives rise to a compound of the invention.

Scheme 6 provides compounds of the invention derived from disubstituted pyrrolotyrosine methyl ester derivative R.

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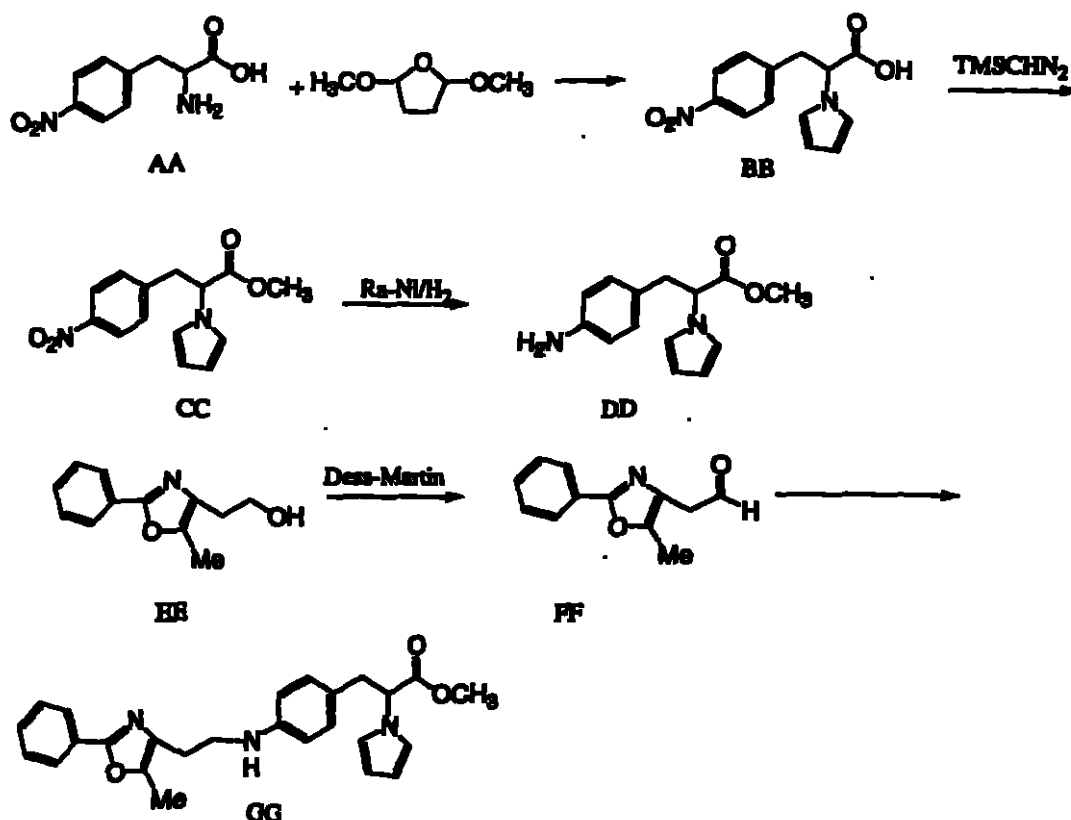
Scheme 6



Upon treatment with base to generate phenoxide, pyrrolotyrosine methyl ester derivative R can undergo reaction with a wide variety of alkylating agents known in the art (See for instance, alkylating agents listed in Aldrich Handbook of Fine Chemicals (2000-2001)). In Scheme 6, the phenoxide of pyrrolotyrosine methyl ester derivative R undergoes reaction with 2-fluorobenzyl bromide Y, followed by hydrolysis to provide compound of the invention Z.

Scheme 7 depicts the synthesis of compounds of Formula I wherein X is $-\text{CH}_2\text{CH}_2\text{NH}-$.

Scheme 7

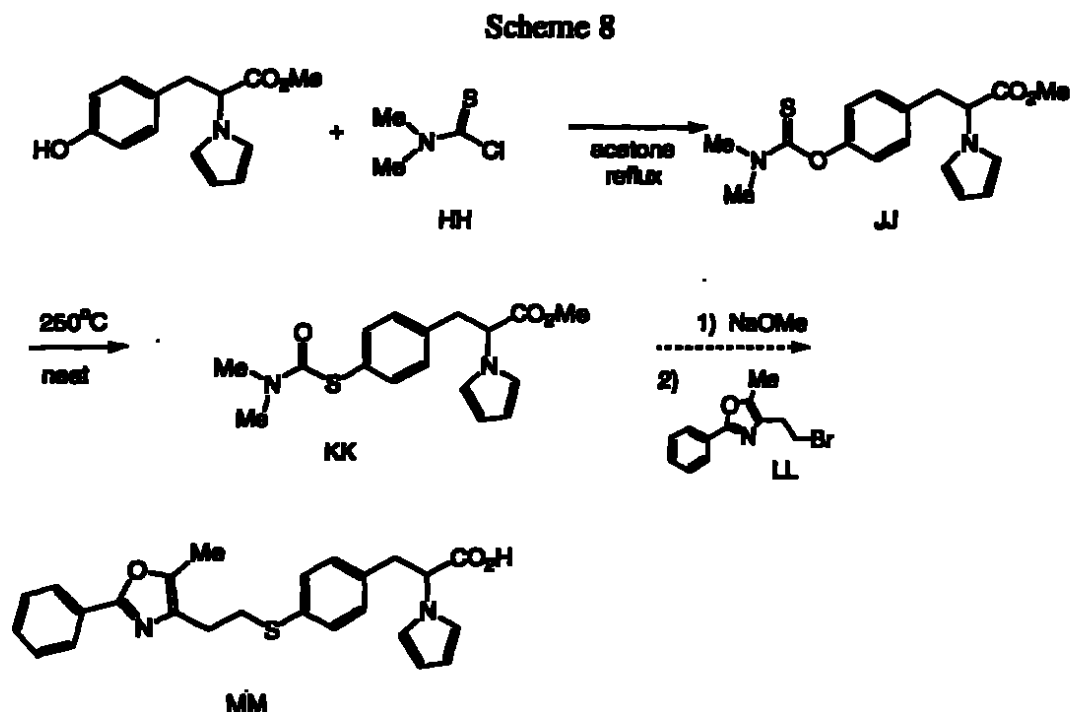




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Thus, nitro compound AA undergoes reaction with 2,5 dimethoxy tetrahydrofuran to provide the pyrrolo derivative BB. Pyrrolo derivative BB is then esterified using trimethylsilyl azide to provide methyl ester CC. Reduction of the nitro group in ester CC using Raney nickel in the presence of Hydrogen provides the amine compound DD. Addition of amine compound DD to aldehyde FF (generated from alcohol EE by oxidation) followed by reduction, provides the amine GG. Amine GG is hydrolyzed as described previously to provide a compound of the invention.

Scheme 8 depicts the synthesis of compounds of Formula I wherein X is $-\text{CH}_2\text{CH}_2\text{S}-$.

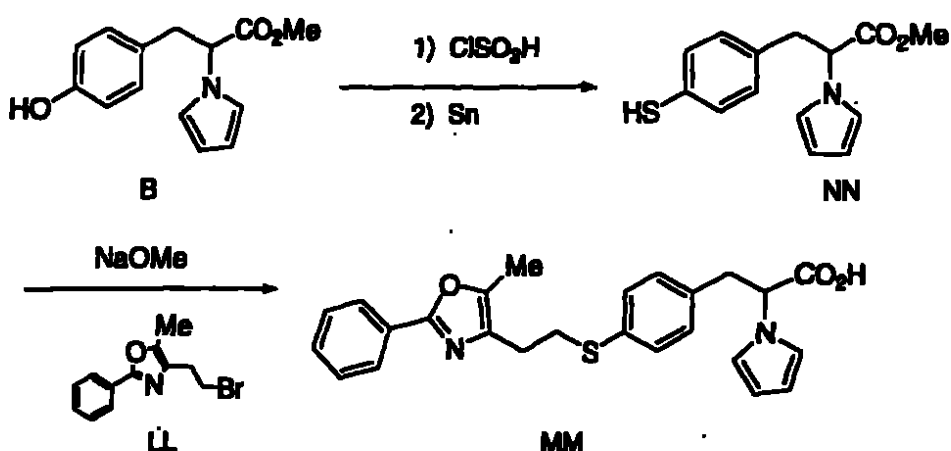


Thus, pyrrolotyrosine methyl ester B undergoes reaction with dimethylthiocarbamoyl chloride to provide compound JJ. When heated to 250 °C, compound JJ undergoes rearrangement to provide compound KK. Treatment of KK with base generated the thiophenoxide, which undergoes reaction with the depicted alkyl halide LL, to provide the thio-variant Formula I compound MM.

An alternative preparation of a thio-variant Formula I compound is depicted in Scheme 9.

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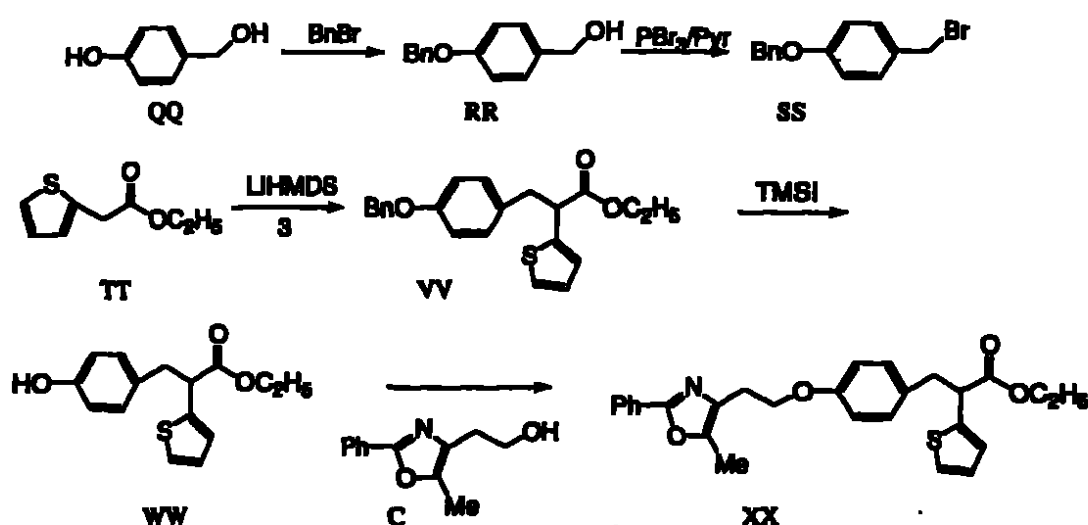
Scheme 9



Thus, pyrrolotyrosine methyl ester B can undergo reaction with chlorosulfonic acid in the presence of elemental tin to provide thiophenol NN. Alkylation of NN and ester hydrolysis can provide the compound of the invention MM.

Scheme 10 depicts the synthesis of additional compounds of the invention wherein the pyrrolyl group is replaced by a thiopyrrolyl group.

Scheme 10



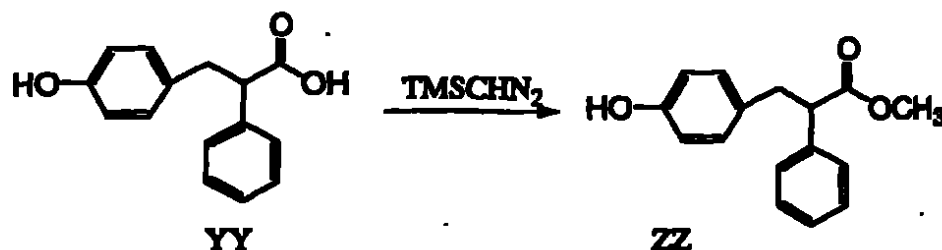
Thus, 4-hydroxy benzyl alcohol QQ undergoes reaction with benzyl bromide to provide alcohol RR. Alcohol RR is converted to the bromide SS by treatment with tribromo phosphine in the presence of pyridine. The bromide SS undergoes reaction with thiopyrrole VV under conventional alkylation conditions

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followed by deprotection to provide compound WW. Mitsunobu-type coupling of WW with alcohol C provided ester XX. Hydrolysis of ester XX provides a compound of the invention.

5 Scheme 11 depicts the synthesis of compounds of the invention wherein the pyrrolyl group is replaced by another aryl group, such as a phenyl-substituted phenyl group.

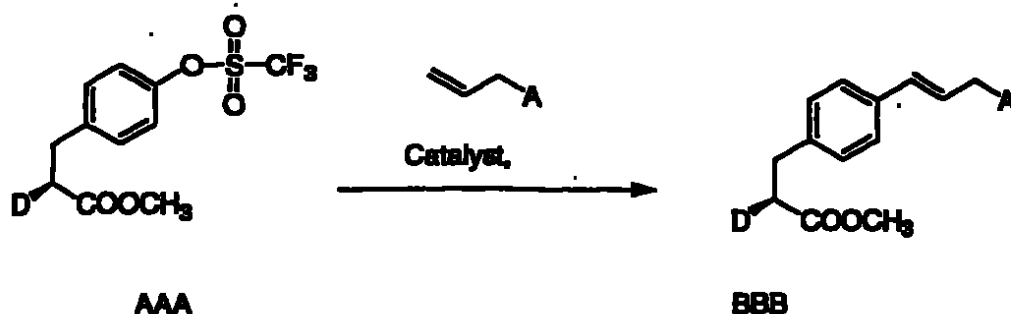
Scheme 11



10 Thus, esterification of 4-hydroxy phenylalanine YY provides methyl ester ZZ. Mitsunobu type coupling and ester hydrolysis of compound ZZ provided a compound of the invention.

Scheme 12 depicts the synthesis of compounds of the invention wherein X is $-\text{CH}=\text{CH}-$ and D is heteroaryl.

Scheme 12



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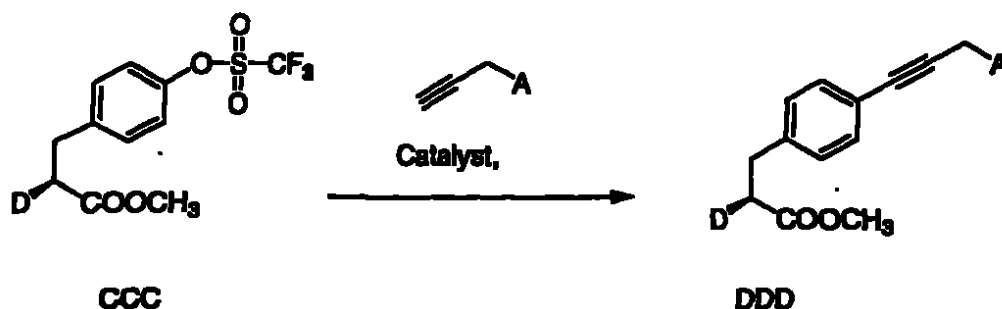
In Scheme 12, coupling of the triflate AAA with a vinyl compound in the presence of an organometallic catalyst provides vinyl ester BBB. Hydrolysis of the ester moiety in BBB as described above provides a compound of the invention wherein R is alkyl or substituted alkyl, aryl or substituted aryl, heteroaryl or

substituted heteroaryl, heterocycloalkyl and substituted heterocycloalkyl, or heteroalkyl or substituted heteroalkyl.

Scheme 13 depicts the synthesis of additional compounds of the invention wherein X is $-\text{C}\equiv\text{C}-\text{CH}_2-$ and D is heteroaryl.

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Scheme 13



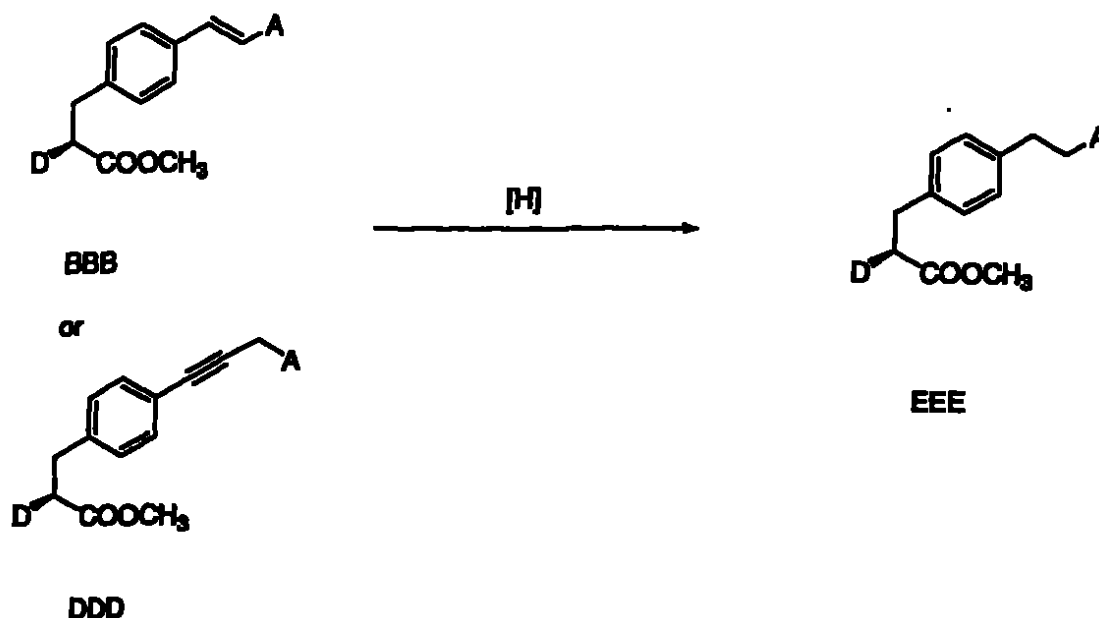
10

In Scheme 13, coupling of the triflate AAA with an alkynyl compound CCC in the presence of an organometallic catalyst provides alkynyl ester DDD. Hydrolysis of the ester moiety in DDD as described above provides a compound of the invention wherein R is alkyl or substituted alkyl, aryl or substituted aryl, heteroaryl or substituted heteroaryl, heterocycloalkyl and substituted heterocycloalkyl, or heteroalkyl or substituted heteroalkyl.

Scheme 14 depicts the synthesis of compounds of the invention wherein X is $-(\text{CH}_2)_3-$ and D is heteroaryl.

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Scheme 14

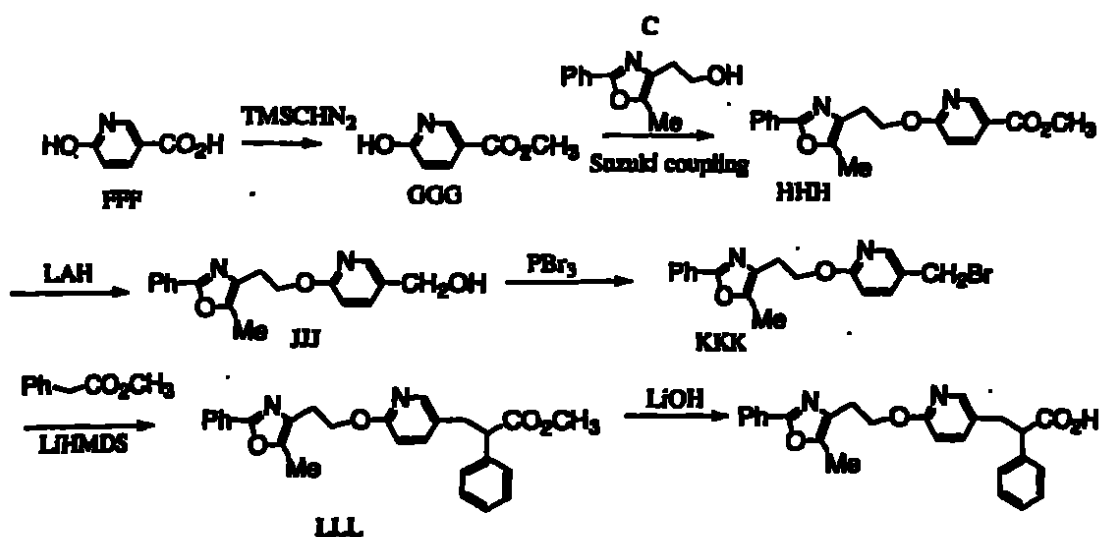


5

Scheme 14 indicates that either the vinyl compound BBB or the alkynyl compound DDD can be reduced under conditions known in the art to provide the saturated variant EEE.

Scheme 15 depicts one approach to preparing compounds of the invention wherein Q is heteroaryl or substituted heteroaryl..

Scheme 15



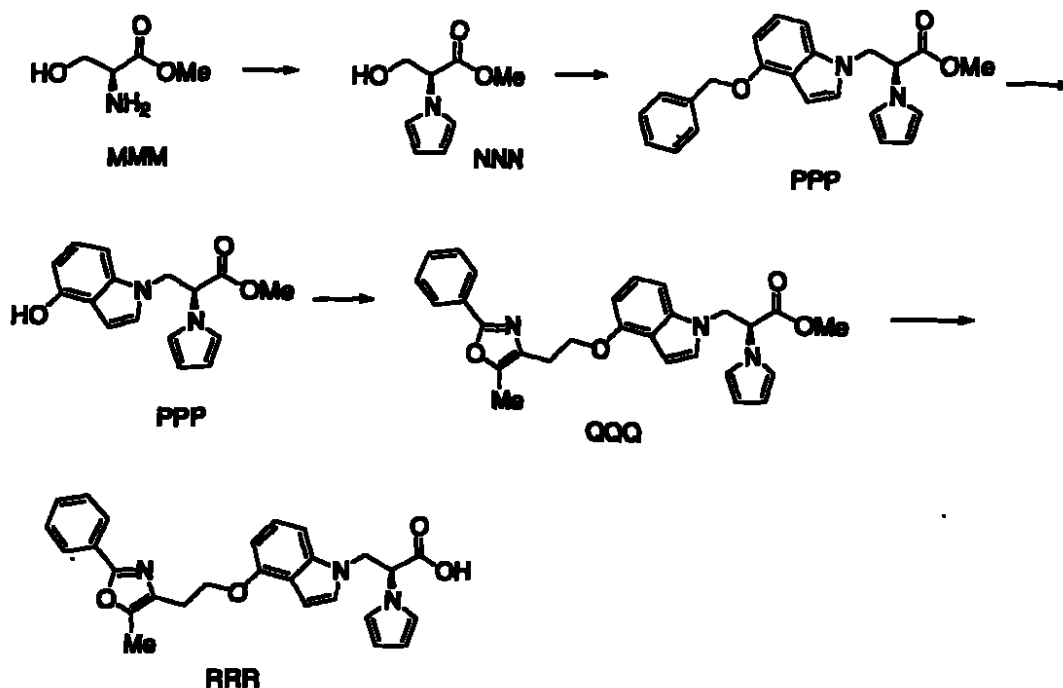
10

Thus, nicotinic acid FPF is esterified to provide GGG. GGG is coupled to C as discussed earlier to give HHH. The ester moiety in HHH is reduced to give

alcohol JJJ, which is then converted to halide KKK using conventional techniques. Alkylation of the methyl ester of phenyl acetic acid using KKK, provides product LLL. LLL is hydrolyzed to a compound of the invention under conditions as discussed previously.

5 Scheme 16 depicts a compound of the invention wherein B is H.

Scheme 16



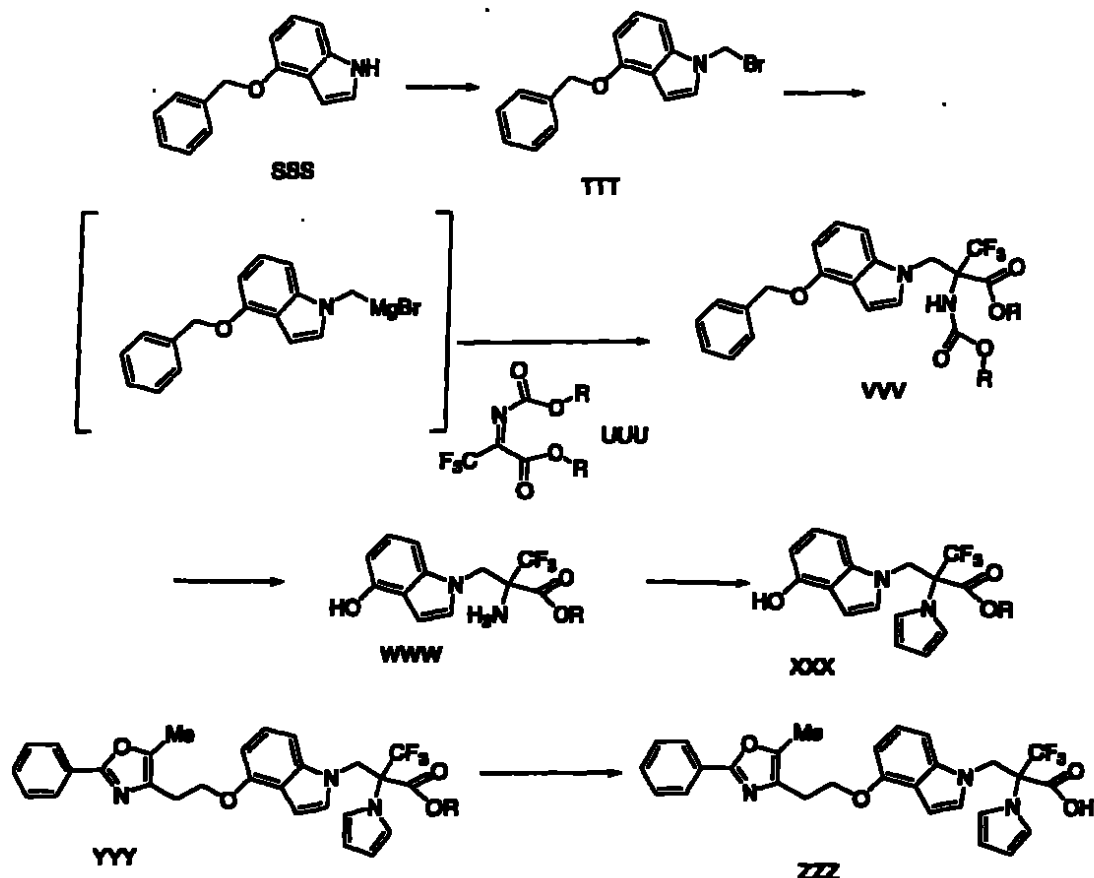
5-substituted indole derivative is prepared the same way, except using 5-benzoyloxyindole in the second step

Thus, MMM is converted to the pyrrole derivative NNN as provided earlier. The hydroxyl group of compound NNN is converted to a leaving group, such as a bromide, mesylate, or tosylate or the like, and then undergoes addition with the benzyl-substituted hydroxyindole derivative at the N position to give OOO. Removal of the benzyl protecting group in OOO, followed by coupling with C is provided earlier, gives rise to QQQ. Saponification of the ester moiety in QQQ gives the invention compound RRR.

15 Scheme 17 depicts the synthesis of a compound of the invention wherein B is haloalkyl.

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Scheme 17

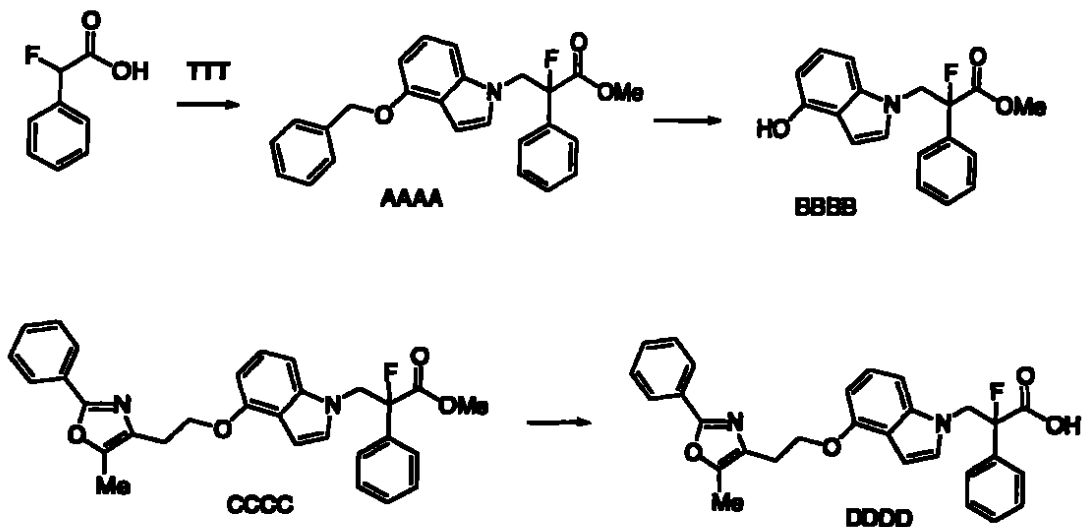
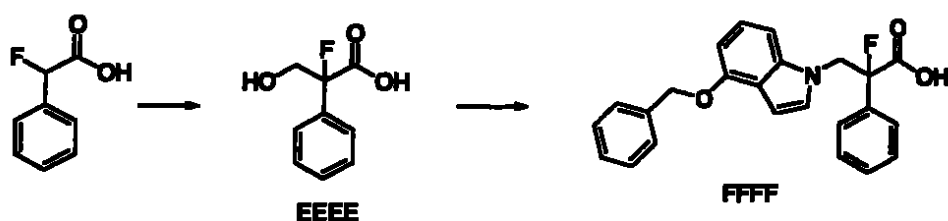


Thus the benzyloxy indole derivative SSS is converted to the bromomethyl compound TTT, by treatment with formaldehyde or its equivalent, followed by
 5 halogenation using conventional conditions. Compound TTT is then converted to the Grignard reagent, which then undergoes 1,2 addition with imine UUU to provide VVV. The amide moiety in VVV is hydrolyzed to provide WWW. Coupling of WWW with C as provided earlier gives rise to XXX. Construction of the pyrrolyl ring to provide XXX, saponification of the ester moiety in YYY as
 10 provided earlier gives rise to the invention compound ZZZ.

Scheme 18 depicts the synthesis of a compound of the invention wherein B is F.

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Scheme 18

Method 1**Method 2**

5-substituted indole derivative is prepared the same way, except using 5-benzyltryptophan

In Method 1 of Scheme 18, 1-fluoro-2-phenylacetic acid is deprotonated and allowed to react with TTT to provide AAA. In Method 2 of Scheme 18, the Grignard reagent derived from TTT is combined with hydroxymethyl derivative EEE to provide FFFF.

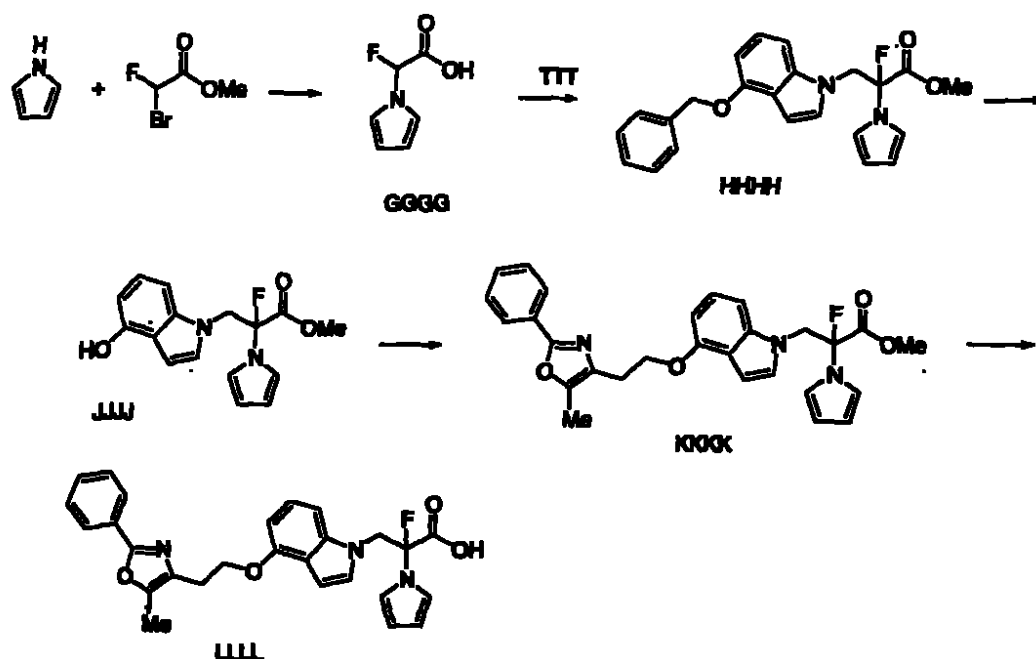
Scheme 19 depicts alternative syntheses of a compound of the invention wherein B is F. The difference between Methods 1 and 2 in Scheme 19 is the route by which pyrrole (GGGG or QQQQ) is used.

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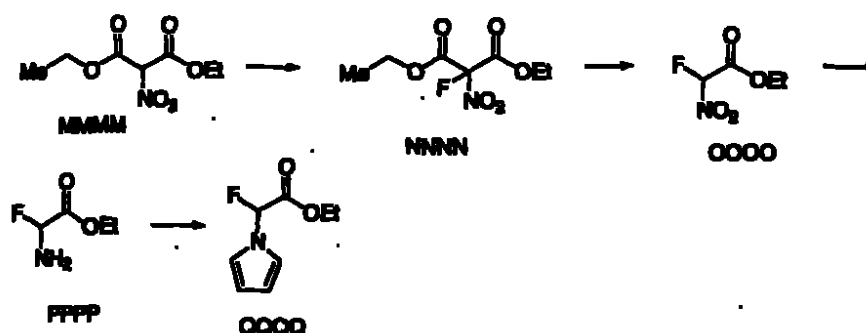
Scheme 19

Method 1



5-substituted indole derivative is prepared the same way, except using 5-benzyloxyindole

Method 2



Thus in Method 1, the requisite pyrrole derivative GGGG is coupled with TTT as provided in Scheme 17 to provide HHHH. Coupling of HHHH to C, followed by saponification, provides the invention compound LLLL. In Method 2, requisite pyrrole QQQQ is prepared from MMMM via fluorination, decarboxylation, and reduction. QQQQ is then used as in Method 1 to provide the invention compound.

Some of the compounds of Formula I are capable of further forming pharmaceutically acceptable acid-addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogen phosphate, metaphosphate, pyrophosphate, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinates suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 1977;66:1-19).

The acid addition salt of basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M., supra., 1977).

The base addition salts of acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

5 Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the *R*(D) or *S*(L) configuration. The present invention includes all enantiomeric and epimeric forms, as well as the appropriate mixtures thereof.

10 The compounds of formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

15 Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of
20 ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will
25 be obtained.

30 The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a
flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to

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materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for

example, sugars, buffers or sodium-chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

5 Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional
10 desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

15 Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional
20 antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid-compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and
25 esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example,
30 see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

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Useful dosages of the compounds of formula I can be determined by comparing their in vitro activity, and in vivo activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

5 Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

10 The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

15 In general, however, a suitable dose will be in the range of from about 0.005 to about 100 mg/kg, e.g., from about 0.1 to about 75 mg/kg of body weight per day, such as 0.03 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 0.06 to 90 mg/kg/day, most preferably in the range of 0.15 to 60 mg/kg/day.

20 The compound may conveniently be administered in unit dosage form; for example, containing 0.05 to 1000 mg, conveniently 0.1 to 750 mg, most conveniently, 0.5 to 500 mg of active ingredient per unit dosage form.

25 Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.005 to about 75 μ M, preferably, about 0.01 to 50 μ M, most preferably, about 0.02 to about 30 μ M. This may be achieved, for example, by the intravenous injection of a 0.0005 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 0.01-1 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.0001-5 mg/kg/hr or by intermittent infusions containing about 0.004-15 mg/kg of the active
30 ingredient(s).

 The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three,

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four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

5 The antidiabetes ability of a compound of the invention is demonstrated using pharmacological models that are well known to the art, for example, using models such as the tests described below.

TEST A—3T3-L1 Adipocyte Differentiation Assay (ADPDIF)

10 This assay is used to determine the potential of putative PPAR- γ ligands to induce fat cell differentiation. A quantitative method was established for determining the ability of potential PPAR- γ ligands to promote adipogenesis of 3T3-L1 preadipocytes. 3T3-L1 preadipocytes are plated onto 96 well plates (20,000 cells per well). Upon confluency, the compounds which were initially scored as positives from the PPAR- γ ligand displacement and PPAR- γ chimeric receptor transcription assays were added for 4 days with the final concentrations of 2.5, 5.0 and 10 μ M ($n=3$). Each plate contains positive controls (5 μ M BRL 49653 and 5 μ M Troglitazone) and a vehicle control (DMSO). Cells are replenished with FBS containing media on day 5 of post-drug treatment and incubated for additional 4-6 days. Cells are stained with BODIPY a fluorescent lipophilic stain to quantitate the lipid content of the cells. The assay is optimized for a 96-well plate format. Approximately after 10 days of post-drug treatment, cells are fixed in 3% formalin solution for 15 min followed by staining with BODIPY (80 μ g/ml) for 20 min at room temperature. The plate is then put through the CYTOFLUOR instrument to measure the fluorescence of BODIPY (excitation=485/20; emission=530/25). A template is created in a spread sheet to calculate the average value of BODIPY measurements and reported as % of BRL 49653 at 5 μ M.

TEST B—ANTCV1 Antagonist Transcription Assay

30 The ANTCV1 transcription assay is an *in vitro* assay in which CV-1 cells, an African green monkey kidney cell line, are transfected with a luciferase

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reporter construct comprised of a fragment of the fatty acid binding protein (FATP) promoter located upstream of the TK TATA box. Transfection efficiency is controlled by co-transfection of the reference plasmid CMV β -galactosidase. The DNAs are transiently transfected into the cells by electroporation and the cells are plated into 96-well dishes. Test compounds are diluted to final concentration of 25 μ M in individual wells containing 300 nM BRL. Control wells include either the 0.5% DMSO vehicle control, the antagonist PD 0157724-0000 at 25 μ M and 300nM BRL, or 300nM BRL alone. Cells are incubated with both the drugs for 48 hrs and then harvested. The lysates are measured for luciferase and β -galactosidase activities using the dual luciferase kit from Tropix on a EG&G Berthold MicroLumat LB96P luminometer. The fold activation of BRL 49653 in each assay must be above 4 in order for the assay to be considered valid.

Raw numbers are transferred to an Excel spreadsheet and luciferase/ β -galactosidase ratios are determined for each compound. The percent BRL 49653 inhibition for each compound is calculated by dividing the luciferase/ β -galactosidase ratio for each compound by the luciferase/ β -galactosidase ratio of the DMSO vehicle control. This number is then plugged into the following equation: % BRL inhibition = (BRL fold activation - test compound fold activation & BRL / BRL fold activation - 1) $\times$ 100.

TEST C—CV-1 NATIVE RECEPTORS TRANSCRIPTION ASSAY (MKNRCV1)

The purpose of this assay is to identify ligands that activate endogenous nuclear receptors in CV-1 cells. Protocol: CV-1 cells are co-transfected with a luciferase reporter containing a fragment of the FATP promoter upstream the TK TATA box and a CMV beta-galactosidase plasmid. Transfected cells are incubated with test ligands for 48 hours. Cell lysates are harvested and the luciferase and beta-galactosidase activities are determined. Description: Luciferase and beta-galactosidase activities in the cell lysates are measured using an EG&G Berthold luminometer. These values are entered into an Excel worksheet which calculates the luciferase to beta-galactosidase ratios and expresses the data as percent activity of the reference compound, BRL 49653.

TEST D—BLOOD GLUCOSE MEASUREMENT (GLUCOSE Δ)

Glucose is obtained 4 hours post dose via tail vein stick (5µl whole blood) in awake, 4 hour fasted animals. Blood is drawn by capillary action into a glucose cuvette and read in a HemoCue Glucose Analyzer (Ryan Diagnostics). Blood is
5 diluted 1:2 with saline if glucose levels are greater than 400mg/dl (meter high range) and results multiplied by two.

TEST E—3T3-L1 TRANSIENT REPORTER ASSAY

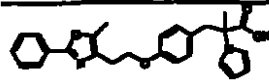
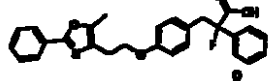
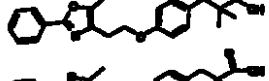
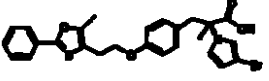
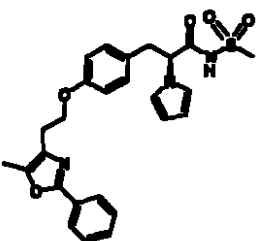
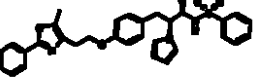
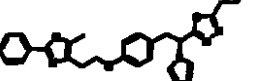
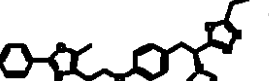
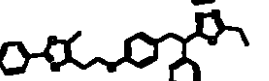
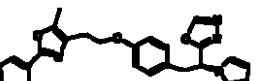
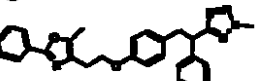
This assay is used to determine the potential of putative PPAR-γ ligands to activate the promoter/enhancer of the murine aP2 gene. 3T3-L1 preadipocytes are
10 cultured on collagen coated plates in DMEM containing 10% Calf serum for 48 hours post-confluence. The cells are then cultured for approximately 3 days in DMEM containing 10% Fetal Bovine Serum (FBS), 0.5-mM methyl isobutylxanthine, 0.25 µM dexamethasone, and 1 µg/ml of insulin. Cells are detached from the plates with Trypsin-EDTA and resuspended in Phosphate
15 Buffered Saline (PBS).

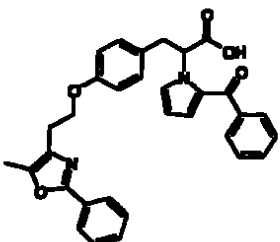
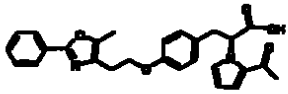
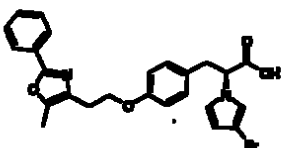
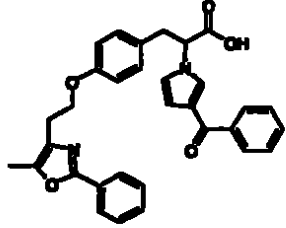
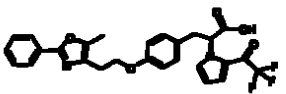
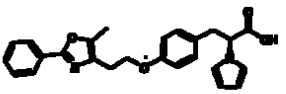
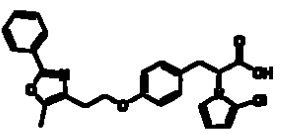
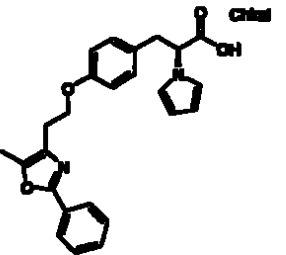
The reporter construct used in this assay is comprised of the ~5.4 Kb 5' flanking region of the murine aP2 gene inserted into the cloning site of the TKpGL3 luciferase vector. Transfection efficiency is controlled by co-transfection of the reference plasmid CMV-β-galactosidase. The reporter
20 construct and the reference plasmid are transiently co-transfected into the cells by electroporation. The transfected cells are plated into collagen coated 96-well plates and cultured overnight. Cells are then incubated for 48 hours with the test compounds and then harvested. The lysates are measured for luciferase and β-galactosidase activities using the Dual-Light® luciferase kit from Tropix on a
25 EG&G Berthold MicroLumat LB96P luminometer.

Data are summarized in Tables 1-3.

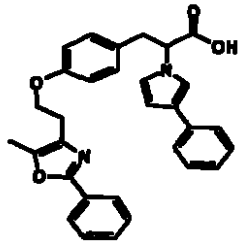
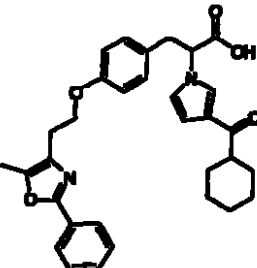
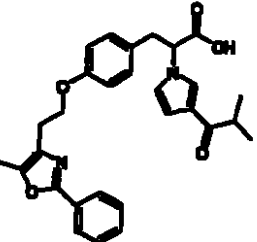
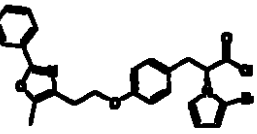
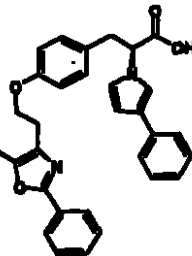
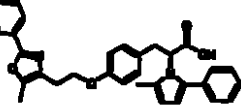
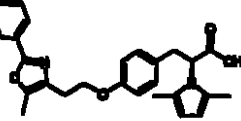
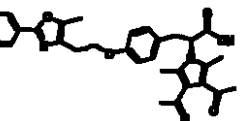
97

TABLE 1

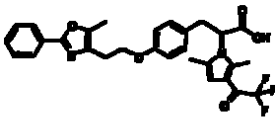
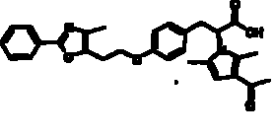
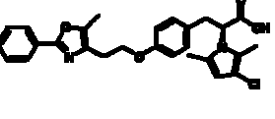
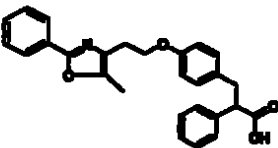
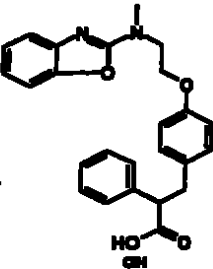
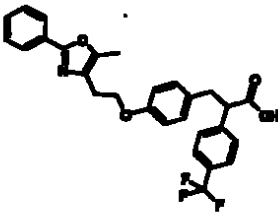
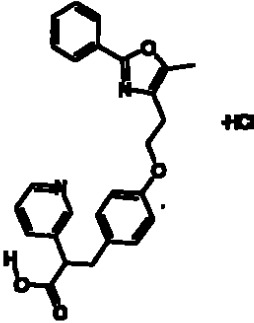
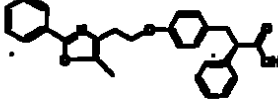
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	117			2	87	-80.3333
	122			9.5	63	37
	131				34	59
	99			13	44	65
				1.4	83 @ 5 μ M	-22
						
	110			3.2	97	-30
	90			3.3	101	-117
	94				0	84
	88	46.5	-20.0	2000	12	53.8
	161				61	47
	45				37 @ 5 μ M	49
						
						

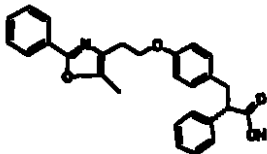
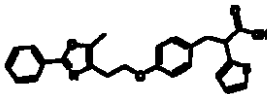
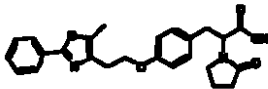
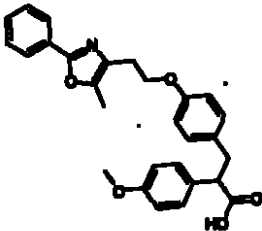
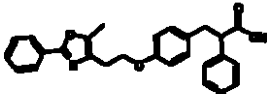
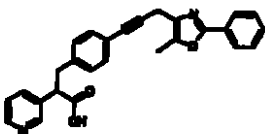
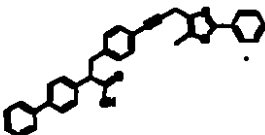
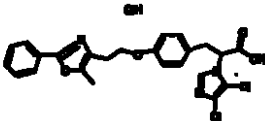
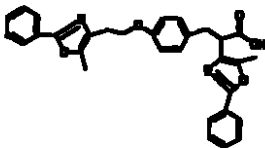
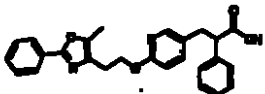
Compound	ADPDIFF %BRL @ 5 μ M 33	Glucose Δ	%BRL	MKNRCV1 EC ₅₀	MKNRCV1 %BRL @ 25 μ M 46	ANTCV1 INHIB @ 25 μ M
		108.6	-50.3	12.9		
	89	12.4	-5.1	3.6	60	20
	84			0.06	85	-57.5
	102	-84.4	60.8	2.2	91	-20
	105	-157.2	113.3	1.7	75	-1
	96			1.9	87 @ 5 μ M	-15
	86	54.8	-40.1	0.01	70	-17.5
	67	-196.0	109.4	0.03	86	-59

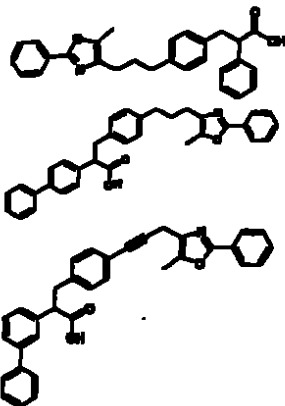
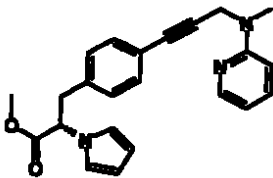
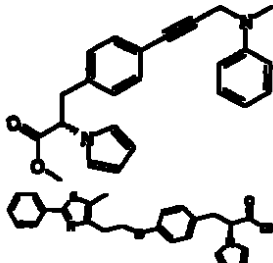
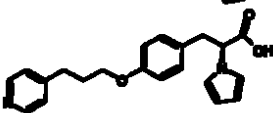
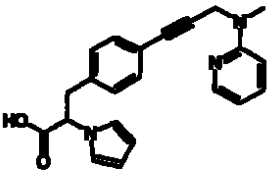
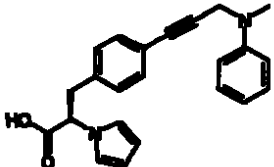
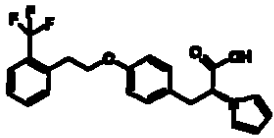
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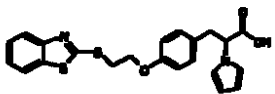
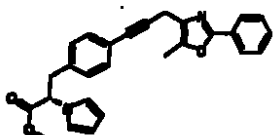
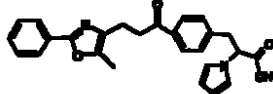
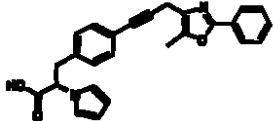
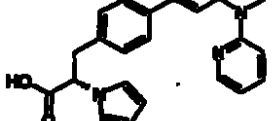
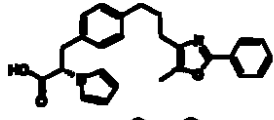
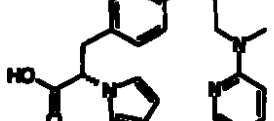
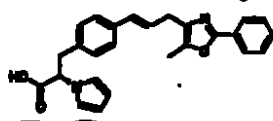
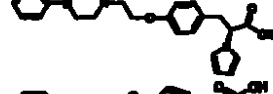
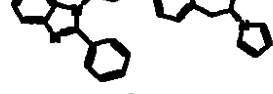
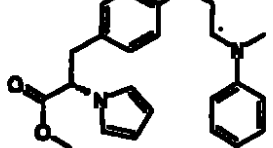
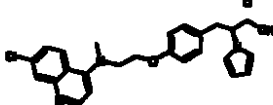
Compound	ADPDIFF %BRL @ 5 μ M 125	Glucose Δ	%BRL	MKNRCV1 EC ₅₀	MKNRCV1 %BRL @ 25 μ M 54	ANTCV1 INHIB @ 25 μ M 29
				0.9		
	82			4.7	83	-12
	120			23.6	70	-10
	95			0.7	42	59
	125	-194.0	83.3	0.9	54	29
	2				24	-3
	26				11	80
	0				24	3

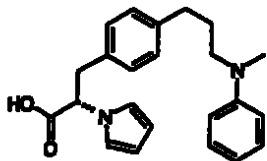
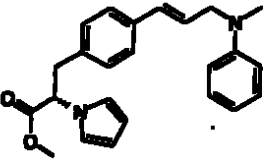
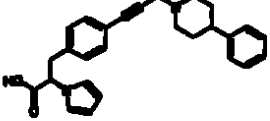
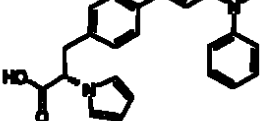
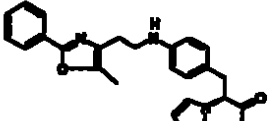
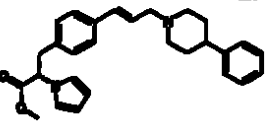
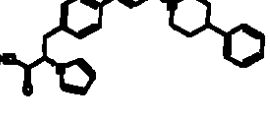
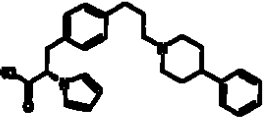
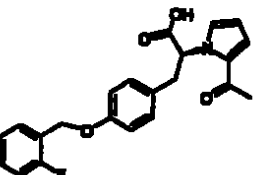
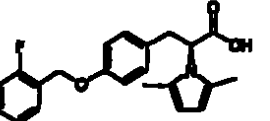
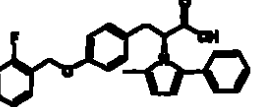
100

Compound	ADPDIFF %BRL @ 5 μM	Glucose Δ	%BRL	MKNRCV1 EC ₅₀	MKNRCV1 %BRL @ 25 μM	ANTCV1 INHIB @ 25 μM
	2			16.0	28	12
	0				27	-15
	28			2000	55	5
	94	49.2	-35.5	0.3	109	-48
	109	172.0	-52.0	1.0	91	-45
	107	246.8	-180.4	0.2	78	-49
	132	-72.5	31.1	0.4	58	-112
	95	-58.8	17.8	0.15	106	-104

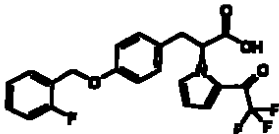
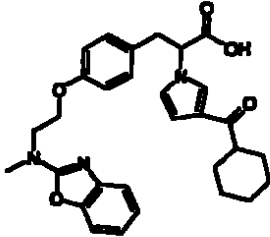
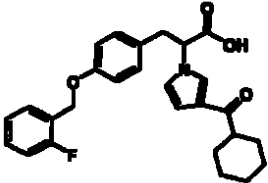
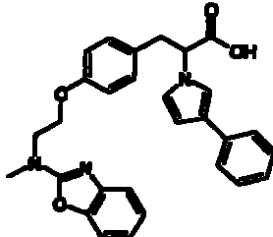
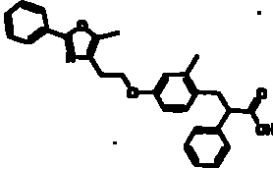
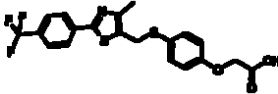
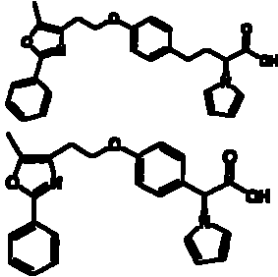
Compound	ADPDIFP %BRL @ 5 μ M 31	Glucose Δ	%BRL MKNRCV1 EC ₅₀ 2000	%BRL MKNRCV1 @ 25 μ M 50	ANTCV1 INHIB @ 25 μ M -44
					
	88			111	-127
	0			29	-94
			2.7	75	-65
	2			20	55
			34	49 @ 5 μ M	-15
			2.7	86 @ 5 μ M	-21
				27 @ 5 μ M	15
				110 @ 5 μ M	18
			1.2		

Compound	ADPDIFP %BRL @ 5 μM	Glucose Δ	%BRL MKNRCV1 EC ₅₀	%BRL MKNRCV1 @ 25 μM 0.1122	ANTCV1 INHIB @ 25 μM	
	21		1.4	92	-46	
	29		5.6	38	71	
	92		9.2	76	-20	
	3			44	3	
	6		2000	71	-32	
	83	182.8	-55.3	2.9	92	-31
	112		0.4	80	-27	

Compound	ADPDIFP %BRL @ 5 μ M	Glucose Δ	%BRL	MKNRCV1 EC ₅₀	MKNRCV1 %BRL @ 25 μ M	ANTCV1 INHIB @ 25 μ M
	97	155.0	-66.5	0.7	102	-102
	90			0.1	123	-114
	3					
	100	62.0	-45.3	0.01	94	-108
	94			0.9	92	-36
	62	-166.6	121.8	0.02	69	-70
	113			1.0	64	-146
	76			0.1	94	-66
	82				32	-40
	19				39	-69
	73			2000	71	-2
	1			2000	83	-87

Compound	ADPDIFF %BRL @ 5 μ M 61	Glucose Δ	%BRL	MKNRCV1 EC ₅₀	MKNRCV1 %BRL @ 25 μ M 68	ANTCV1 INHIB @ 25 μ M -57
	61	63.0	-27.0	5.4	68	-57
	110			0.7	96	2
	112			1.3	78	-42
	117			1.7	79	-29
	120			1.4	157	0
	32			2000	47	25
	183				40	44
	38				22	50
	3				25	-40
	2				34	-218
	2				30	-44

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Compound	ADPDIFF %BRL @ 5 µM 14	Glucose Δ	%BRL EC ₅₀	MKNRCV1 %BRL @ 25 µM 18	MKNRCV1 %BRL @ 25 µM 18	ANTCV1 INHIB @ 25 µM 28
	112		11.1	65	4	
	12			28	1	
	113		2000	59	-41	
			1.0			
				70	-58	
			1.3	82 @ 5 µM	62	
			3.6	57 and 47 @ 5 µM	39	

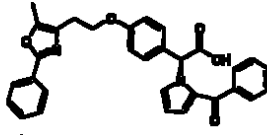
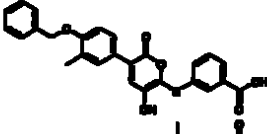
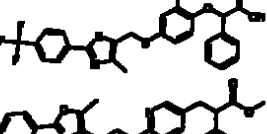
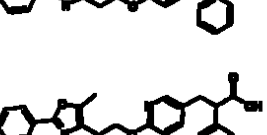
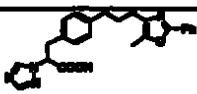
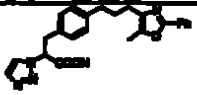
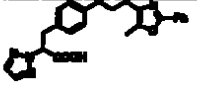
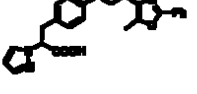
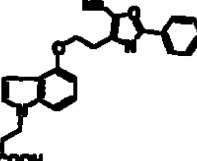
Compound	ADPDIFF %BRL @ 5 μ M	Glucose Δ	%BRL MKNRCV1 EC ₅₀	MKNRCV1 %BRL @ 25 μ M 58 and 39 @ 5 μ M	ANTCV1 INHIB @ 25 μ M -5
				26 @ 5 μ M	-29
				40	12
					
				75 @ 5 μ M	-58

Table 2
Biological Activity

PD Number	Structure	AD3T3-L1 Reporter		In vivo	
		EC ₅₀ (nM)	Max. %Rosi	Δ Glucose@ 20 mg/kg	% Rosiglitazone
0336683 94		9700	62.8	-53	24.38
0338227 92		9570	59	Not tested	
0338228 91		1.06	96	-293.07	128.9%
0339165 93		10.0 <i>activity of racemate</i>	90	Activity for <i>S</i> - enantiomer: PD 344170: - 219 @ 10 mg/kg	102.49%
0333941 53		113	50		96%

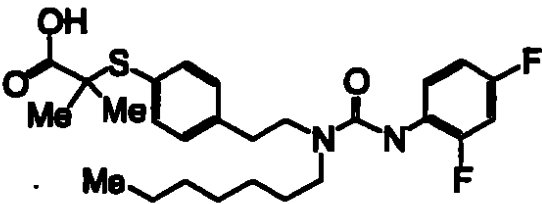
Referring to Table 2, PD 0333941 was shown to lower blood glucose in Ob/Ob diabetic mouse model at 3 mg/Kg. The compound shows a dose response with a maximal effect at 30 mg/Kg.

Referring again to Table 2, PD 0338228 was evaluated for its selective activity against the three types of PPARs using HepG2 cells. In these screens, PD 338228 showed an EC₅₀ = 71.8 nM in the HepG2-hALPHA assay (PPAR alpha) and an EC₅₀ = 92.5 nM in the HepG2-mGAMMA assay (PPAR gamma). It was inactive against PPAR beta. In the PPAR alpha assay, PD 3328228 at max. effect gives only 61% of the max. activity of the reference agent (GW9578). The results obtained with Rosiglitazone and PD 326234 are included in the table shown below.

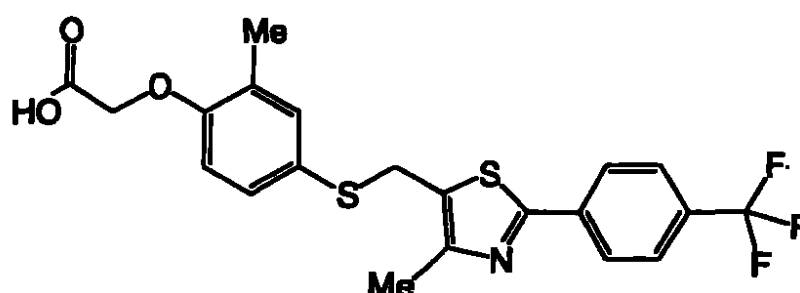
Table 3

Summary of Selective Activity for 338228 with HepG2 cells (2-1-2002)									
Compounds	HepG2-hAlpha			HepG2-hBeta			HepG2-mGamma		
	Max. Res.			Max. Res.%			Max. Res.%		
	Fold (uM)	% GW9578	EC50	Fold (uM)	% GW501516	EC50	Fold (uM)	% Rosi.	EC50
GW9578	48.8(1)	100.0	130nM						
GW501516				54.8(1)	100.0	2.48nM			
Rosiglitazone							7.02(20)	100.0	289.7nM
0338228-0000(P)	27.9(10)	61.8	71.8nM	4.9(20)	9.0	in	28.7(10)	381.0	82.5nM

In the table, GW9578 refers to:



GW501516 refers to:



PD 338228 was identified as a potent, PPARgamma full agonist in the AD3T3-L1 reporter assay. In addition, this compound acts as a dual alpha/gamma agonist as demonstrated in the selectivity assays. It showed a partial agonist profile for PPARalpha. When evaluated in the Ob/Ob mice model for diabetes, PD 338228 was capable of completely normalizing plasma glucose levels at 20 mg/kg in 14 days. Its activity was comparable, or even better, than that of rosiglitazone. PD 338228 is a potential agent for the treatment of type II diabetes and dislipidemias, as that condition is described, for instance, in the Merck Manual (1992).

In general, compounds of the invention may induce fat cell differentiation as described in test A. Results from test E, in particular, demonstrate that the compounds of the invention may lower glucose levels in mice.

Because compounds of the invention induce adipocyte differentiation and lower blood glucose levels, they may be useful in treating disorders associated with insulin resistance. Such disorders include: NIDDM, diabetic angiopathy, atherosclerosis, diabetic nephropathy, diabetic neuropathy, and diabetic ocular complications such as retinopathy, cataract formation and glaucoma, as well as glucocorticoid induced insulin resistance, dyslipidemia, polycystic ovarian syndrome, obesity, hyperglycemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hyperinsulinemia, and hypertension.

Accordingly, the invention also includes a method for treating a disease in a human or other mammal in need thereof in which insulin resistance has been implicated and glucose lowering is desired, comprising administering to said human or mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. The invention also includes a method for treating or preventing insulin resistance in a mammal comprising administering to

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said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. Additionally, compounds of the invention can be used in vitro or in vivo as pharmacological and biochemical tools to assist in the discovery and evaluation of other glucose lowering agents and PPAR γ agonists.

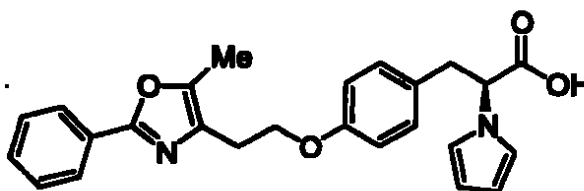
Esters of the general formula VI are readily hydrolyzed to compounds of the invention. Accordingly, the invention also includes a method of preparing a compound of formula I by hydrolyzing a compound of formula VI.

Additionally, esters of the general formula VI may be determined to function as prodrugs for compounds of formula I. Accordingly, the invention also includes a method for treating a disease in a human or other mammal in need thereof in which insulin resistance has been implicated and glucose lowering is desired, comprising administering to said human or mammal an effective amount of a compound of formula VI; or a pharmaceutically acceptable salt thereof.

EXAMPLES

Example 1

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid (3).



General Procedure for Ester Hydrolysis (General Procedure A). (S)-

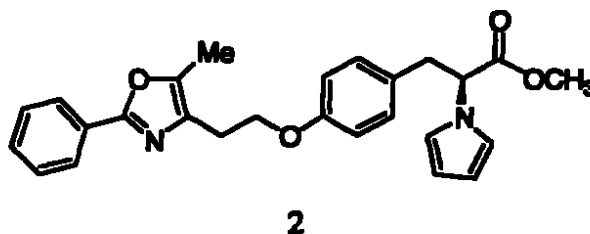
3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (400 mg, 0.930 mmol) was dissolved in THF (10 mL) and H₂O (10 mL). LiOH monohydrate (45 mg, 1.07 mmol) was added in one portion and the suspension stirred for 1 hour. The reaction was diluted with EtOAc (20 mL) and H₂O (20 mL) and organic layer separated. After acidification of the aqueous layer to pH of approximately 2 with aq.HCl and extraction with

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EtOAc (2x20 mL), the organic layers were combined and washed with H₂O (10 mL), brine (10 mL), and dried over MgSO₄. Removal of solvent *in vacuo* gave 3 as white crystals (320 mg, 0.769 mmol). Recrystallized from EtOAc/Hex as fine white needles in 51% yield. M.P. = 155-56 °C. C₂₃H₂₄N₂O₄ Mass Calc. = 416.475; M+1(obs) = 417.2. ¹H NMR (400MHz) CDCl₃ δ: 7.91 (2H, m), 7.38 (3H, m), 6.90 (2H, d, J=8.5 Hz), 6.71 (2H, d, J=8.5 Hz), 6.69 (2H, t, J=2.0, 2.1 Hz), 6.12 (2H, t, J=1.9, 1.9 Hz), 4.69 (1H, dd, J=7.08, 8.03 Hz), 4.16 (2H, t, 6.5, 6.5 Hz), 3.34 (1H, dd, J=6.6, 6.6 Hz), 3.17 (1H, dd, J=8.3, 8.3 Hz), 2.93 (2H, t, J=6.6, 6.6 Hz), 2.32 (3H, s). CHN (theoretical=C=72.10, H=5.81, N=6.73, CHN obs.; C=72.09, H=5.58, N=6.63).

(S)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (2) was prepared in the following manner.

(a) (S)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (2).



General Coupling Procedure (General Procedure B). Pyrrolotyrosine methyl ester (1) (2.68 g, 10.9 mmol), 2-(5-Methyl-2-phenyloxazol-4-yl) ethanol (2.22g, 10.9 mmol) and triphenylphosphine (3.15g, 12.0 mmol) were dissolved in anhydrous THF (100 mL) under N₂ at 0 °C. A solution of diethyl azodicarboxylate (DEAD) (1.89 mL, 12.0 mmol) in THF (50 mL) was added slowly over 30 min. and allowed to equilibrate to 23 °C over 18 hr. The solution was diluted with EtOAc (50mL) and washed with water (30 mL), brine (30 mL) and dried over MgSO₄. After removal of solvent *in vacuo*, SiO₂ gel chromatography with 10%EtOAc/Hex gave 2.4 g of 2 in 51% as a clear oil. Low Resolution Mass Spectroscopy (LRMS) C₂₆H₂₆N₂O₄ MW=430.501 calc. M+1 = 431.2 obs. ¹H NMR (400MHz) CDCl₃ δ: 7.95 (2H, d, J=5.8Hz), 7.40 (3H, m),

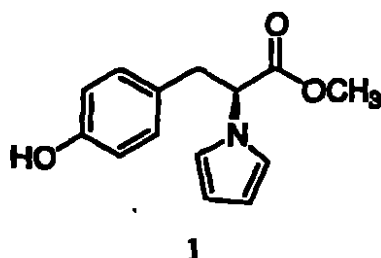
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6.85 (2H, d, $J=8.3$ Hz), 6.72 (2H, d, $J=8.5$ Hz), 6.66 (2H, s), 6.10 (2H, s), 4.63 (1H, dd, $J=6.83, 8.30$ Hz), 4.16 (2H, t, 6.6, 6.6 Hz), 3.65 (3H, s), 3.29 (1H, dd, $J=6.3, 6.3$ Hz), 3.13 (1H, dd, $J=8.8, 8.8$ Hz), 2.93 (2H, t, $J=6.6, 6.6$ Hz), 2.32 (3H, s).

5

(b) Pyrrolotyrosine methyl ester (1).



10 S-tyrosine methyl ester (25.6 g, 131 mmol), 2,5-dimethoxy-tetrahydrofuran (17 mL, 223 mmol) and NaOAc (21.5 g, 262 mmol) were dissolved in a 1:1 mixture of H₂O and acetic acid (150 mL:150 mL) and stirred until homogeneous (ca. 30 min.). The temperature was then raised to 100°C for 20 min. in an oil bath during which time the solution turned a dark brown color.

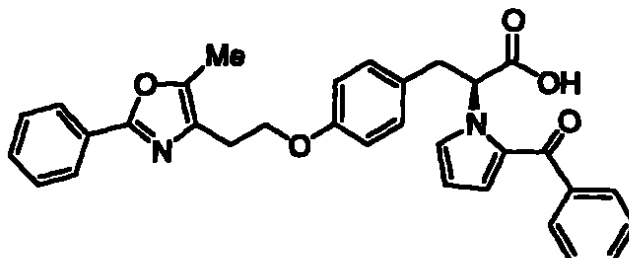
15 After the indicated period of time, the solution was removed from the hot bath and allowed to cool to 23°C. The reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (3 x 75 mL). The organic layers were combined and washed consecutively with H₂O (2 x 75 mL), brine (50 mL) and dried over Mg₂SO₄. The solvent was removed *in vacuo* and the crude residue was

20 chromatographed with 5% MeOH/CHCl₃ to give 15 g (35% yield) of cream colored crystals. ¹H NMR (400MHz) δ (CDCl₃) 6.83 (2H, d, 8 Hz), 6.67 (2H, d, 2Hz), 6.65 (2H, d, 8Hz), 6.11 (2H, d, 2Hz), 4.65 (1H, q, 6Hz), 4.66 (1H, s), 3.66 (3H, s), 3.31 (1H, dd, 6 Hz), 3.28 (1H, dd, 6 Hz).

25 The procedures described in Example 1 were used to prepare (R)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid and racemic (S)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid.

Example 2

(S)-2-(2-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (9).



5

9

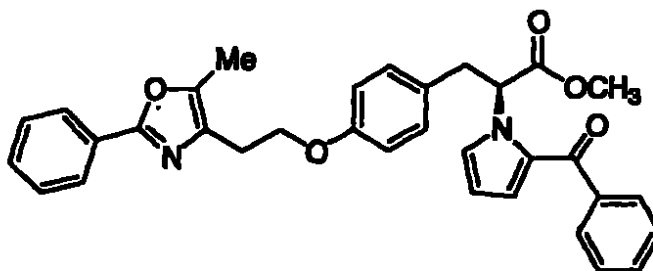
Ester hydrolysis of (S)-2-(2-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (8) was carried out in a manner similar to General Procedure A. After treatment with LiOH, (S)-2-(2-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (9) (498mg, 0.932 mmol) gave 430 mg of (S)-2-(2-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (10) (0.827 mmol) in 89% yield. $C_{32}H_{28}N_2O_5$ Mol. Wt.: 520.5752; $M+1(\text{obs}) = 521.2$. ^1H NMR (400 MHz, CDCl_3) δ : 7.93 (2H, d, $J=8.1\text{Hz}$), 7.66 (2H, d, $J=7.6\text{Hz}$), 7.48 (1H, m), 7.37 (6H, m), 7.16 (1H, s), 6.92 (2H, d, $J=8.3\text{Hz}$), 6.67 (2H, d, $J=8.3\text{Hz}$), 6.64 (1H, d, $J=3.2\text{Hz}$), 6.16 (1H, t, $J=2.9, 2.9\text{Hz}$), 5.78 (1H, s), 4.09 (2H, m), 3.52 (1H, dd, $J=6.1, 14.4\text{Hz}$), 3.21 (1H, dd, $J=9.03, 14.1\text{Hz}$), 2.91 (2H, t, $J=6.6, 6.6\text{Hz}$), 2.31 (3H, s).

20

(S)-2-(2-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (8) was prepared in the following manner.

- (a) (S)-2-(2-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (8).

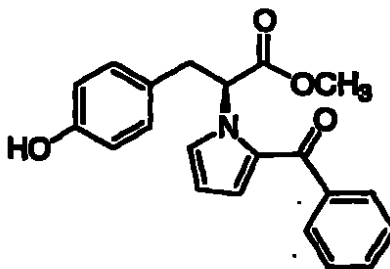
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8

(S)-2-(2-Benzoyl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (7) was coupled to 2-(5-Methyl-2-phenyloxazol-4-yl) ethanol in a manner similar to that described in General Procedure B. Phenol 7 (3.1 g, 8.88 mmol), was treated with 1 mole equivalent each of alcohol (1.8 g, 8.88 mmol), triphenylphosphine (2.33 g, 8.88 mmol), and diethyl azodicarboxylate (1.40 mL, 8.88 mmol) and gave 2.3g (4.31 mmol) of 2-substituted product in 49% yield as a pale yellow oil. $C_{33}H_{30}N_2O_5$ Mol. Wt.: 534.602; $M+1(\text{obs})=535.2$. ^1H NMR (CDCl_3) δ : 7.96 (2H, dd, $J=1.9, 7.8$ Hz), 7.54 (2H, m), 7.40 (6H, m), 7.09 (1H, s), 6.88 (2H, d, $J=8.5$ Hz), 6.66 (2H, d, $J=8.5$ Hz), 6.56 (1H, dd, $J=1.5, 3.9$ Hz), 6.12 (1H, dd, $J=1.5, 2.7$ Hz), 6.10 (1H, bs), 4.10 (2H, m), 3.74 (3H, s), 3.44 (1H, dd, $J=5.4, 13.9$ Hz), 3.18 (1H, dd, $J=10, 14$ Hz), 2.91 (2H, t, $J=6.6, 6.6$ Hz), 2.32 (3H, s).

(b) (S)-2-(2-Benzoyl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (7).



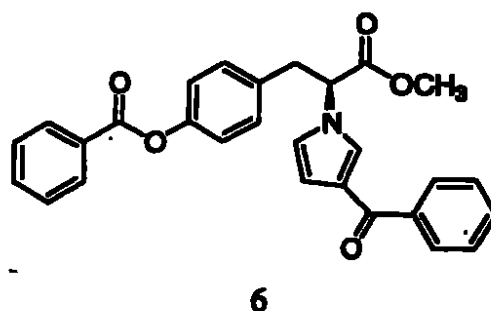
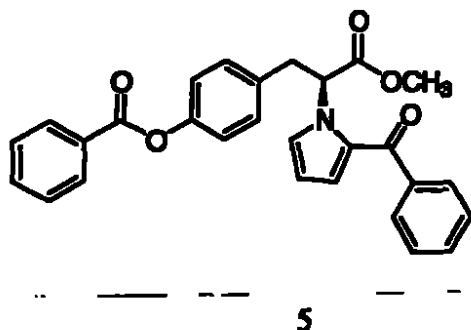
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General Procedure C. Benzoic acid (S)-4-[2-(2-benzoyl-pyrrol-1-yl)-2-methoxycarbonyl-ethyl]-phenyl ester (5) (300mg, 0.661 mmol) was dissolved in

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anhydrous methyl alcohol (10 mL) and placed under N₂ at 23°C. After addition of K₂CO₃ (136 mg, 0.991 mmol) the suspension was vigorously stirred for 3 hours and periodically monitored by TLC. Once complete, the methanol was removed *in vacuo* and the residue chromatographed with 10% EtOAc/Hexanes to give free phenol 7 in 90% yield (200 mg, 0.60 mmol) as white powder. (S)-2-(2-Benzoyl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (7). C₂₁H₁₉NO₄ Mol. Wt.: 349.380; M+1 (obs) = 350.3. ¹H NMR (400 MHz, CDCl₃) δ: 7.57 (2H, dd, J=1.5, 7.5 Hz) 7.46 (1H, m), 7.36 (2H, m), 7.09 (1H, s), 6.86 (2H, d, J=8.5 Hz), 6.60 (2H, d, J=8.5 Hz), 6.60 (1H, s), 6.13 (1H, dd, J=2.7, 4.1 Hz), 6.09 (1H, s), 4.62 (1H, s), 3.73 (3H, s), 3.44 (1H, dd, J=5.6, 14.1 Hz), 3.17 (1H, dd, J=9.8, 14.1 Hz).

(c) Benzoic acid (S)-4-[2-(2-benzoyl-pyrrol-1-yl)-2-methoxycarbonyl-ethyl]-phenyl ester (5) and Benzoic acid (S)-4-[2-(3-benzoyl-pyrrol-1-yl)-2-methoxycarbonyl-ethyl]-phenyl ester (6).



General Procedure D. Trifluoromethane sulfonic acid (45 μL, 0.516 mmol) was added to a stirring solution of Benzoic acid 4-(2-methoxycarbonyl-2-pyrrol-1-yl-ethyl)-phenyl ester (4) (150 mg, 0.430 mmol) and benzoyl chloride (60 μL, 0.516 mmol) in dichloromethane (20 mL) at 28°C under N₂. After stirring for 18 hours, solvent was removed *in vacuo*. SiO₂ gel chromatography of the resulting residue with 10%EtOAc/Hexanes gave 80 mg of 2 substituted pyrrole (5) (0.177mmol, 40%) and 37 mg of 3-substituted (6) (0.082 mmol, 20% yield).

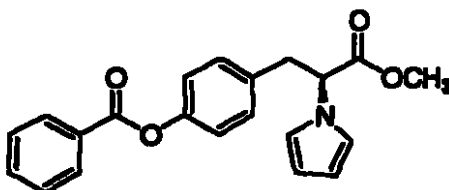
Benzoic acid (S)-4-[2-(2-benzoyl-pyrrol-1-yl)-2-methoxycarbonyl-ethyl]-phenyl ester (5) C₂₈H₂₃NO₅: Mass (calc) 453.4860; M+1 (obs)=454.2. ¹H NMR

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(400 MHz, CDCl_3) δ : 8.13 (2H, dd, $J=1.2, 8.5$ Hz), 7.61 (3H, m), 7.47 (3H, m), 7.40 (2H, m), 7.07 (2H, d, $J=8.8$ Hz), 7.04 (1H, s), 7.00 (2H, d, $J=8.8$ Hz), 6.62 (1H, t, $J=1.7, 2.4$ Hz), 6.15 (1H, dd, $J=2.7, 3.9$ Hz), 6.15 (1H, s), 3.76 (3H, s), 3.55 (1H, dd, $J=5.6, 14.1$ Hz), 3.29 (1H, dd, $J=10, 14.1$ Hz).

5 Benzoic acid (S)-4-[2-(3-benzoyl-pyrrol-1-yl)-2-methoxycarbonyl-ethyl]-phenyl ester (6). $\text{C}_{28}\text{H}_{23}\text{NO}_5$; Mass (calc) 453.4860; $M+1$ (obs)=454.2. ^1H NMR (400 MHz, CDCl_3) δ : 8.14 (2H, d, $J=7.1$ Hz), 7.70 (2H, d, $J=7.1$ Hz), 7.60 (1H, m), 7.43 (5H, m), 7.16 (1H, t, $J=1.7, 1.9$ Hz), 7.09 (2H, d, $J=8.8$), 7.04 (2H, d, $J=8.5$ Hz), 6.76 (1H, q, $J=1.0, 1.9, 2.2$ Hz), 6.69 (1H, q, $J=1.2, 1.7, 1.7$ Hz), 4.73
10 (1H, dd, $J=5.9, 9.5$ Hz), 3.74 (3H, s), 3.43 (1H, dd, 5.8, 14.1 Hz), 3.25 (1H, dd, $J=9.2, 13.9$ Hz).

(d) Benzoic acid 4-(2-methoxycarbonyl-2-pyrrol-1-yl-ethyl)-phenyl ester (4).



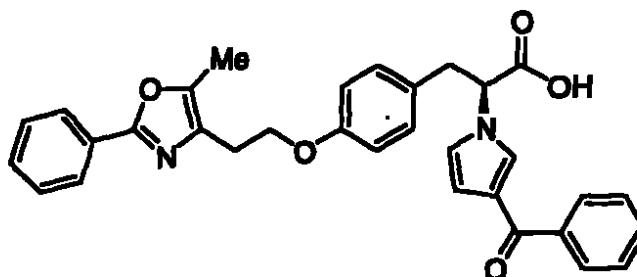
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General Procedure E. Triethylamine (290 μL , 2.06 mmol) was added to a stirring solution of Pyrrolotyrosine methyl ester (252 mg, 1.03 mmol) in dichloromethane (20 mL) under N_2 at 23°C. Benzoyl chloride (143 μL , 1.23
20 mmol) was added dropwise over a 5 minute period and the reaction was stirred for 2 hours. Solvent was removed *in vacuo* and chromatographed via SiO_2 with 10% EtOAc/hexanes to give the benzoyl ester 4 in 86% yield (310 mg, 0.89 mmol) as a white foam. $\text{C}_{21}\text{H}_{19}\text{NO}_4$ Mass Calc. = 349.380; $M+1$ (obs)= 350.2. ^1H NMR (400MHz, CDCl_3) δ : 8.17 (2H, d, $J=6.35$ Hz), 7.62 (1H, m), 7.47 (2H, m), 7.09
25 (2H, d, $J=8.8$ Hz), 7.04 (2H, d, $J=8.6$ Hz), 6.71 (2H, t, $J=2.2, 2.1$ Hz), 6.16 (2H, t, $J=2.2, 2.2$ Hz), 4.72 (1H, dd, $J=2.4, 2.4$ Hz), 3.70 (3H, s), 3.43 (1H, dd, $J=6.3, 6.3$ Hz), 3.25 (1H, dd, $J=9.0, 9.0$ Hz).

Example 3

(S)-2-(3-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (12).



5

12

Ester hydrolysis was carried out in a manner similar to General Procedure A. After treatment with LiOH, (S)-2-(3-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (11) (400mg, 0.749 mmol) gave 260mg of carboxylic acid (S)-2-(3-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (12). (0.500 mmol) in 67% yield. $C_{32}H_{28}N_2O_5$ Mol. Wt.: 520.5752; $M+1(\text{obs}) = 521.2$. ^1H NMR (400 MHz, CDCl_3) δ : 7.92 (2H, m), 7.62 (2H, d, $J=8.0\text{Hz}$), 7.26 (6H, m), 7.06 (1H, s), 6.85 (2H, d, $J=8.3\text{ Hz}$), 6.69 (2H, d, $J=7.8\text{Hz}$), 6.68 (1H, s), 6.60 (1H, t, $J=1.5, 1.5\text{ Hz}$), 4.65 (1H, t, $J=6.8, 8.1\text{Hz}$), 4.09 (3H, m), 3.31 (1H, dd, $J=6.6, 14.0\text{ Hz}$), 3.10 (1H, dd, $J=9.0, 14.1\text{Hz}$), 2.95 (2H, $J=6.6, 6.1\text{Hz}$), 2.31 (3H, s).

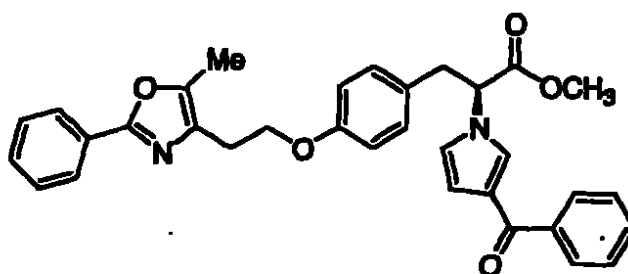
15

(S)-2-(3-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (11) was prepared in the following manner.

20

- (a) (S)-2-(3-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (11).

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11

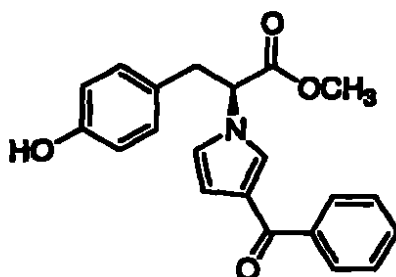
Prepared in a manner similar to that described in General Procedure B.

5 (S)-2-(3-Benzoyl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (8) (800 mg, 2.29 mmol), was treated with 1 mole equivalent each of 2-(5-Methyl-2-phenyloxazol-4-yl) ethanol (465 mg, 2.29 mmol), triphenylphosphine (600 mg, 2.29 mmol), and diethyl azodicarboxylate (360 μ L, 2.29 mmol) and gave 400 mg (0.749 mmol) of 3-substituted product (11) in 32% yield as a pale yellow oil.

10 $C_{33}H_{30}N_2O_5$ Mol. Wt.: 534.602; $M+1(\text{obs})=535.2$. ^1H NMR (400 MHz, CDCl_3) δ : 8.00 (2H, m), 7.67 (2H, d, $J=6.8\text{Hz}$), 7.40 (6H, m), 7.08 (1H, t, $J=1.9, 1.9\text{Hz}$), 6.84 (2H, d, $J=8.5\text{Hz}$), 6.72 (2H, d, $J=8.5\text{Hz}$), 6.71 (1H, t, $J=2.2, 2.2\text{Hz}$), 6.66 (1H, t, $J=1.7\text{Hz}$), 4.65 (1H, dd, $J=5.6\text{Hz}$), 4.16 (2H, m), 3.71 (3H, s), 3.31 (1H, dd, $J=5.8, 14.1\text{Hz}$), 3.13 (1H, dd, $J=9.3, 14.0\text{Hz}$), 2.98 (2H, m), 2.01 (3H, s).

15

(b) (S)-2-(3-Benzoyl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (10).



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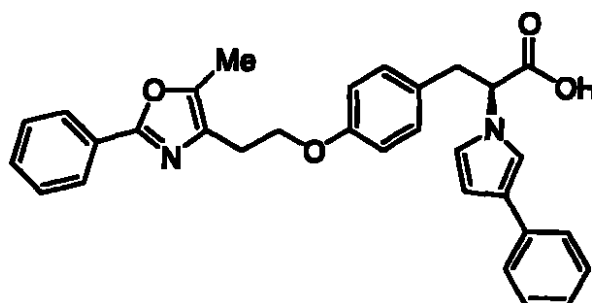
Prepared from benzoic acid (S)-4-[2-(3-benzoyl-pyrrol-1-yl)-2-methoxycarbonyl-ethyl]-phenyl ester (6) according to General Procedures C-E. $C_{21}H_{19}NO_4$ Mol. Wt.: 349.380; $M+1(\text{obs}) = 350.3$. ^1H NMR (400 MHz, CDCl_3)

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δ : 7.68 (2H, d, $J=6.8$ Hz), 7.48 (1H, m), 7.40 (3H, m), 7.10 (1H, t, $J=1.7, 1.9$ Hz), 6.81 (2H, d, $J=8.5$ Hz), 6.73 (1H, t, $J=2.9$ Hz, 2.2 Hz), 6.67 (2H, d, $J=8.5$ Hz), 6.65 (1H, s), 4.66 (1H, dd, $J=5.6, 9.2$ Hz), 3.72 (3H, s), 3.31 (1H, dd, $J=5.6, 13.9$ Hz), 3.13 (1H, dd, $J=9.5, 14.1$ Hz).

5 Example 4

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid (15).



15

10

The compound was prepared as described in General Procedure A. (S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester (14) (1.6g, 3.14 mmol) was hydrolyzed to give (S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid (15) (1.2 g, 2.43 mmol) in 77% yield as cream colored crystals, which were recrystallized from EtOAc/Hexanes. Mp. 146°C-147°C. $C_{31}H_{28}N_2O_4$ Mol. Wt.: 492.565; $M+1 = 493.2$. ^1H NMR (400 MHz, $CDCl_3$) δ : 7.91 (2H, dd, $J=3.7, 7.3$ Hz), 7.44 (2H, d, $J=7.3$ Hz), 7.37 (3H, m), 7.27 (2H, t, $J=7.5, 7.8$ Hz), 7.11 (1H, t, $J=7.3, 7.3$ Hz), 7.01 (1H, s), 6.93 (2H, d, $J=8.5$ Hz), 6.71 (2H, d, $J=8.5$ Hz), 6.69 (1H, t, $J=2.4, 2.4$ Hz), 6.42 (1H, t, $J=2.0, 2.7$ Hz), 4.67 (1H, t, $J=7.1, 7.8$ Hz), 4.10 (2H, t, $J=6.3, 6.6$ Hz), 3.36 (1H, dd, $J=6.8, 14.2$ Hz), 3.18 (1H, dd, $J=8.0, 13.9$ Hz), 2.93 (2H, m), 2.32 (3H, s). CHN(theoretical) C= 75.59; H= 5.73; N= 5.69; (Obs) C= 75.42; H= 5.80; N= 5.50.

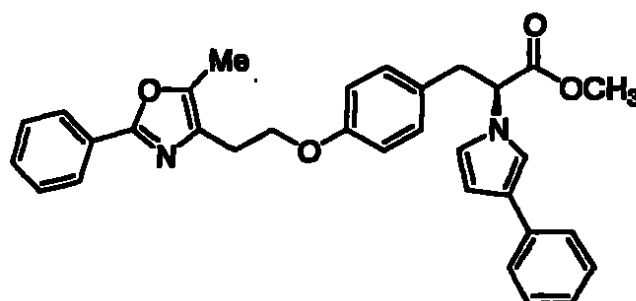
20

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(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester (14) was prepared in the following manner.

- 5 (a) (S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester (14).

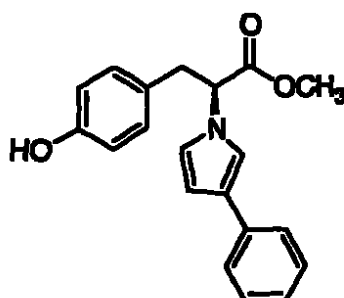


14

- 10 The compound was prepared via Mitsunobu coupling as described in General Procedure B. (S)-3-(4-Hydroxy-phenyl)-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester (13) (2.0 g, 6.23 mmol) gave coupled product (S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester (14) (1.6g, 3.16 mmol) in 51% yield as a pale yellow oil. C₂₂H₃₀N₂O₄ Mol. Wt.: 506.592; M+1(obs)=507.1. ¹H NMR (400 MHz, CDCl₃) δ: 7.94 (2H, d, J=8.1Hz), 7.46 (2H, d, J=8.1Hz), 7.40 (3H, m), 7.29 (2H, t, J=7.3, 7.6Hz), 7.12 (1H, t, J=7.3, 7.2Hz), 7.00 (1H, s), 6.90 (2H, d, J=8.1Hz), 6.74 (2H, d, J=8.1Hz), 6.68 (1H, s), 6.42 (1H, s), 4.65 (1H, t, J=7.8, 7.3 Hz), 4.17 (2H, t, J=6.6, 6.8Hz), 3.69 (3H, s), 3.33 (1H, dd, J=6.6, 13.9Hz), 3.19 (1H, dd, J=9.3, 13.7Hz), 2.92 (2H, t, J=6.6, 7.1 Hz), 2.35 (3H, s).
- 15
- 20

- (b) (S)-3-(4-Hydroxy-phenyl)-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester (13).

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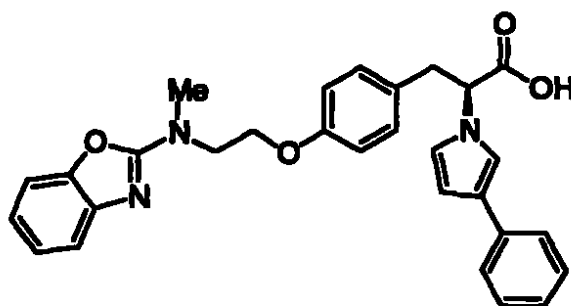


13

Tyrosine methyl ester (390 mg, 2.0 mmol) was added to a suspension of 3-phenyl-2,5-dimethoxy-tetrahydrofuran (500 mg, 2.4 mmol) and NaOAc (328 mg, 2.4 mmol) in H₂O (10 mL) and HOAc (10 mL). After heating at reflux for 1 hour, 562 mg (1.75 mmol) of (S)-3-(4-Hydroxy-phenyl)-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester (13) was obtained in 87% yield as a pale yellow oil. C₂₀H₁₉NO₃ Mol. Wt.: 321.370; M+1(obs)=322.1. ¹H NMR (400 MHz, CDCl₃) δ: 7.47 (2H, d, J=7.3Hz), 7.30 (2H, t, J=7.6, 7.8Hz), 7.14 (1H, t, J=7.3, 7.3Hz), 7.01 (1H, s), 6.88 (2H, d, J=8.3Hz), 6.67 (1H, s), 6.67 (2H, d, J=8.5Hz), 6.43 (1H, s), 4.65 (1H, dd, J=6.3, 8.5Hz), 4.60 (1H, s), 3.71 (3H, s), 3.34 (1H, dd, J=6.3, 13.9Hz), 3.20 (1H, dd, J=8.8, 13.9 Hz).

Example 5

(S)-3-[4-[2-(Benzoxazol-2-yl-methyl-amino)-ethoxy]-phenyl]-2-(3-phenyl-pyrrol-1-yl)-propionic acid (16).



16

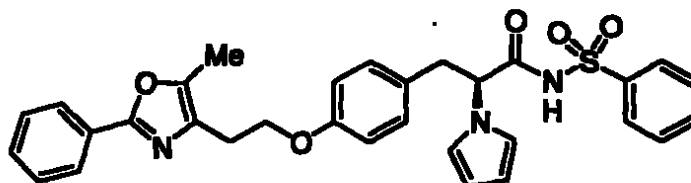
(S)-3-(4-Hydroxy-phenyl)-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester (13) was coupled with 2-(Benzoxazol-2-yl-methyl-amino)-ethanol as in General Procedure B (24 yield). Hydrolysis of the ester as in General Procedure

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A gave acid (S)-3-[4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl]-2-(3-phenyl-pyrrol-1-yl)-propionic acid (16) in 34% yield. $C_{29}H_{27}N_3O_4$, Mol. Wt.: 481.543; $M+1 = 482.2$; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.49 (2H, d, $J=7.1$ Hz), 7.30 (5H, m), 7.13 (2H, dt, $J=1.5, 7.3$ Hz), 7.09 (1H, t, $J=2.0, 2.0$ Hz), 7.00 (2H, d, $J=8.3$ Hz), 6.77 (1H, t, $J=2.4, 2.7$ Hz), 6.73 (2H, d, $J=8.5$ Hz), 6.47 (1H, t, $J=2.0, 2.7$ Hz), 4.73 (1H, t, $J=7.6, 7.8$ Hz), 4.15 (1H, m), 4.02 (1H, m), 3.92 (1H, m), 3.80 (1H, m), 3.40 (1H, dd, $J=7.6, 13.9$ Hz), 3.26 (3H, s), 3.25 (1H, m).

Example 6

N-(S)-(3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionyl)-Benzenesulfonamide (17).



17

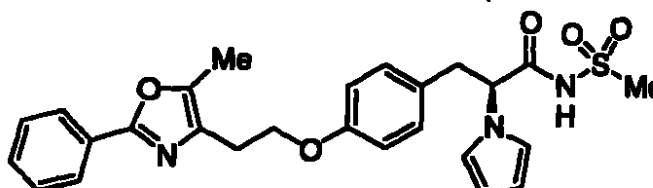
(S)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid (3) (275 mg, 0.661 mmol) was dissolved in CH_2Cl_2 (10 mL) under N_2 and at 23 °C. 1,1-carbonyldiimidazole (128 mg, 0.793 mmol) was then added and the solution stirred for 16 hours. In a separate flask, a 60% suspension of sodium hydride (26 mg, 0.661 mmol) was added to a stirring solution of benzenesulfonamide (124 mg, 0.793 mmol) in dry DMF (5 mL) at $-78^\circ C$ under N_2 . After 30 minutes, the solution was allowed to equilibrate to 23°C over 1 hour, then transferred drop-wise via syringe to the aforementioned solution of mixed anhydride. After two hours, the reaction was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (20 mL), brine (20 mL), and dried over $MgSO_4$. SiO_2 gel chromatography with 30% EtOAc/Hex gave acylsulfonamide 17 (37 mg, 0.067 mmol) in 10% yield as a clear oil. $C_{31}H_{29}N_3O_5S$; Mol. Wt.: 555.645; $M+1=556.0$. ^1H NMR (400 MHz, $CDCl_3$) δ : 8.01 (4H, m), 7.70 (1H, m), 7.55 (3H, m), 7.44 (2H, d, $J=1.9$ Hz), 6.74 (2H, d, $J=8.5$ Hz), 6.67 (2H, d, $J=8.3$ Hz), 6.48 (2H, s),

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6.21 (2H, s), 4.73 (1H, s), 4.55 (1H, dd, $J=4.4, 10.5$ Hz), 4.19 (2H, t, $J=6.3, 6.1$ Hz), 3.41 (1H, dd, $J=3.9, 14.6$ Hz), 3.02 (3H, m), 2.37 (3H, s).

Example 7

5 N-(S)-(3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionyl)-Methanesulfonamide (18).



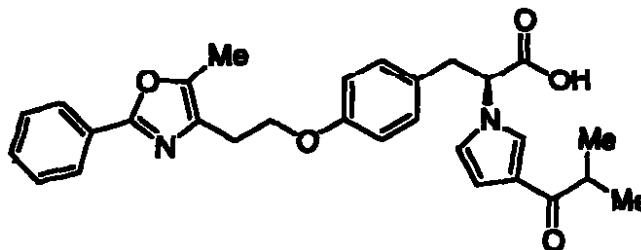
18

10 Using the procedure described in Example 6, (S)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid (3) (200 mg, 0.481 mmol) gave N-(S)-(3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionyl)-methanesulfonamide (18) (130 mg, 0.263) in 55% yield as a clear oil in a manner similar to that used to obtain N-(S)-(3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionyl)-

15 Benzenesulfonamide (17). $C_{26}H_{27}N_3O_5S$; Mol. Wt.: 493.576; $M+1=494.2$. ^1H NMR (400 MHz, $CDCl_3$) δ : 7.93 (2H, dd, $J=2.4, 7.8$ Hz), 7.4 (3H, m), 6.99 (1H, s), 6.85 (2H, d, $J=8.3$ Hz), 6.68 (2H, d, $J=8.5$ Hz), 6.66 (2H, s), 6.03 (2H, s), 4.62 (1H, bs), 4.57 (1H, m), 4.13 (2H, t, $J=6.5, 6.8$ Hz), 3.35 (1H, dd, $J=5.1, 14.2$ Hz), 3.09 (1H, m), 3.09 (3H, s), 2.91 (2H, t, $J=6.6, 6.6$ Hz), 2.33 (3H, s).

20 **Example 8**

(S)-2-(3-Isobutyryl-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid (21).

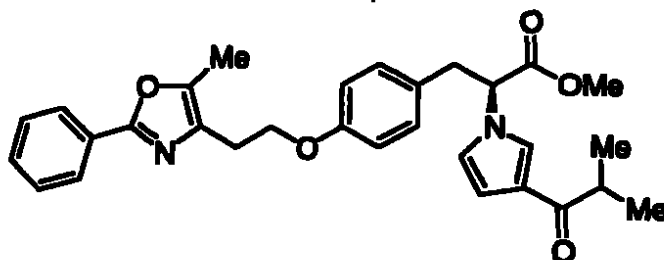


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21

Hydrolysis of 107 mg of (S)-2-(3-Isobutyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (20) according to General Procedure A gave (S)-2-(3-Isobutyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (21) (23 mg, 0.047 mmol) in 22% yield as a yellow oil. $C_{29}H_{30}N_2O_5$ Mol. Wt. for (S)-2-(3-Isobutyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (21): 486.559; $M-1=485.2$. ^1H NMR (400 MHz, $CDCl_3$) δ : 7.96 (2H, dd, $J=2.2, 2.2$ Hz), 7.41 (3H, m), 7.31 (1H, t, $J=2.0, 2.0$ Hz), 6.92 (2H, d, $J=8.8$ Hz), 6.73 (2H, d, $J=8.8$ Hz), 6.69 (1H, d, $J=2.2$ Hz), 6.53 (1H, dd, $J=1.4, 2.9$ Hz), 4.72 (1H, dd, $J=7.1, 8.1$ Hz), 4.12 (2H, t, $J=6.6, 6.8$ Hz), 3.38 (1H, dd, $J=6.8, 13.9$ Hz), 3.17 (1H, dd, $J=8.1, 13.9$ Hz), 3.12 (1H, m), 2.99 (2H, t, $J=6.6, 6.6$ Hz), 2.37 (3H, s), 1.11 (6H, dd, 6.8, 8.8Hz).

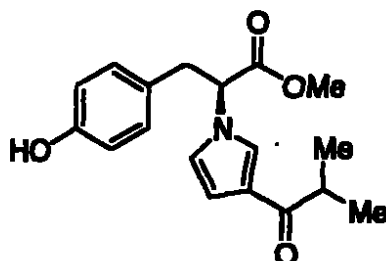
(a) (S)-2-(3-Isobutyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (20) was prepared in the following manner.



(S)-2-(3-Isobutyryl-pyrrol-1-yl)-propionic acid methyl ester (19) (300 mg, 0.952 mmol) was coupled with 2-(5-Methyl-2-phenyloxazol-4-yl) ethanol as in General Procedure B to give (S)-2-(3-Isobutyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (20) (120 mg, 0.240 mmol) in 25% yield.

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(b) (S)-2-(3-Isobutyryl-pyrrol-1-yl)-propionic acid methyl ester (19).

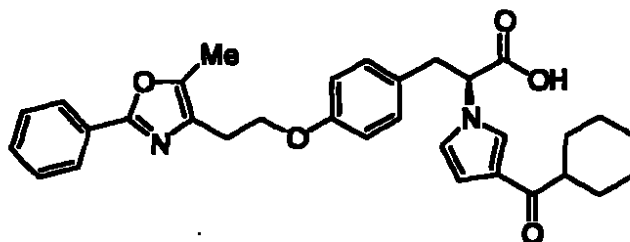


19

Prepared according to General Procedures C-E. The title compound was
 5 obtained in a manner similar to that used to obtain compound #10 utilizing
 isobutyryl chloride. NMR (δ ; CHCl_3); 7.22 (1H, s); 6.79 (2H, d, $J=8.5\text{Hz}$); 6.69
 (2H, d, $J=8.4\text{Hz}$); 6.67 (1H, m); 6.57 (1H, m); 4.68 (1H, m); 3.74 (3H, s); 3.34
 (1H, m); 3.11 (2H, m); 1.13 (6H, t, $J=7.0, 7.0\text{ Hz}$). CIMS m/z 316.1 (M^+)

Example 9

10 (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-
 oxazol-4-yl)-ethoxy]-phenyl]-propionic acid (24).



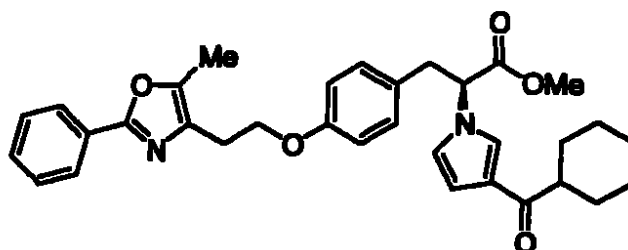
24

15 Prepared from (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-[2-(5-
 methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester (23) as
 in General Procedure A. $\text{C}_{32}\text{H}_{34}\text{N}_2\text{O}_5$ Mol. Wt.: 526.623; $\text{M}+1=527.2$. ^1H NMR
 (400 MHz, CDCl_3) δ : 7.91 (2H, dd, $J=3.7, 7.1\text{Hz}$), 7.39 (3H, t, $J=3.2, 2.7\text{Hz}$), 7.30
 (1H, s), 6.89 (2H, m), 6.75 (3H, m), 6.45 (1H, m), 4.68 (1H, m), 4.09 (2H, m),
 20 3.34 (1H, m), 3.13 (1H, m), 2.95 (2H, m), 2.79 (1H, m), 2.34 (3H, s), 1.74 (5H,
 m), 1.66 (1H, m), 1.45 (2H, m), 1.26 (1H, m).

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(S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester (23) was prepared in the following manner.

- 5 (a) (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester (23).

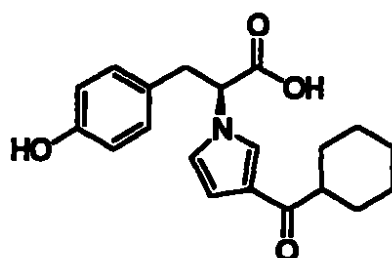


23

10

(S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-propionic acid methyl ester (22) was coupled with 2-(5-Methyl-2-phenyloxazol-4-yl) ethanol according to General Procedure B to give the title compound.

- 15 (b) (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-propionic acid methyl ester (22).



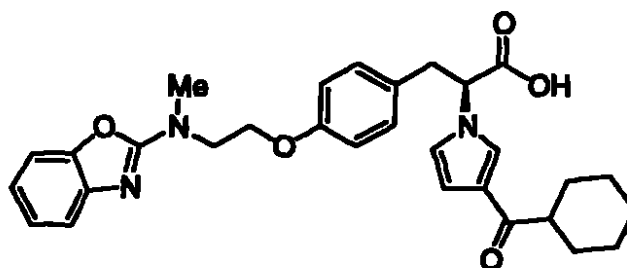
22

20 The title compound was obtained in 43% yield in a manner similar to that used to obtain compound #10 utilizing cyclohexane carbonylchloride. NMR (δ ;CHCl₃); 6.80 (2H, d, J=8.5Hz); 6.65 (2H, d, J=8.5Hz); 6.63 (1H, s); 6.54 (1H, s); 4.90 (1H, s); 4.65 (1H, m); 3.71 (3H, s); 3.30 (1H, m); 3.13 (1H, m); 2.81 (1H, m); 1.79 (4H, m); 1.67 (1H, m); 1.45 (2H, m); 1.29 (3H, m).

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Example 10

(S)-3-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-cyclohexanecarbonyl-pyrrol-1-yl)-propionic acid (26).

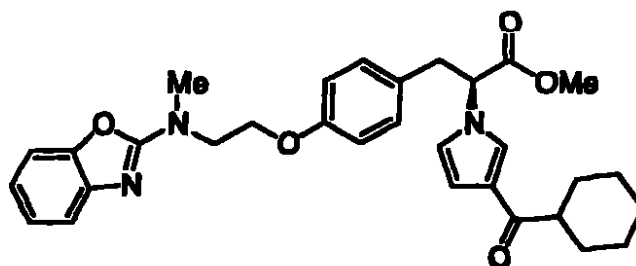


26

Hydrolysis of (S)-3-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-cyclohexanecarbonyl-pyrrol-1-yl)-propionic acid methyl ester (25) as in General Procedure A gave the title compound. $C_{30}H_{33}N_3O_5$ Mol. Wt.: 515.600; $M+1=516.2$. ^1H NMR (400 MHz, $CDCl_3$) δ : 7.35 (2H, m), 7.34 (1H, s), 7.23 (1H, s), 7.15 (1H, dt, $J=1.0, 7.5$ Hz), 7.02 (1H, dt, $J=1.2, 7.8$ Hz), 6.97 (2H, d, $J=8.5$ Hz), 6.74 (1H, s), 6.72 (2H, d, $J=8.5$ Hz), 6.57 (1H, dd, $J=1.5, 2.9$ Hz), 4.73 (1H, t, $J=7.6, 7.6$ Hz), 4.07 (2H, m), 3.88 (2H, m), 3.37 (1H, dd, $J=7.6, 13.9$ Hz), 3.28 (3H, s), 3.18 (1H, dd, $J=7.6, 13.9$ Hz), 2.83 (1H, t, $J=8.8, 8.8$ Hz), 1.77 (4H, m), 1.66 (1H, m), 1.46 (2H, dd, $J=2.4, 3.9$ Hz), 1.27 (3H, m).

(S)-3-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-cyclohexanecarbonyl-pyrrol-1-yl)-propionic acid methyl ester (25) was prepared in the following manner.

- (a) (S)-3-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-cyclohexanecarbonyl-pyrrol-1-yl)-propionic acid methyl ester (25).



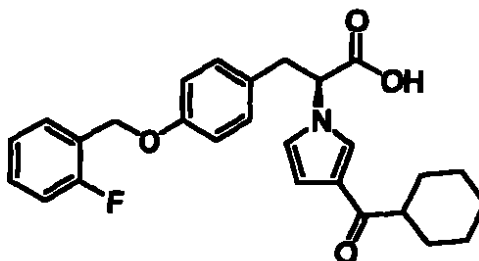
-110-

25

Prepared according to General Procedure B using 2-(Benzooxazol-2-yl-methyl-amino)-ethanol as the alcohol. NMR (δ ; CHCl_3); 7.34 (1H, d, $J=7.5\text{Hz}$); 7.25 (1H, s); 7.15 (1H, t, $J=7.5, 7.8\text{Hz}$); 7.00 (1H, t, $J=7.5, 7.8\text{Hz}$); 6.86 (2H, d, $J=8.3\text{Hz}$); 6.73 (2H, d, $J=8.3\text{Hz}$); 6.65 (1H, s); 6.55 (1H, s); 4.66 (1H, m); 4.20 (2H, t, $J=5.1, 5.1\text{Hz}$); 3.92 (2H, t, $J=5.1, 5.1\text{Hz}$); 3.72 (3H, s); 3.32 (1H, m); 3.32 (3H, s); 3.18 (1H, m); 2.81 (1H, m); 1.79 (4H, m); 1.65 (1H, m); 1.42 (2H, m); 1.22 (3H, m).

10 Example 11

(S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-(2-fluoro-benzyloxy)-phenyl]-propionic acid (28).



28

15

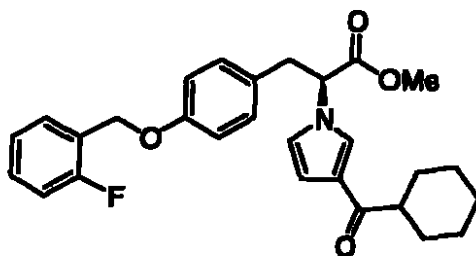
Hydrolysis of (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-(2-fluoro-benzyloxy)-phenyl]-propionic acid methyl ester (27) according to General Procedure A gave (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-(2-fluoro-benzyloxy)-phenyl]-propionic acid (28) (20mg, 0.044mmol) in 16% yield as a pale yellow oil. $\text{C}_{27}\text{H}_{28}\text{FNO}_4$ Mol. Wt.: 449.514; $M+1 = 450.1$ ^1H NMR (400 MHz, CDCl_3) δ : 7.46 (1H, t, $J = 7.5, 7.5\text{Hz}$), 7.20 (1H, m), 7.14 (1H, t, $J=7.3, 7.3\text{Hz}$), 7.07 (1H, t, $J=9.0, 9.5\text{Hz}$), 6.91 (2H, d, $J=8.5, 8.5\text{Hz}$), 6.90 (1H, s), 6.84 (2H, d, $J=8.5, 8.5\text{Hz}$), 6.66 (1H, s), 6.58 (1H, s), 5.06 (2H, s), 4.74 (1H, m), 3.40 (1H, m), 3.22 (1H, m), 2.83 (1H, t, $d=12.2, 12.2\text{Hz}$), 1.80 (2H, m), 1.68 (2H, m), 1.47 (3H, m), 1.29 (3H, m).

25

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(S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-(2-fluoro-benzyloxy)-phenyl]-propionic acid methyl ester (27) was prepared in the following manner.

- (a) (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-(2-fluoro-benzyloxy)-phenyl]-propionic acid methyl ester (27).

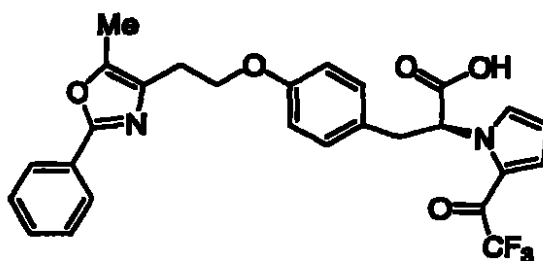


27

According to General Procedure B by coupling of (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-propionic acid methyl ester (27) with 2-fluorobenzyl alcohol. The title compounds was isolated in 70% yield.

Example 12

(S)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid (33).



33

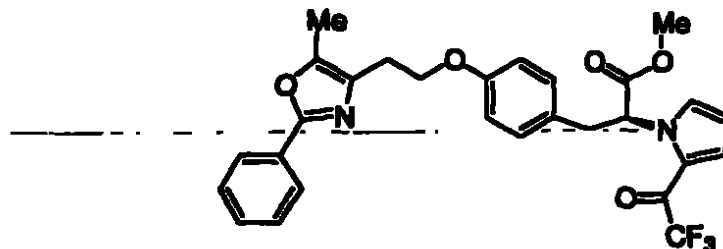
According to General Procedure A. To a stirred solution of (S)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid methyl ester (32) (2.608 g, 4.7 mmol) in 2-methoxy ethanol, (8 mL) and water (2 mL) was added lithium hydroxide (113 mg). The reaction mixture stirred at room temperature for 20 minutes, poured into water,

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acidified with aqueous HCl, extracted with EtOAc and dried over MgSO₄. The solvent was removed under reduced pressure. The remaining residue was purified by chromatography on silica gel eluting with 1:1 EtOAc:Hexane. The resulting white foam was recrystallized using ethyl acetate hexane to give white needle crystals. Yield = 1.232g, 51%. Mp 187-188°C. 500 MHz ¹H NMR (CDCl₃) δ 7.87 (m, 2H), 7.35 (m, 3H), 7.17 (m, 1H), 7.0 (s, 1H, br) 6.80 (d, 2H *J*=8Hz), 6.66 (d, 2H, *J*=8Hz), 6.15 (m, 1H), 4.07 (t, 2H, *J* = 6.7 Hz), 3.41 (d,d 1H *J*=14.4, 5.0) 3.11 (dd, 1H *J*=14.4, 9.28) 2.89 (m, 2H), 2.29 (s, 3H); MS *m/z* 513 (M+1), 514 Anal. Calc'd for C₂₇H₂₃F₃N₂O₅ C, 63.28; H 4.52; N 5.47 found: C, 63.19; H, 4.48; N 5.27.

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid methyl ester (32) was prepared in the following manner.

(a) (S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid methyl ester (32).



32

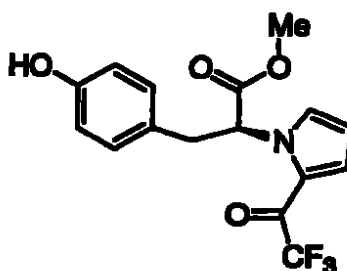
By Procedure 32-A: To a stirred solution of (S)-3-(4-Hydroxy-phenyl)-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid methyl ester (31) (1.0g, 2.93 mmol) in anhydrous THF (10 mL) was added triphenyl phosphine (768 mg, 2.93 mmol) and 2-(5-methyl-2-phenyloxazol-4-yl) ethanol (595 mg, 2.93 mmol). A solution of diethyl azodicarboxylate (DEAD) (461 μL, 2.93 mmol) in anhydrous THF (5 mL) was added dropwise and the reaction mixture stirred at

room temperature for 48 hr. The solvent was then removed under reduced pressure to give a yellow oil.

By Procedure 32-B: To a stirred solution of of (S)-3-(4-Hydroxy-phenyl)-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid methyl ester (32) (800 mg, 2.34 mmol) in anhydrous THF (10 mL) was added triphenyl phosphine (615 mg, 2.34 mmol) and 2-(5-methyl-2-phenyloxazol-4-yl) ethanol (476 mg, 2.34 mmol). A solution of diisopropylazodicarboxylate (DIAD) (369 μ L, 2.34 mmol) in anhydrous THF (5 mL) was added dropwise and the reaction mixture stirred at room temperature for 48hr. The solvent was then removed under reduced pressure to give a yellow oil.

The combined reaction mixtures from Procedures 32-A and 32-B were combined and purified by chromatography eluting with 1:10 to 1:1 EtOAc: Hexane. The title compound was isolated as an opaque oil (2.608g, 89% yield). 500 MHz ^1H NMR (CDCl_3) δ 7.96 (m, 2H), 7.39 (m, 3H), 7.18 (m, 1H), 7.0 (s, 1H, br) 6.79 (d, 2H $J=8.3$ Hz), 6.68 (d, 2H, $J=8.3\text{Hz}$), 6.20 (m, 1H), 4.15 (t, 2H, $J=6.6$ Hz), 3.70 (s, 3H) 3.43 (d,d 1H $J=14.4$, 5.12) 3.12 (dd, 1H $J=14.4$, 9.5) 2.92 (t, 2H $J=6.6$) , 2.32 (s, 3H); MS m/z 526 ($M+1$), 527.

(b) (S)-3-(4-Hydroxy-phenyl)-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid methyl ester (31).



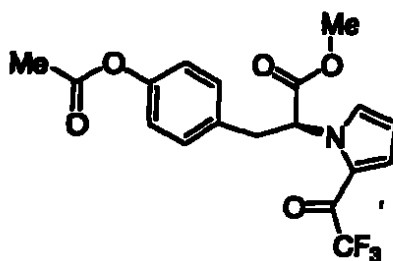
31

To a stirred solution of (S)-3-(4-Acetoxy-phenyl)-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid methyl ester (30) (2.13g, 5.57 mmol) in anhydrous methanol (20 mL) was added K_2CO_3 (770 mg, 5.57 mmol). The reaction mixture was stirred at room temperature for 20 min. and poured into water, acidified with aqueous HCl, extracted with EtOAc, dried MgSO_4 and the

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solvent removed under reduced pressure to give a pale yellow oil. (1.826 g, 96% yield). 500 MHz ^1H NMR (CDCl_3) δ 7.19 (m, 1H), 7.1 (s, 1H, br), 6.79 (d, 2H $J=8.6$ Hz), 6.62 (d, 2H, $J=8.6$ Hz), 6.22 (m, 1H), 4.67 (s, 1H) 3.72 (s, 3H), 3.44 (d,d 1H $J=14.4$, 5.4), 3.12 (dd, 1H $J=14.4$, 9.8), 2.01 (s, 3H); MS m/z 342 (M+1), 343.

(c) (S)-3-(4-Acetoxy-phenyl)-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid methyl ester (30).

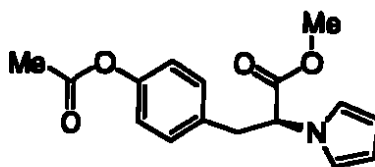


30

To a stirred solution of (S)-3-(4-Acetoxy-phenyl)-2-[pyrrol-1-yl]-propionic acid methyl ester (29) (2.9 g, 10.1 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic anhydride (1.71 mL, 12.1 mmol) and trifluoromethanesulfonic acid (1.07 μL , 12.1mmol). The reaction mixture turned orange in color. The reaction mixture was stirred for 5 minutes and poured into NH_4Cl solution, extracted with EtOAc, dried (MgSO_4). The solvent removed under reduced pressure. The resulting orange oil was purified by chromatography 1:10 to 1:1 EtOAc: Hexane to give the desired product as a clear oil (2.13 g, 55% yield) 500 MHz ^1H NMR (CDCl_3) δ 7.21 (m, 1H), 7.19 (s, 1H, br), 6.94 (d, 2H $J=8.6$ Hz), 6.90 (d, 2H, $J=8.6$ Hz), 6.23 (m, 1H), 3.72 (s, 3H), 3.51 (dd, 1H, $J=14.4$, 5.4), 3.18 (dd, 1H $J=14.4$, 9.5), 2.23 (s, 3H); MS m/z 384 (M+1), 385.

(d) (S)-3-(4-Acetoxy-phenyl)-2-[pyrrol-1-yl]-propionic acid methyl ester (29).

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29

To a stirred solution of (S)-3-(4-hydroxy-phenyl)-2-[pyrrol-1-yl]-propionic acid methyl ester 1 (10 g, 40 mmol) in CH_2Cl_2 (100 mL), was added 2,6-lutidine (9.5 mL, 81.6 mmol) and acetyl chloride (5.8 mL, 8.16 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into water, extracted with EtOAc, dried (MgSO_4) and the solvent removed under reduced pressure. The residual oil was purified by chromatography, 1:5 EtOAc:Hexane and the product obtained as a clear oil (8.25 g, 71%). 500 MHz ^1H NMR (CDCl_3) 6.96 (d, 2H $J=8.8$ Hz), 6.91 (d, 2H, $J=8.8\text{Hz}$), 6.67 (t, 2H, $J=2.0\text{Hz}$), 6.11 (t, 2H, $J=2.0\text{Hz}$), 4.68 (dd, 1H, $J=6.3, 8.8$), 3.67 (s, 3H), 3.37 (dd, 1H, $J=14.4, 6.3$), 3.25 (dd, 1H $J=14.4, 8.8$), 2.24 (s, 3H); MS m/z 288 ($M+1$), 289.

Example 13

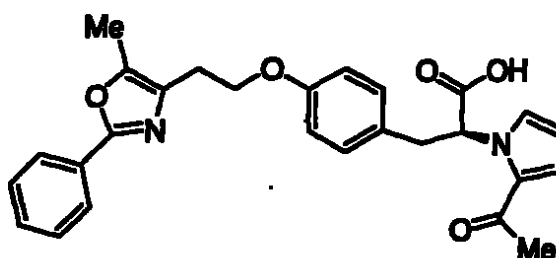
3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyridin-4-yl-propionic acid (34, PD 0330732).

This compound was synthesized as described for Compound 33 using ethyl 4-pyridyl acetate as the starting material. ^1H NMR d_6 -DMSO δ 2.30 (s, 3H) 2.85 (m, 3H) 3.02 (m, 2H) 4.11 (t, 2H) 6.80 (d, 2H) 7.06 (d, 2H) 7.44 (m, 3H) 7.65 (d, 2H) 7.84 (d, 2H) 8.63 (s, 2H). MS(M-44) (minus carboxylate): 385.1. Anal. Calcd for $\text{C}_{26}\text{H}_{24}\text{O}_4\text{N}_2 \cdot 1.67 \text{ H}_2\text{O}$: C, 68.05; H, 5.82; N, 6.11. Found: C, 68.03; H, 6.00; N, 6.11.

Example 14

(S)-2-(2-Acetyl-pyrrol-1-yl)-3-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-propionic acid (37).

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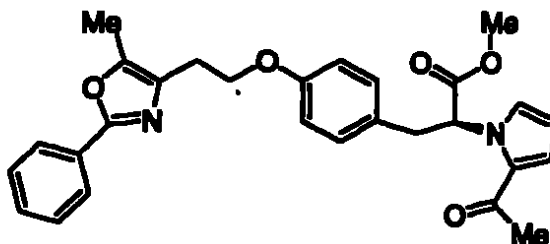


37

(S)-2-(2-Acetyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (36) (601 mg, 1.27 mmol) was hydrolyzed as described in General Procedure A to give the title compound as a white foam (129 mg, 22% yield). Mp 110°C-112°C. 500 MHz ^1H NMR (CDCl_3) δ 7.91 (m, 2H), 7.37 (m, 3H), 6.95 (m, 1H), 6.87 (m, 3H, br) 6.70 (d, 2H, $J=8.6\text{Hz}$), 6.09 (m, 1H), 4.12 (t, 2H, $J=6.8\text{ Hz}$), 3.47 (d,d 1H $J=14.4, 4.0$) 3.15 (dd, 1H $J=14.4, 9.0$) 2.90 (t, 2H, $J=6.8\text{Hz}$), 2.37 (s, 3H), 2.31 (s, 3H); MS m/z 459 ($M+1$), 460.

(S)-2-(2-Acetyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (36) was prepared in the following manner.

(a) (S)-2-(2-Acetyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (36).



36

By Procedure 36-A: To a stirred solution of (S)-2-(2-Acetyl-pyrrol-1-yl)-3-{4-[hydroxy]-phenyl}-propionic acid methyl ester (35) (500 mg, 1.74 mmol) in anhydrous THF (15 mL) was added triphenyl phosphine (685 mg, 2.61 mmol) and

434

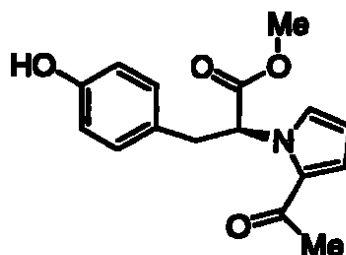
-117-

2-(5-methyl-2-phenyloxazol-4-yl) ethanol (388 mg, 1.91 mmol). A solution of DEAD (411 μ L, 2.61 mmol) in anhydrous THF (5 mL) was added dropwise and the reaction mixture stirred at room temperature for 48 hours. The solvent was removed under reduced pressure and the residue obtained as a yellow oil.

5 By Procedure 36-B: To a stirred solution of (S)-2-(2-Acetyl-pyrrol-1-yl)-3-{4-[hydroxy]-phenyl}-propionic acid methyl ester (35) (500 mg, 1.74 mmol) in anhydrous THF (15 mL) was added triphenyl phosphine (685 mg, 2.61 mmol) and 2-(5-methyl-2-phenyloxazol-4-yl) ethanol (388 mg, 1.91 mmol). A solution of DIAD (514 μ L, 2.61 mmol) in anhydrous THF (5 mL) was added dropwise and
10 the reaction mixture stirred at room temperature for 48 hours. The solvent was removed under reduced pressure and the residue obtained as a yellow oil.

The crude products from reactions 36-A and 36-B were combined and purified by chromatography 1:10 to 1:1 Ethyl Acetate: Hexane to give the title compound as an opaque oil. (601 mg, 73% yield). 500 MHz ^1H NMR (CDCl_3) δ
15 7.94 (m, 2H), 7.40 (m, 3H), 6.92 (m, 1H), 6.88 (s, 1H, br) 6.82 (m, 2H) 6.61 (m, 2H), 6.09 (m, 1H), 4.12 (t, 2H, $J = 6.8$ Hz), 3.69 (s, 3H) 3.42 (dd 1H $J = 14.2$, 5.37) 3.12 (dd, 1H $J = 14.4$, 9.76) 2.91 (t, 2H, $J = 6.8$ Hz), 2.35 (s, 3H), 2.31 (s, 3H); MS m/z 473 ($M+1$), 474.

20 (b) (S)-2-(2-Acetyl-pyrrol-1-yl)-3-{4-[hydroxy]-phenyl}-propionic acid methyl ester (35).



35

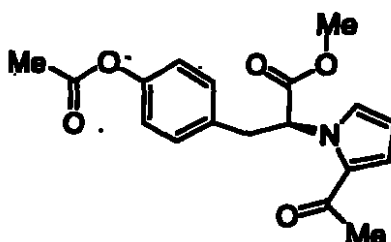
25 The intermediate (S)-2-(2-Acetyl-pyrrol-1-yl)-3-{4-[Acetoxy]-phenyl}-propionic acid methyl ester (34) was deacetylated according to the General Procedure C. The product was purified by chromatography EtOAc: Hexane 1:1 to give a clear oil which solidified on standing (1.756 g, 88% yield). 500 MHz ^1H

435

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NMR (CDCl₃) δ 6.93 (m, 1H), 6.83 (d, 2H *J*=8.3Hz) 6.63 (d, 2H, *J*=8.3Hz), 6.10 (m, 1H), 5.37 (s, 1H, br), 3.68 (s, 3H) 3.40 (d,d 1H *J*=14.2, 5.61Hz) 3.12 (dd, 1H *J*=14.2, 9.52) 2.35 (s, 3H), MS *m/z* 288 (M+1), 289.

- 5 (c) (S)-2-(2-Acetyl-pyrrol-1-yl)-3-[4-[Acetoxy]-phenyl]-propionic acid methyl ester (34).



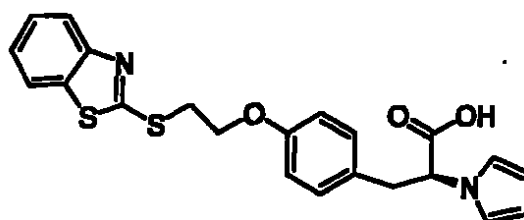
34

- 10 According to General Procedures D and E. To a stirred solution of (S)-3-(4-Acetoxy-phenyl)-2-[pyrrol-1-yl]-propionic acid methyl ester (30) (4.40 g, 15.3 mmol) in CH₂Cl₂ (50 mL) was added acetyl chloride (1.31 mL, 18.4 mmol) and trifluoromethanesulfonic acid (1.63 mL, 18.4 mmol). The reaction mixture turned orange in color. The reaction mixture was stirred for 5 minutes and poured into
- 15 NH₄Cl solution, extracted with EtOAc, and dried (MgSO₄). The solvent was removed *in vacuo*. The resulting orange oil was purified by chromatography 1:2 EtOAc: Hexane to give the desired product as a clear-oil (2.27g, 45%). 500 MHz ¹H NMR (CDCl₃) δ 500 MHz ¹H NMR (CDCl₃) δ 6.96 (d, 2H *J*=8.3Hz) 6.92 (m, 2H) 6.89 (d, 2H, *J*=8.3Hz), 6.10 (m, 1H), 3.70 (s, 3H) 3.47 (d,d 1H *J*=14.4, 5.62Hz) 3.12 (dd, 1H *J*=14.4, 9.52) 2.35 (s, 3H), 2.24 (s, 3H), MS *m/z* 330 (M+1), 331.
- 20

Example 15

3-[4-[2-(Benzothiazol-2-ylsulfanyl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid (39).

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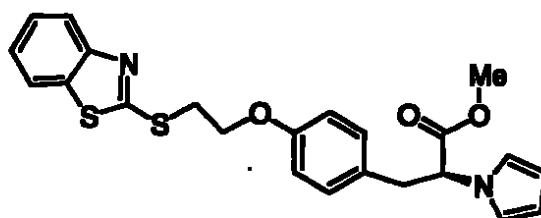


39

According to General Procedure A. The intermediate 3-{4-[2-(Benzothiazol-2-ylsulfanyl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (38) was hydrolyzed to give a white solid which was recrystallised using EtOAc and Hexane to give a white crystalline powder (390mg, 79%) Mp 165°C-166°C; 500 MHz ^1H NMR (CDCl_3) δ 7.85 (d, 1H, $J=8.05\text{Hz}$), 7.75 (d, 8.05Hz), 7.42 (m, 1H), 7.30 (m, 1H), 6.91 (d, 2H $J=8.54\text{Hz}$), 6.82 (d, 2H, $J=8.54\text{Hz}$), 6.69 (m, 2H), 6.14 (m, 2H), 4.72 (dd, 1H, $J=5.86, 8.79\text{Hz}$), 4.31 (t, 2H, $J=6.59\text{Hz}$), 3.70 (t, 2H, $J=6.59\text{Hz}$), 3.38 (d,d 1H $J=14.16, 5.86\text{Hz}$), 3.22 (dd, 1H $J=14.16, 8.79$); MS m/z 404 ($M+1$).

(S)-3-{4-[2-(Benzothiazol-2-ylsulfanyl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (38) was prepared in the following manner.

(a) (S)-3-{4-[2-(Benzothiazol-2-ylsulfanyl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (38).



38

According to General Procedure B. To a stirred solution of (S)-3-(4-hydroxy-phenyl)-2-[pyrrol-1-yl]-propionic acid methyl ester (1) (828 mg, 3.38 mmol) in anhydrous THF (15 mL) was added triphenyl phosphine (886 mg, 3.38 mmol) and 2-(Benzothiazol-2-ylsulfanyl)-ethanol (800 mg, 3.38 mmol). A

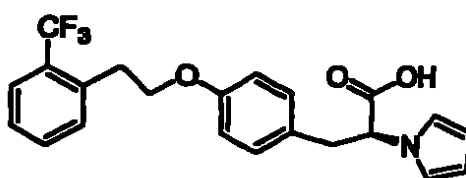
437

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solution of DIAD (665 μ L, 3.38 mmol) in anhydrous THF (5 mL) was added dropwise and the reaction mixture stirred at room temperature for 48 hours. The solvent was removed under reduced pressure and the residue purified by chromatography 1:10 to 1:1 EtOAc: Hexane. The product was obtained as an opaque oil. Yield = 510 mg, 29%. 500 MHz ^{1} H NMR ($CDCl_3$) δ 7.85 (d, 1H, $J=8.06$ Hz), 7.75 (d, 8.06Hz), 7.40 (m, 1H), 7.30 (m, 1H), 6.90 (d, 2H $J=8.8$ Hz), 6.83 (d, 2H, $J=8.8$ Hz), 6.70 (m, 2H), 6.14 (m, 2H), 4.68 (dd, 1H, $J=6.34, 8.79$ Hz), 4.32 (t, 2H, $J=6.59$ Hz), 3.71 (t, 2H, $J=6.59$ Hz), 3.693 (s, 3H), 3.33 (d, d 1H $J=13.9, 6.59$ Hz), 3.19 (dd, 1H $J=13.9, 8.79$); MS m/z 439 (M+1).

Example 16

(S)-2-Pyrrol-1-yl-3-{4-[2-(2-trifluoromethyl-phenyl)-ethoxy]-phenyl}-propionic acid (41).



41

15

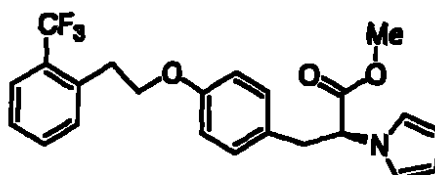
Prepared from (S)-2-Pyrrol-1-yl-3-{4-[2-(2-trifluoromethyl-phenyl)-ethoxy]-phenyl}-propionic acid methyl ester (40) using the hydrolysis method described in General Procedure A. (S)-2-Pyrrol-1-yl-3-{4-[2-(2-trifluoromethyl-phenyl)-ethoxy]-phenyl}-propionic acid (42) was obtained as clear oil. (454 mg, 45% yield) δ 7.85 (d, 1H, $J=8.05$ Hz), 7.45 (m, 2H), 7.33 (t, 1H, $J=8.05$ Hz) 6.90 (d, 1H, $J=8.54$), 6.75 (d, 2H $J=8.54$) 6.69 (m, 2H), 6.15 (m, 2H) 4.73 (dd, 1H, $J=5.86, 9.3$), 4.12 (t, 2H, $J=6.84$) 3.37 (dd, 1H, $J=13.9, 5.86$) 3.25 (m, 5H) MS m/z 425 (M+1) Anal. Calc'd for $C_{22}H_{20}F_3NO_3$ C, 65.50; H 5.00; N 3.47 found: C, 64.92; H, 5.15; N 3.28.

25

(S)-2-Pyrrol-1-yl-3-{4-[2-(2-trifluoromethyl-phenyl)-ethoxy]-phenyl}-propionic acid methyl ester (40) was prepared in the following manner.

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- (a) (S)-2-Pyrrol-1-yl-3-{4-[2-(2-trifluoromethyl-phenyl)-ethoxy]-phenyl}-propionic acid methyl ester (40).



40

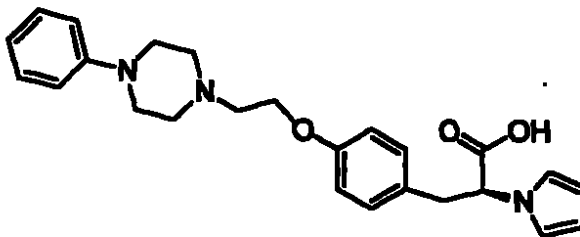
5

According to General Procedure B. Prepared from the intermediate (S)-3-(4-hydroxy-phenyl)-2-[pyrrol-1-yl]-propionic acid methyl ester (1) and 2-(2-trifluoromethyl-phenyl)-ethanol. (S)-2-Pyrrol-1-yl-3-{4-[2-(2-trifluoromethyl-phenyl)-ethoxy]-phenyl}-propionic acid methyl ester (40) was obtained as an opaque oil (1.04 g, 61% yield). δ 7.64 (d, 1H, $J=7.8$ Hz), 7.46 (m, 2H), 7.33 (t, 1H, $J=7.8$), 6.89 (d, 1H, $J=6.59$), 6.75 (d, 2H $J=6.59$), 6.69 (m, 2H), 6.14 (m, 2H), 4.68 (dd, 1H, $J=6.59$, 8.78), 4.12 (t, 2H, $J=6.8$), 3.69 (s, 3H), 3.33 (dd, 1H, $J=13.9$, 6.59), 3.25 (t, 2H, $J=6.8$), 3.16 (dd, 1H, $J=13.9$, 8.78); MS m/z 418 (M+1).

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Example 17

(S)-3-{4-[2-(4-Phenyl-piperazin-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid (43).



43

20

Prepared from (S)-3-{4-[2-(4-Phenyl-piperazin-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (42) using the hydrolysis method described in General Procedure A to give the desired product as a pink foam. Yield = 270 mg, 38%. 500 MHz ^1H NMR (CDCl_3) δ 7.28 (m, 2H), 7.09 (d, 2H, $J=9$ Hz), 7.18 (m, 1H), 6.90 (m, 3H), 6.73 (m, 4H), 6.10 (m, 2H), 4.65 (d, 1H,

25

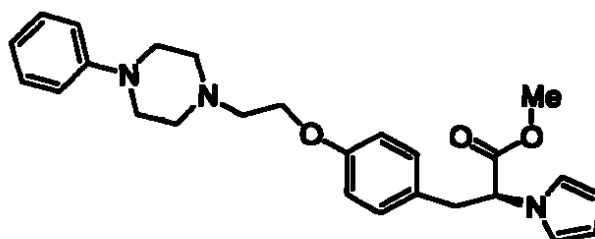
439

-122-

$J=5.85, 8.79\text{Hz}$), 4.125 (t, 2H, $J = 5.15\text{ Hz}$), 3.40 (dd, 1H $J=13.7, 8.79$), 3.27-3.08 (m, 11H); MS m/z 420 ($M+1$), 419 ($M-1$).

5 (S)-3-{4-[2-(4-Phenyl-piperazin-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (42) was prepared in the following manner.

(a) (S)-3-{4-[2-(4-Phenyl-piperazin-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (42).



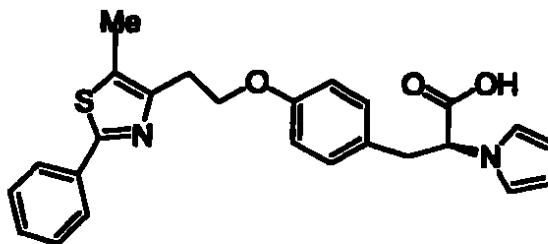
10

41

According to General Procedure B. Prepared from the intermediate (S)-3-(4-hydroxy-phenyl)-2-[pyrrol-1-yl]-propionic acid methyl ester (1) and 2-(4-Phenyl-piperazin-1-yl)-ethanol. (S)-3-{4-[2-(4-Phenyl-piperazin-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (41) was obtained as a clear oil (740 mg, 70% yield). 500 MHz ^1H NMR (CDCl_3) δ 7.26 (m, 2H), 6.91 (d, 2H, $J=9\text{Hz}$), 6.98-6.76 (m, 5H), 6.70(m, 2H), 6.14 (m, 2H), 4.69 (d,d 1H, $J=6.95, 8.79\text{Hz}$), 4.12 (t, 2H, $J = 7.08\text{ Hz}$), 3.69 (s, 3H), 3.43 (dd, 1H $J=6.35, 13.9$), 3.21-3.16 (m, 5H), 2.85 (br s, 2H), 2.73 (br s, 4H); MS m/z 434 ($M+1$).

20 **Example 18**

(S)-3-{4-[2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid (45).



45

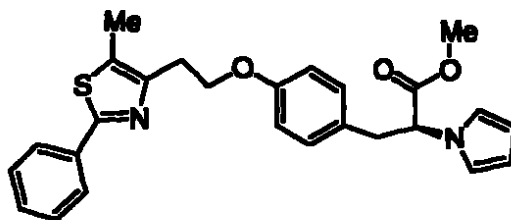
140

-123-

Prepared from (S)-3-[4-[2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (44) using the hydrolysis method described in General Procedure A. The product was recrystallized from ethyl acetate and hexane to give the desired product as white needles. Yield = 1.20g, 58% M.P. = 157-158°C. ¹H NMR (500MHz) CDCl₃ δ: 7.80 (2H, m), 7.34 (3H, m), 6.87 (d, 2H J=8.5 Hz), 6.73 (2H, d, J=8.5 Hz), 6.66 (2H, m), 6.11 (2H, m), 4.68 (1H, dd, J=6.35, 8.79 Hz), 4.20 (2H, t, 6.83 Hz), 3.34 (1H, dd, J=6.1, 13.9 Hz), 3.17 (1H, dd, J=, 8.79, 13.9 Hz), 3.12 (2H, t, J=6.59 Hz), 2.40 (3H, s). Anal. Calc'd for C₂₅H₂₄N₂O₃S: C 69.42, H 5.59, N 6.48 found: C 69.41, H 5.53, N 6.29 MS m/z 433 (M+1), 431 (M-1).

(S)-3-[4-[2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (44) was prepared in the following manner.

(a) (S)-3-[4-[2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid (44).



44

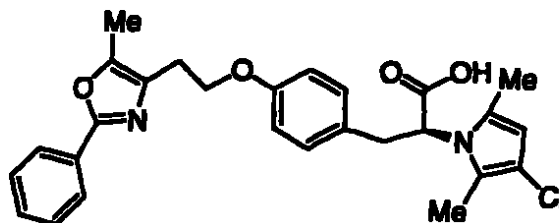
According to General Procedure B. Prepared from the intermediate (S)-3-(4-hydroxy-phenyl)-2-[pyrrol-1-yl]-propionic acid methyl ester (1) and 2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethanol. (S)-3-[4-[2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid (44) was obtained as a clear oil. Yield = 2.15g, 59%. ¹H NMR (500MHz) CDCl₃ δ: 7.82 (2H, m), 7.35 (3H, m), 6.84 (m, 2H), 6.73 (2H, m), 6.66 (2H, m), 6.10 (2H, m), 4.65 (1H, dd, J = 6.59, 8.78 Hz), 4.23 (2H, t, 6.83 Hz), 3.65 (3H, m), 3.30 (1H, dd, J=6.59, 13.9 Hz), 3.17-3.11 (3H, m), 2.41 (3H, s). MS m/z 447 (M+1).

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Example 19

(S)-2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (49).

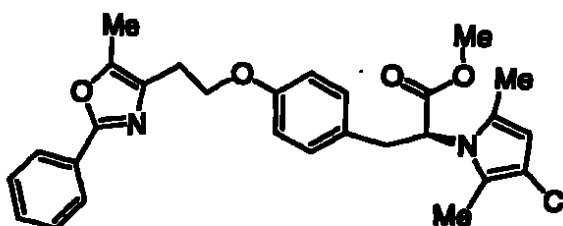


49

Prepared from the intermediate 2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (48) using the hydrolysis method described in General Procedure A. The product was purified by chromatography and recrystallized from EtOAc/hexane to give the desired product as white crystalline powder. Yield = 158mg, 25%. ¹H NMR (500MHz) CDCl₃ δ: 7.98 (2H, m), 7.43 (3H, m), 6.75 (dd, 4H, J=9.0Hz), 5.75 (1H, s), 4.70 (1H, dd, J = 4.64, 10.25 Hz), 4.19 (2H, t, 6.59 Hz), 3.30 (1H, dd, J=4.64, 14.16 Hz), 3.08 (1H, dd, J=14.16, 10.25 Hz), 2.98 (2H, t, 6.59), 2.37 (3H, s), 1.99 (3H, br,s), 1.88 (3H br,s) MS m/z 479 (M+1) 477 (M-1).

(S)-2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-{4-[Acetoxy]-phenyl}-propionic acid methyl ester (48) was prepared in the following manner.

(a) (S)-2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (48).



48

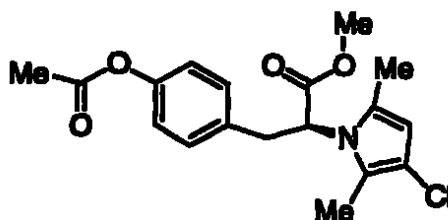
142

-125-

To a stirred solution of (S)-2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-(4-[acetoxyl-phenyl])-propionic acid methyl ester (674 mg, 1.93 mmol) described in Example 47 in anhydrous methanol (10 mL) was added K_2CO_3 (266 mg, 1.93 mmol). The reaction was stirred at room temperature for 40 minutes, poured into EtOAc, washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo* to give 2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-(4-[hydroxy]-phenyl)-propionic acid methyl ester as an oil. This material was used in the General Procedure B coupling reaction.

To a stirred solution of (S)-2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-(4-[hydroxy]-phenyl)-propionic acid methyl ester (47) in THF (10mL) at room temperature was added triphenyl phosphine (541 mg, 2.06 mmol) and 2-(5-methyl-2-phenyloxazol-4-yl) ethanol (541 mg 2.06 mmol). A solution of DIAD (406 μ L, 2.06 mmol) in anhydrous THF (5 mL) was added dropwise and the reaction mixture stirred at room temperature for 72 hours. The solvent was then removed *in vacuo* and the residue purified by chromatography eluting with 1:10 EtOAc: hexane to 1:1 EtOAc: Hexane. This gave the desired product as a clear oil. Yield = 651 mg, 68%. ^1H NMR (500MHz) $CDCl_3$ δ : 7.95 (2H, m), 7.40 (3H, m), 6.76 (m, 4H), 5.75 (1H, s), 4.65 (1H, dd, $J = 4.64, 10.25$ Hz), 4.20 (2H, t, 6.59 Hz), 3.78 (3H,s), 3.42 (1H, dd, $J=4.64, 14.16$ Hz), 3.06 (1H, dd, $J=14.16, 10.25$ Hz), 2.91 (2H, t, 6.59), 2.30 (3H, s), 1.90 (3H, br,s), 1.82 (3H br,s) MS m/z 493 (M+1), 492 (M-1).

(b) (S)-2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-(4-[Acetoxy]-phenyl)-propionic acid methyl ester (47).

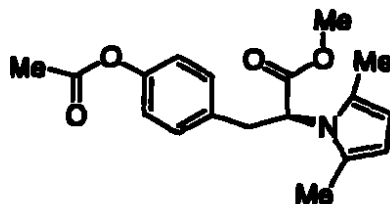


47

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To a stirred solution of (S)-2-(2,5-dimethyl-pyrrol-1-yl)-3-{4-[Acetoxy]-phenyl}-propionic acid methyl ester (46) (2.45 g, 7.77 mmol) in THF (20 mL) at 0 °C was added N-chlorosuccinamide (1.04 g, 7.77 mmol). After 30 minutes, the solvent was removed *in vacuo* and the residue purified by chromatography 1:10 to 1;1 EtOAc: Hexane to give a yellow oil. Yield = 674mg, 25%. ¹H NMR (500MHz) CDCl₃ δ: 6.92-6.83 (m, 4H), 5.71 (s, 1H), 4.66 (1H, dd, J = 4.64, 10.01 Hz), 3.49 (1H, dd, J=4.64, 14.16 Hz), 3.08 (1H, dd, J=14.16, 10.01 Hz), 2.23 (3H, s), 2.30 (3H, s), 1.92 (3H, br,s), 1.82 (3H br,s) MS *m/z* 350 (M+1) 348 (M-1).

(c) (S)-2-(2,5-dimethyl-pyrrol-1-yl)-3-{4-[Acetoxy]-phenyl}-propionic acid methyl ester (46).



46

To a stirred solution of L-tyrosine methyl ester (25 g, 0.128 mol) in toluene (300 mL) was added 2,5-hexandione (15 mL, 0.128 mol) and p-toluenesulfonic acid (1.22 g, 6.4 mmol). The mixture was heated at reflux with a Dean-Stark trap for 12 hours. The solvent was removed *in vacuo* and the residue redissolved in ethyl acetate and filtered through a bed of silica gel. The solvent was removed *in vacuo* and the product, a yellow oil used in the next step without further purification. 500 MHz ¹H NMR (CDCl₃) δ 6.60 (d, 2H, J = 6.6 Hz), 6.47 (d, 2H, J = 8.5 Hz), 5.47 (s, 2H), 4.90 (dd, 1H, J = 11.2, 4.3 Hz), 3.63 (s, 3H), 3.24 (dd, 1H, J = 13.9, 4.3 Hz), 2.92 (dd, 1H, J = 13.9, 11.2 Hz), 1.85 (s, 6H); MS *m/z* 274 (M+1).

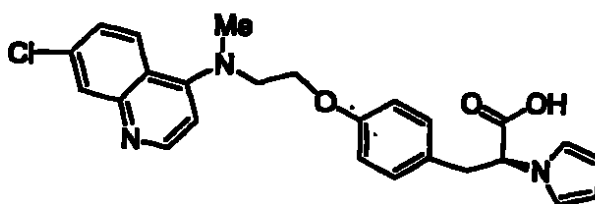
The (S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester was then dissolved in dichloromethane (300 mL), and acetyl chloride (9.1 mL, 0.128 mol) and 2,6 lutidine (14.9 mL, 0.128 mol) were added. The reaction mixture was stirred overnight and was then poured into ethyl acetate and

-127-

extracted with brine. The organic layer was dried over MgSO_4 and the solvent removed in vacuo to give a brown oil. This was purified by chromatography ethyl acetate: hexane 1:5 to 1:1 to give a clear oil. Yield= 22.14g 55% ^1H NMR 500 MHz (CDCl_3) δ 6.89-6.83(m, 4H) 5.70 (s, 2H), 4.70 (dd, 1H, $J = 9.77, 4.88$ Hz), 3.72 (s, 3H), 3.50 (dd, 1H, $J = 13.9, 4.88$ Hz), 3.11 (dd, 1H, $J = 13.9, 9.77$ Hz), 2.23 (3H, s), 1.93 (s, 6H); MS m/z 316 (M+1), 314 (M-1)

Example 20

(S)-3-(4-{2-[(7-Chloro-quinolin-4-yl)-methyl-amino]-ethoxy}-phenyl)-2-pyrrol-1-yl-propionic acid (51).



51

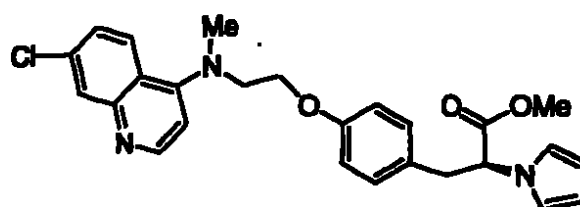
3-(4-{2-[(7-Chloro-quinolin-4-yl)-methyl-amino]-ethoxy}-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (50) was hydrolyzed using the method described in General Procedure A to provide 3-(4-{2-[(7-Chloro-quinolin-4-yl)-methyl-amino]-ethoxy}-phenyl)-2-pyrrol-1-yl-propionic acid 253 mg, 19%. ^1H NMR 500 MHz (D_6 DMSO) δ 8.59 (1H, d, $J=5.13\text{Hz}$), 8.22 (1H, d, $J=9.03\text{Hz}$), 7.90 (1H, d, $J=2.13\text{Hz}$) 7.46 (1H, d, $J=9.03\text{Hz}$), 6.95 (1H, d, $J=5.13\text{Hz}$), 6.85 (1H, d, $J=8.05$) 6.66-6.64 (4H, m), 5.80 (2H, s), 4.20 (1H br s), 4.17 (2H, br s), 3.60 (2H, br s) 3.26-3.19 (1H, m), 2.96, (3H, s), 2.91-2.88 (1H, m) MS m/z 448 (M-1).

(S)-3-(4-{2-[(7-Chloro-quinolin-4-yl)-methyl-amino]-ethoxy}-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (50) was prepared in the following manner.

- (a) (S)-3-(4-{2-[(7-Chloro-quinolin-4-yl)-methyl-amino]-ethoxy}-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (50).

125

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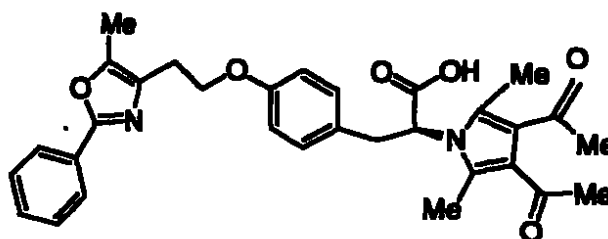


50

According to General Procedure B. To a stirred solution of 3-(4-hydroxy-phenyl)-2-[pyrrol-1-yl]-propionic acid methyl ester described in example 1 (828 mg, 3.38 mmol) in anhydrous THF (15 mL) was added triphenyl phosphine (886 mg, 3.38 mmol) and 2-[(7-chloro-4-quinolyl)methylamino] ethanol (800 mg, 3.38 mmol). A solution of DIAD (665 μ L, 3.38 mmol) in anhydrous THF (5 mL) was added dropwise and the reaction mixture stirred at room temperature for 48 hours. The solvent was removed *in vacuo* and the residue purified by chromatography 1:10 EtOAc/Hexane to 1:1 EtOAc/Hexane. The product was obtained as an oil. Yield = 1.36g 87%. MS m/z 464 (M+1), 462 (M-1).

Example 21

(S)-2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(4-methyl-2-phenyl-oxazol-5-yl)-ethoxy]-phenyl}-propionic acid (55).



55

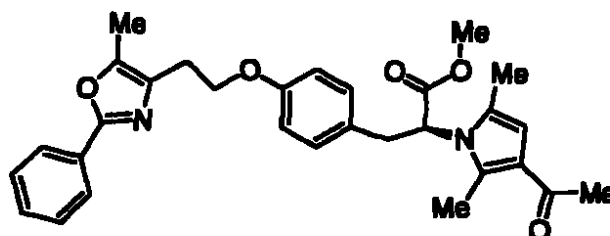
Prepared from (S)-2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(4-methyl-2-phenyl-oxazol-5-yl)-ethoxy]-phenyl}-propionic acid methyl ester (54) described in General Procedure A. The desired product was obtained as cream crystalline powder. Yield = 148mg.

146

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(S)-2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(4-methyl-2-phenyl-oxazol-5-yl)-ethoxy]-phenyl}-propionic acid methyl ester (54) was prepared in the following manner.

- 5 (a) (S)-2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(4-methyl-2-phenyl-oxazol-5-yl)-ethoxy]-phenyl}-propionic acid methyl ester (54).



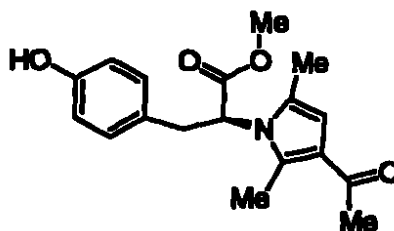
54

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Prepared from (S)-2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-{4-[Hydroxy]-phenyl}-propionic acid methyl ester (53) and 2-(5-methyl-2-phenyloxazol-4-yl) ethanol using the method described in General Procedure B. The desired product was obtained as a clear oil. Yield = 474mg.

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- (b) (S)-2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-{4-[Hydroxy]-phenyl}-propionic acid methyl ester (53).



53

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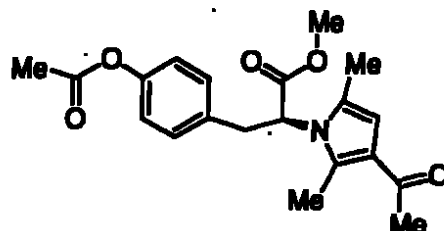
2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-{4-[Acetoxy]-phenyl}-propionic acid methyl ester (52) was deacetylated using the method described in Example ##. The product was purified using chromatography 1:1 EtOAc : Hexane and the product obtained as an oil which solidified on standing to give a white crystalline solid. Yield= 487mg, 72%.

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117

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(c) (S)-2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-{4-[Acetoxy]-phenyl}-propionic acid methyl ester (52).



5

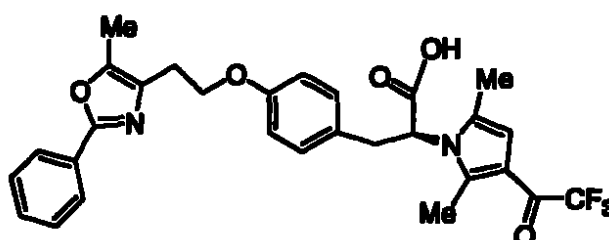
52

To a stirred solution of 2-(2,5-dimethyl-pyrrol-1-yl)-3-{4-[Acetoxy]-phenyl}-propionic acid methyl ester (2.45 g, 7.77 mmol) in CH_2Cl_2 was added acetyl chloride and trifluoromethane sulfonic acid. The solvent was removed *in vacuo*. The residue was purified by chromatography 1:10 to 1:1 EtOAc: Hexane to give the title compound as a yellow oil. Yield = 674mg, 25%.

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Example 22

(S)-2-[2,5-Dimethyl-3-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (59).



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59

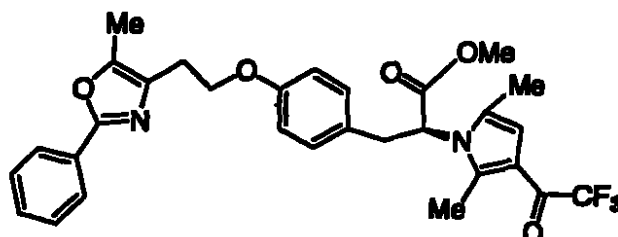
According to General Procedure A. Prepared from the ester (58) (1.48g, 2.62mmol) to give the desired product as a white powder 0.50g, 34%. Mass spectra (M+1), 541 (M-1) 539

20

(S)-2-[2,5-Dimethyl-3-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (58) was prepared in the following manner.

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- (a) (S)-2-[2,5-Dimethyl-3-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (58)



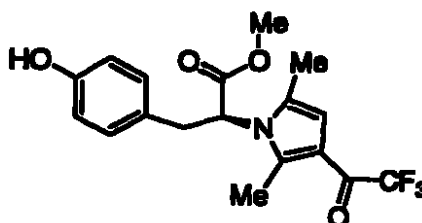
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58

Prepared according to General Procedure B using (S)-2-[2,5-Dimethyl-3-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-3-{4-[hydroxy]-phenyl}-propionic acid methyl ester (57) (1.08g, 2.9mmol) to give the desired product isolated by chromatography (1:10: 1:1 ethyl acetate: hexane as a white foam. Yield=1.48g, 92% Mass spectra (M+1), 555 (M-1) 553

10

- (b) (S)-2-[2,5-Dimethyl-3-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-3-{4-[hydroxy]-phenyl}-propionic acid methyl ester (57).



15

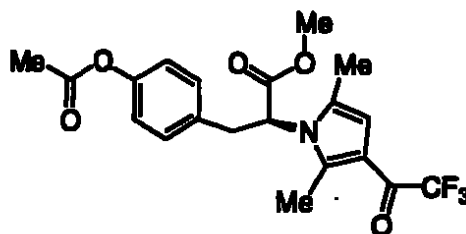
57

Prepared from the intermediate described in example (S)-2-[2,5-Dimethyl-3-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-3-{4-[Acetoxy]-phenyl}-propionic acid methyl ester (56) deacetylated using the method described in General Procedure C. The product was purified using chromatography 1:1 EtOAc : Hexane and the product obtained as an oil which solidified on standing to give a white crystalline solid. Yield= 4.5g, 81% (M+1) 370 (M-1) 368.

20

- (c) (S)-2-[2,5-Dimethyl-3-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-3-{4-[Acetoxy]-phenyl}-propionic acid methyl ester (57)

-132-

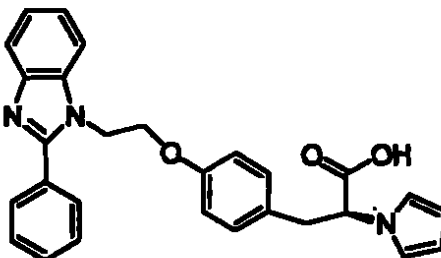


56

To a stirred solution of 2-(2,5-dimethyl-pyrrol-1-yl)-3-[4-[Acetoxy]-phenyl]-propionic acid methyl ester (6.0g, 19 mmol) in CH₂Cl₂ (50mL) was added trifluoroacetic anhydride (4.0mL, 28.5 mmol) and trifluoromethane sulfonic acid (4.0mL, 28.5 mmol). The reaction was stirred at room temperature for 20 minutes. The reaction mixture was poured into ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried (MgSO₄) and the solvent removed *in vacuo*. The residue was purified by chromatography 1:10 to 1:1 EtOAc: Hexane to give a yellow oil. Yield = 6.22g, 80% (M+1) 412 (M-1) 410.

Example 23

3-[4-[2-(2-Phenyl-benzimidazol-1-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid (61).



61

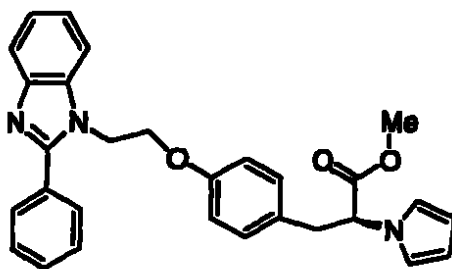
Prepared from 3-[4-[2-(2-Phenyl-benzimidazol-1-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (60) using the hydrolysis method described in General Procedure A to give the desired product as a white foam. Yield = 697mg, 65%. Mp 210-212 °C. (M+1) 452, (M-1) 450.

3-[4-[2-(2-Phenyl-benzimidazol-1-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (60) was prepared in the following manner.

450

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- (a) 3-{4-[2-(2-Phenyl-benzimidazol-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (60).



60

5

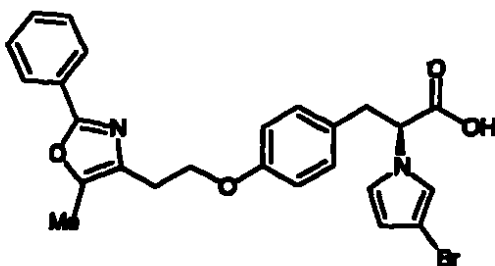
Prepared from the intermediate 3-(4-hydroxy-phenyl)-2-[pyrrol-1-yl]-propionic acid methyl ester (1) described in Example 1 and 2-(2-Phenyl-benzimidazol-1-yl)-ethanol using the method described in General Procedure B. The desired product was obtained as a white foam. 1.125g, 71% yield.

10

M+1(obs)=466

Example 24

2-(3-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (64).



64

15

A mixture of (S)-2-(3-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (64) (150 mg, 0.29 mmol) and lithium hydroxide (35 mg, 1.47 mmol) in 2-methoxyethanol (4 mL) and water (1 mL) and stirred at room temperature for 1 hour. The mixture was poured into water, acidified with aqueous 2N HCl, extracted with EtOAc and dried over MgSO₄. The solvent was removed under reduced pressure to yield the desired propionic acid (125 mg, 87%) as a white solid. 500 MHz ¹H NMR

20

-134-

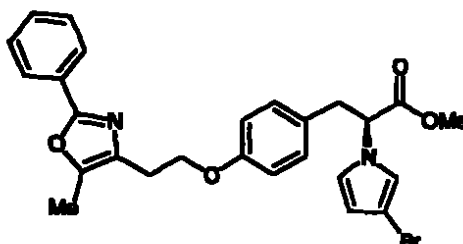
(CDCl₃) δ 7.96 (m, 2H), 7.43 (m, 3H), 6.92 (d, 2H, J = 8.5 Hz), 6.74 (m, 3H), 6.57 (m, 1H), 6.12 (m, 1H), 4.63 (dd, 1H, J = 8.3, 6.8 Hz), 4.16 (t, 2H, J = 6.6 Hz), 3.33 (dd, 1H, J = 13.9, 6.8 Hz), 3.14 (dd, 1H, J = 13.9, 8.3 Hz), 2.98 (t, 2H, J = 6.6 Hz), 2.37 (s, 3H); MS m/z 495, 497 (M+1).

5

(S)-2-(3-Bromo-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester (63) was prepared in the following manner.

10

(a) (S)-2-(3-Bromo-pyrrol-1-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid methyl ester (63).



63

15

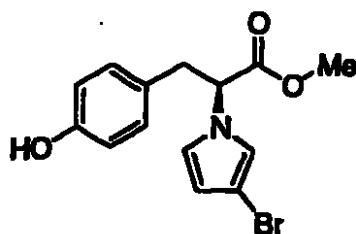
According to General Procedure B. To a stirred solution of (S)-2-(2-Bromo-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (63) (1.00 g, 3.08 mmol), triphenylphosphine (809 mg, 3.08 mmol) and 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethanol (626 mg, 3.08 mmol) in THF (15 mL) was added dropwise a solution of diethylazodicarboxylate (500 μ L, 3.08 mmol) in THF (4 mL). The mixture was stirred overnight, then concentrated. The residue was chromatographed on silica gel eluting with 30%-40% EtOAc in hexanes to yield the coupled product (590 mg, 38%) as a yellow oil. 500 MHz ¹H NMR (CDCl₃) δ 7.99 (m, 2H), 7.43 (m, 3H), 6.87 (m, 2H), 6.73 (m, 3H), 6.55 (m, 1H), 6.11 (m, 1H), 4.59 (dd, 1H, J = 9.0, 6.1 Hz), 4.20 (t, 2H, J = 6.6 Hz), 3.71 (s, 3H), 3.29 (dd, 1H, J = 13.9, 6.1 Hz), 3.14 (dd, 1H, J = 13.9, 9.0 Hz), 2.97 (t, 2H, J = 6.6 Hz), 2.36 (s, 3H); MS m/z 509, 511 (M+1).

25

152

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- (b) (S)-2-(3-Bromo-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (62).



62

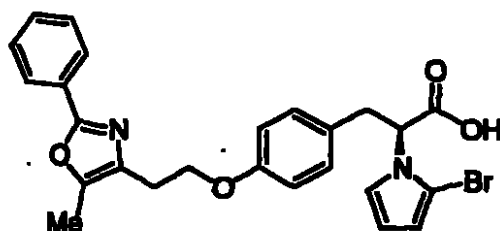
5

To a stirred, cooled (-78°C) solution of (S)-3-(4-Hydroxy-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (1.00 g, 4.08 mmol) in THF (20 mL) was added *N*-bromosuccinimide (724 mg, 4.08 mmol). The resulting mixture was warmed to 0°C and stirred for 3 hours. The solvent was removed under reduced pressure and the residue chromatographed on silica gel eluting 17%-27% EtOAc in hexanes to provide the desired product (1.08 g, 82%) as a light brown oil. 500 MHz ¹H NMR (CDCl₃) δ 6.86 (d, 2H, *J* = 8.5 Hz), 6.71 (m, 3H), 6.55 (m, 1H), 6.11 (m, 1H), 4.59 (dd, 1H, *J* = 9.0, 6.3), 3.71 (s, 3H), 3.29 (dd, 1H, *J* = 13.9, 6.3), 3.12 (dd, 1H, *J* = 13.9, 9.0); MS *m/z* 325 (*M*+1).

15

Example 25

2-(2-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (67).



67

20

Prepared by the method described in General Procedure A from (S)-2-(2-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (67) to provide the desired propionic acid (93%) as an off-white solid. 500 MHz ¹H NMR (CDCl₃) δ 7.95 (m, 2H), 7.41 (m, 3H), 6.94

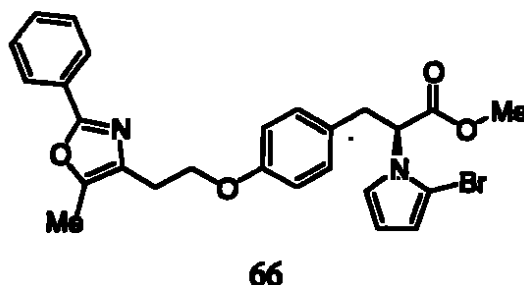
153

-136-

(m, 2H), 6.88 (m, 1H), 6.75 (m, 2H), 6.18 (t, 1H, $J = 3.4$ Hz), 6.10 (m, 1H), 5.10 (dd, 1H, $J = 8.8, 6.1$ Hz), 4.15 (m, 2H), 3.41 (dd, 1H, $J = 14.2, 6.1$ Hz), 3.18 (dd, 1H, $J = 14.2, 8.8$ Hz), 2.96 (m, 2H), 2.35 (s, 3H); MS m/z 495, 497 ($M+1$).

5 (S)-2-(2-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (66) was prepared in the following manner.

10 (a) (S)-2-(2-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (66).

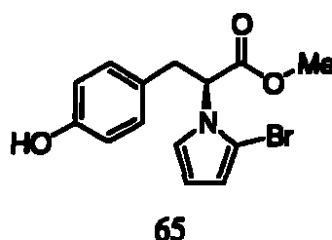


Prepared by the method described in General Procedure B from (S)-2-(2-Bromo-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (65) yielding a mixture of starting material and desired product. To a solution of the residue (0.61 mmol) in acetonitrile (10 mL) was added triethylamine (110 μ L, 0.93 mmol) and benzoyl chloride (130 μ L, 0.93 mmol). The mixture stirred at room temperature for 30 minutes and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with 20% to 30% EtOAc in hexanes to afford the desired ester (190 mg, 12% overall) as a yellow oil. 500 MHz ^1H NMR (CDCl_3) δ 7.97 (m, 2H), 7.41 (m, 3H), 6.89 (m, 3H), 6.76 (d, 2H, $J = 8.5$ Hz), 6.17 (m, 1H), 6.09 (m, 1H), 5.05 (dd, 1H, $J = 9.0, 6.1$ Hz), 4.19 (t, 2H, $J = 6.6$ Hz), 3.71 (s, 3H), 3.35 (dd, 1H, $J = 14.2, 6.1$ Hz), 3.15 (dd, 1H, $J = 14.2, 9.0$ Hz), 2.95 (t, 2H, $J = 6.6$ Hz), 2.35 (s, 3H); MS m/z 509, 511 ($M+1$).

154

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- (b) (S)-2-(2-Bromo-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (65).



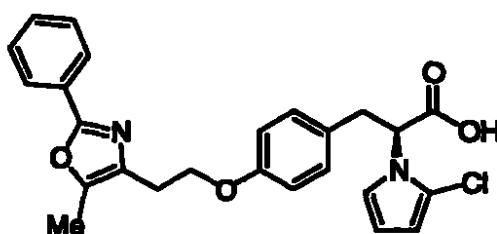
5

To a stirred, cooled (-78°C) solution of (S)-3-(4-Hydroxy-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (1.00 g, 4.08 mmol) in THF (20 mL) was added *N*-bromosuccinimide (724 mg, 4.08 mmol). The resulting mixture was stirred at -78°C for 15 minutes, then warmed to 0°C and stirred for 3 hours. The solvent was removed under reduced pressure and the residue chromatographed on silica gel eluting 17% to 27% EtOAc in hexanes to yield the desired pyrrole (1.01 g, 77%) as a light brown oil. 500 MHz ¹H NMR (CDCl₃) δ 6.89 (m, 3H), 6.69 (d, 2H, *J* = 8.5 Hz), 6.18 (m, 1H), 6.09 (m, 1H), 5.05 (dd, 1H, *J* = 9.0, 6.3 Hz), 3.72 (s, 3H), 3.35 (dd, 1H, *J* = 14.2, 6.3 Hz), 3.15 (dd, 1H, *J* = 14.2, 9.0 Hz); MS *m/z* 324, 326 (*M*+1).

15

Example 26

2-(2-Chloro-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (70).



20

Prepared by the method described in General Procedure A. Hydrolysis of the methyl ester (70) afforded the desired acid (59%) as a white solid. 500 MHz ¹H NMR (CDCl₃) δ 8.03 (m, 2H), 7.44 (m, 3H), 6.93 (m, 2H), 6.75 (m, 3H), 6.13 (m, 1H), 6.00 (m, 1H), 5.08 (dd, 1H, *J* = 9.0, 6.1 Hz), 4.20 (t, 2H, *J* = 6.4 Hz),

25

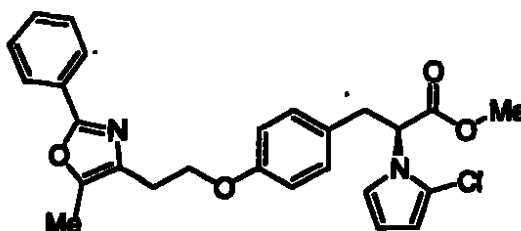
155

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3.40 (dd, 1H, $J = 14.2, 6.1$ Hz), 3.19 (dd, 1H, $J = 14.2, 9.0$ Hz), 3.00 (t, 2H, $J = 6.4$ Hz), 2.37 (s, 3H); MS m/z 451, 453 ($M+1$).

(S)-2-(2-Chloro-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (69) was prepared in the following manner.

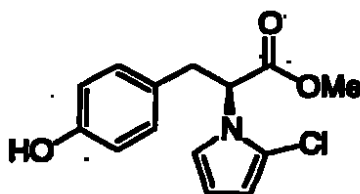
(a) (S)-2-(2-Chloro-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (69).



69

Prepared by the method described in General Procedure B from (S)-2-(2-Chloro-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (70) to afford the desired product (45%) as a yellow oil. 500 MHz ^1H NMR (CDCl_3) δ 7.97 (m, 2H), 7.40 (m, 3H), 6.90 (d, 2H, $J = 8.5$ Hz), 6.75 (m, 3H), 6.12 (m, 1H), 5.98 (m, 1H), 5.02 (dd, 1H, $J = 9.3, 6.1$ Hz), 4.19 (t, 2H, $J = 6.7$ Hz), 3.71 (s, 3H), 3.36 (dd, 1H, $J = 14.2, 6.1$ Hz), 3.15 (dd, 1H, $J = 14.2, 9.3$ Hz), 2.95 (t, 2H, $J = 6.7$ Hz), 2.35 (s, 3H); MS m/z 465, 467 ($M+1$).

(b) (S)-2-(2-Chloro-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (68).



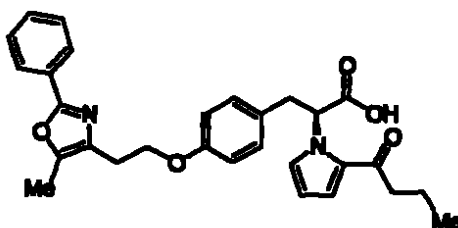
68

-139-

Prepared from (S)-3-(4-Hydroxy-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (1) and *N*-chlorosuccinimide to provide the desired pyrrole (41%) as a yellow oil. 500 MHz ^1H NMR (CDCl_3) δ 6.88 (d, 2H, $J = 8.5$ Hz), 6.77 (m, 1H), 6.6 (d, 2H, $J = 8.5$ Hz), 6.13 (m, 1H), 5.98 (m, 1H), 5.02 (dd, 1H, $J = 9.3, 6.1$ Hz), 3.72 (s, 3H), 3.36 (dd, 1H, $J = 14.2, 6.1$ Hz), 3.15 (dd, 1H, $J = 14.2, 9.3$ Hz); MS m/z 314, 316 ($M+1$).

Example 27

(S)-2-(2-Butyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (74).



74

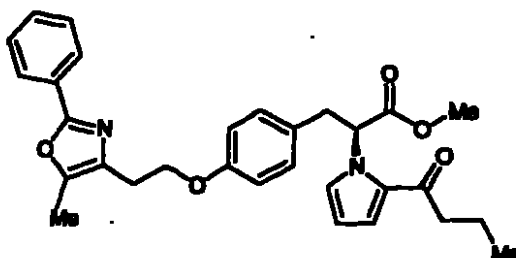
Prepared by the method described in General Procedure A from (S)-2-(2-Butyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (75) to afford the title acid. 500 MHz ^1H NMR (CDCl_3) δ 7.97 (m, 2H), 7.42 (m, 3H), 6.98 (m, 1H), 6.89 (m, 3H), 6.71 (d, 2H, $J = 8.8$ Hz), 6.12 (m, 1H), 4.16 (t, 2H, $J = 6.6$ Hz), 3.51 (m, 1H), 3.19 (dd, 1H, $J = 14.5, 9.4$ Hz), 2.95 (t, 2H, $J = 6.6$ Hz), 2.71 (m, 2H), 2.35 (s, 3H), 1.67 (q, 2H, $J = 7.3$ Hz), 0.92 (t, 3H, $J = 7.3$ Hz). MS m/z 487 ($M+1$).

(S)-2-(2-Butyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (73) was prepared in the following manner.

(a) (S)-2-(2-Butyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (73).

457

-140-

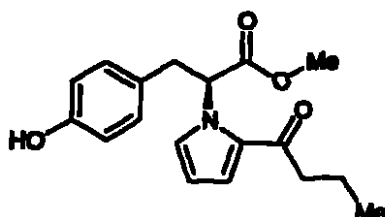


73

Prepared by the method described in General Procedure B from (S)-2-(2-Butyryl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (74) to afford the desired product (27%) as a colorless oil. 500 MHz ^1H NMR (CDCl_3) δ 7.96 (m, 2H), 7.42 (m, 3H), 6.94 (m, 1H), 6.84 (d, 2H, $J = 8.3$ Hz), 6.08 (m, 1H), 4.16 (t, 2H, $J = 6.6$ Hz), 3.70 (s, 3H), 3.44 (dd, 1H, $J = 14.2, 5.4$ Hz), 3.15 (dd, 1H, $J = 14.2, 9.8$ Hz), 2.93 (t, 2H, $J = 6.6$ Hz), 2.66 (m, 2H), 2.34 (s, 3H), 1.64 (m, 2H), 0.90 (t, 3H, $J = 7.3$ Hz); MS m/z 501 ($M+1$).

The following compounds were prepared according to General Procedures C-E.

(b) (S)-2-(2-Butyryl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (72).



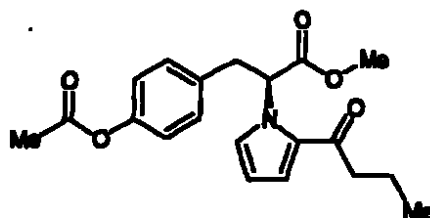
72

To a stirred solution of (S)-3-(4-Acetoxy-phenyl)-2-(2-butyryl-pyrrol-1-yl)-propionic acid methyl ester (73) (790 mg, 2.21 mmol) in anhydrous methanol (20 mL) was added potassium carbonate (306 mg, 2.21 mmol). The mixture was stirred at room temperature for 30 minutes. Solvent was removed under reduced pressure. The residue was taken up in EtOAc, washed with 2N aqueous HCl, and dried over MgSO_4 . The solvent was removed under reduced pressure to provide

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the desired phenol (580 mg, 83%) as a colorless oil. 500 MHz ^1H NMR (CDCl_3) δ 6.90 (m, 4H), 6.65 (d, 2H, $J = 8.5$ Hz), 6.12 (m, 1H), 3.70 (s, 3H), 3.44 (dd, 1H, $J = 14.3, 5.6$ Hz), 3.15 (dd, 1H, $J = 14.3, 9.5$ Hz), 2.68 (m, 2H), 1.66 (m, 2H), 0.92 (t, 3H, $J = 7.4$ Hz); MS m/z 316 ($M+1$).

(c) (S)-3-(4-Acetoxy-phenyl)-2-(2-butyryl-pyrrol-1-yl)-propionic acid methyl ester (71).



71

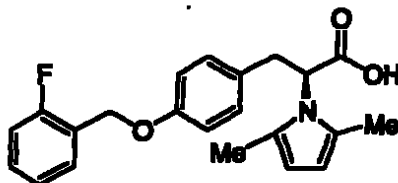
To a stirred solution of (S)-3-(4-Hydroxy-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (1) (1.0 g, 4.04 mmol) in acetonitrile (40 mL) was added triethylamine (735 μL , 5.26 mmol) and acetyl chloride (375 μL , 5.26). After stirring at room temperature overnight, the reaction was concentrated. The residue was taken up in water, extracted with EtOAc, dried over MgSO_4 , and concentrated. The crude material was then dissolved in dichloromethane (15 mL). Butyryl chloride (505 μL , 4.85 mmol) was added, followed by triflic acid (430 μL , 4.85 mmol). The reaction stirred for 10 seconds, poured into saturated aqueous NH_4Cl solution, and extracted with EtOAc. The organic layer was dried and the solvent removed under reduced pressure. The residue was chromatographed on silica gel eluting with 25% to 30% EtOAc in hexanes to afford the desired pyrrole (790 mg, 55%) as a clear oil. 500 MHz ^1H NMR (CDCl_3) δ 6.91 (m, 6H), 6.14 (m, 1H), 4.86 (m, 1H), 3.72 (s, 3H), 3.52 (m, 1H), 3.23 (m, 1H), 2.70 (m, 2H), 2.25 (s, 3H), 1.66 (m, 2H), 0.93 (t, 3H, $J = 8.5$ Hz); MS m/z 358 ($M+1$).

959

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Example 28

(S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-[4-(2-fluoro-benzyloxy)-phenyl]-propionic acid (76).



76

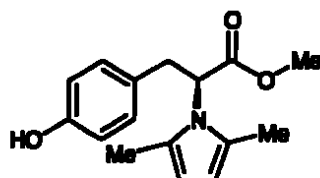
5

To a stirred solution of (S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (1) (500 mg, 1.82 mmol) in dimethylformamide (20 mL) was added sodium hydride (218 mg, 5.46 mmol).
10 The mixture was stirred at room temperature for 15 minutes and 2-fluorobenzyl bromide (440 μ L, 3.64 mmol) was added. The mixture was stirred at room temperature overnight. The reaction was diluted with water, acidified with aqueous 2N HCl, extracted with EtOAc. The solvent was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was taken up in methanol (20 mL) and lithium hydroxide (437 mg, 18.2 mmol) was added. The reaction was stirred at room temperature for 3 hours. The reaction was diluted with water, acidified with aqueous 2N HCl, extracted with EtOAc. The solvent was dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed eluting with 10% to 25% 6:1 EtOAc:HOAc in hexanes to yield the desired propionic acid
15 (300 mg, 45%). 500 MHz ^1H NMR (DMSO) δ 7.46 (m, 1H), 7.35 (m, 1H), 7.16 (m, 2H), 6.76 (m, 4H), 5.47 (s, 2H), 5.00 (s, 2H), 4.82 (dd, 1H, J = 11.2, 4.4 Hz), 3.29 (m, 1H), 2.96 (dd, 1H, J = 13.8, 11.2 Hz), 2.45 (s, 6H); MS m/z 368 (M+1).
20

(S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (75) was prepared in the following manner.
25

(S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid methyl ester (75).

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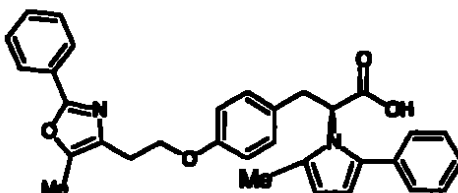


75

To a stirred solution of L-tyrosine methyl ester (3.90 g, 20.0 mmol) in
 5 toluene (200 mL) was added 2,5-hexandione (2.34 mL, 20.0 mmol) and p-
 toluenesulfonic acid (100 mg, 0.5 mmol). The mixture was heated to reflux 96
 hours, then concentrated. The insoluble solid was filtered and washed with
 EtOAc. The filtrate was concentrated and chromatographed eluting with 10% to
 25% 6:1 EtOAc:HOAc in hexanes to yield the desired pyrrole (3.14 g, 57%) as a
 10 yellow oil. 500 MHz ^1H NMR (CDCl_3) δ 6.60 (d, 2H, $J = 6.6$ Hz), 6.47 (d, 2H, $J =$
 8.5 Hz), 5.47 (s, 2H), 4.90 (dd, 1H, $J = 11.2, 4.3$ Hz), 3.63 (s, 3H), 3.24 (dd, 1H, J
 = 13.9, 4.3 Hz), 2.92 (dd, 1H, $J = 13.9, 11.2$ Hz), 1.85 (s, 6H); MS m/z 274
 (M+1).

Example 29

15 (S)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-(2-
 methyl-5-phenyl-pyrrol-1-yl)-propionic acid (80).



80

20 Prepared according to General Procedure A from (S)-3-[4-[2-(5-Methyl-2-
 phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-(2-methyl-5-phenyl-pyrrol-1-yl)-
 propionic acid methyl ester (79) which was hydrolyzed to afford the desired
 propionic acid (98%) as a brown solid. 500 MHz ^1H NMR (CDCl_3) δ 81.3 (m,
 2H), 7.46 (m, 3H), 7.16 (m, 3H), 6.83 (m, 2H), 6.60 (d, 2H, $J = 9.0$ Hz), 6.55 (d,
 25 2H, $J = 8.8$ Hz), 5.96 (m, 1H), 5.89 (d, 1H, $J = 3.4$ Hz), 4.95 (dd, 1H, $J = 10.0, 5.1$

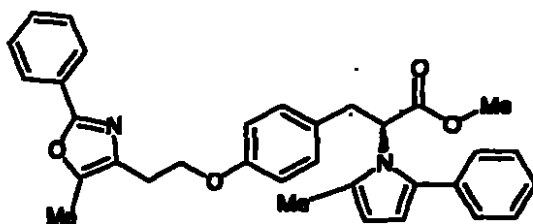
4.61

-144-

Hz), 4.22 (t, 2H, $J = 6.1$ Hz), 3.25 (m, 2H), 3.07 (m, 3H), 2.86 (m, 1H), 2.40 (s, 3H), 2.33 (s, 3H); MS m/z 507 (M+1).

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-methyl-5-phenyl-pyrrol-1-yl)-propionic acid methyl ester (79) was prepared in the following manner.

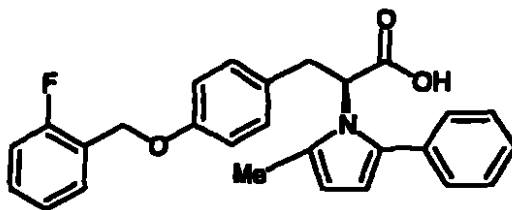
(a) (S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-methyl-5-phenyl-pyrrol-1-yl)-propionic acid methyl ester (79).



79

Prepared according to General Procedure B from 3-(4-Hydroxy-phenyl)-2-(2-methyl-5-phenyl-pyrrol-1-yl)-propionic acid methyl ester (1) and chromatographed on silica gel eluting with 15% to 50% EtOAc in hexanes to afford the desired pyrrole (300 mg, 39%) as a yellow oil. 500 MHz ^1H NMR (CDCl_3) δ 8.03 (m, 2H), 7.43 (m, 3H), 7.17 (m, 3H), 6.84 (m, 2H), 6.59 (d, 2H, $J = 8.8$ Hz), 6.53 (d, 2H, $J = 8.8$ Hz), 5.94 (d, 1H, $J = 3.4$ Hz), 5.87 (d, 1H, $J = 3.4$ Hz), 4.92 (dd, 1H, $J = 9.9, 5.0$ Hz), 4.18 (m, 2H), 3.76 (s, 3H), 3.25 (m, 2H), 2.99 (m, 3H), 2.86 (t, 1H, $J = 6.3$ Hz), 2.37 (s, 3H), 2.25 (s, 3H); MS m/z 521 (M+1).

(b) 3-[4-(2-Fluoro-benzyloxy)-phenyl]-2-(2-methyl-5-phenyl-pyrrol-1-yl)-propionic acid (78).

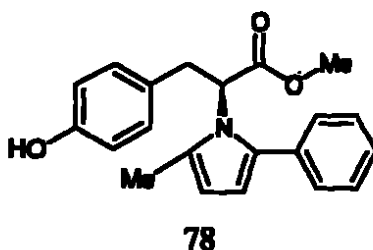


78

-145-

Prepared according to General Procedure A from 3-(4-Hydroxy-phenyl)-2-(2-methyl-5-phenyl-pyrrol-1-yl)-propionic acid methyl ester (77) to afford the desired propionic acid (23%) as a yellow solid. 500 MHz ^1H NMR (DMSO) δ 7.49 (t, 1H, $J = 7.3$ Hz), 7.38 (m, 1H), 7.19 (m, 5H), 6.78 (m, 2H), 6.67 (d, 2H, $J = 8.8$ Hz), 6.53 (d, 2H, $J = 8.5$ Hz), 5.81 (d, 2H, $J = 3.2$ Hz), 5.70 (d, 2H, $J = 3.4$ Hz), 5.02 (s, 2H), 4.85 (dd, 1H, $J = 10.7, 4.6$ Hz), 3.17 (m, 1H), 2.92 (m, 1H), 2.23 (s, 3H); MS m/z 430 ($M+1$).

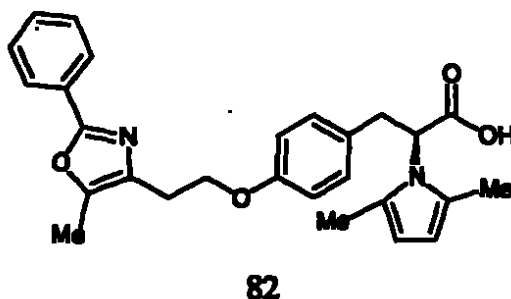
(c) 3-(4-Hydroxy-phenyl)-2-(2-methyl-5-phenyl-pyrrol-1-yl)-propionic acid methyl ester (77).



Prepared by the method described in Example 27(a) from 1-phenyl-1,4-pentanedione to afford the crude pyrrole which was used in subsequent steps. MS m/z 336 ($M+1$).

Example 30

(S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (82).



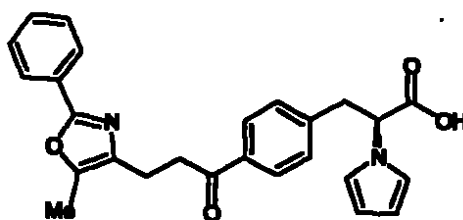
963

-146-

Prepared by the method described General Procedure A by in situ hydrolysis of the methyl ester (81). The product was chromatographed on silica gel eluting with 30% to 60% EtOAc in hexanes to isolate the desired propionic acid (5%) as red crystals. 500 MHz ^1H NMR (CDCl_3) δ 7.96 (m, 2H), 7.40 (m, 3H), 6.63 (m, 4H), 5.61 (s, 2H), 4.63 (dd, 1H, $J = 10.0, 4.9$ Hz), 4.38 (t, 2H, $J = 6.5$ Hz), 3.38 (dd, 1H, $J = 13.9, 4.9$ Hz), 3.00 (dd, 1H, $J = 13.9, 10.0$ Hz), 2.77 (m, 2H), 2.09 (s, 3H), 1.84 (s, 6H); MS m/z 445 ($M+1$).

Example 31

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl}-2-pyrrol-1-yl-propionic acid (87).

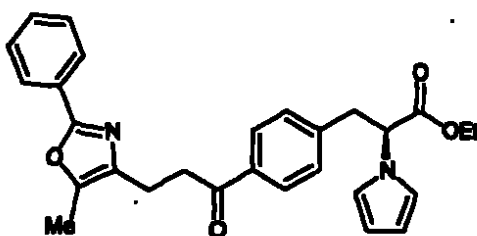


According to General Procedure A. LiOH (0.24 g, 10 mmole) in 10 mL H_2O was added to a solution of 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl}-2-pyrrol-1-yl-propionic acid ethyl ester (86) in 20 mL of THF/Methanol (1/1) and stirred for 17 hours. The solvent was removed and the residue was redissolved in H_2O . This mixture was acidified with 1N HCl, and the product was collected by filtration. 0.36g (56% yield). Mp: 90°C to 92°C, MS ($M+1$) 429.

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl}-2-pyrrol-1-yl-propionic acid ethyl ester (86) was prepared in the following manner.

(a) 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl}-2-pyrrol-1-yl-propionic acid ethyl ester (86).

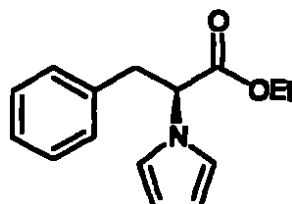
-147-



86

Oxalyl chloride (0.5 mL) was added to a solution of 2-(5-methyl-2-phenyloxazol-4-yl)acetic acid (84) (0.7 g, 2.88 mmole) in 10 mL of CH_2Cl_2 with a drop of DMF, and stirred at room temperature for one hour. The solvent was then evaporated, and the residue was redissolved in CH_2Cl_2 (20 mL). To this mixture was added ethyl 3-phenyl-2-pyrrolopropionate (85), followed by AlCl_3 (0.77 g, 5.75 mmole). The mixture was stirred for 17 hours. Water and EtOAc were then added. The organic layer was washed with brine and saturated aqueous NaHCO_3 . The pure product was isolated by column chromatography (2/1 = hexane/EtOAc) (0.62 g, 45%). MS: $M+1$: 457.2.

(b) Ethyl 3-phenyl-2-pyrrolopropionate (85).



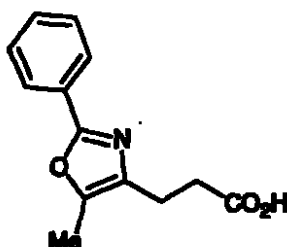
85

Triethylamine (3.3 mL) was added to a solution of ethyl phenylalanine in 50 mL CH_2Cl_2 . The mixture was stirred at room temperature for 20 minutes. The solvent was then removed and the residue was redissolved in diethyl ether. The triethylamine HCl salt was removed by filtration, and the filtrate was concentrated to obtain an oil. To this oil was added H_2O (25 mL), acetic acid (25 mL), and NaOAc (3.87 g, 47.2 mmole), and 2,5-dimethoxytetrahydrofuran (5.2 mL, 40.1 mmole). The mixture was heated at 100°C for 15 minutes then cooled to room temperature and diluted with EtOAc/ H_2O . The organic layer was washed with

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brine and dried over MgSO_4 , and the solvent was removed at reduced pressure. Purification of the residue by column chromatography (10% EtOAc/hexanes) afforded 2.54 g of the pure product (47%).

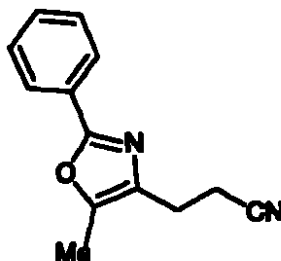
- 5 (c) 2-(5-methyl-2-phenyloxazol-4-yl)acetic acid (84).



84

10 KOH (1.79 g, 31.8 mmole) was added to a solution of 4-(2-Cyanoethyl)-5-methyl-2-phenyloxazole (83) (1.5 g, 7.07 mmole) in ethanol/ H_2O at room temperature. The mixture was then heated at reflux for 20 hours. The solvent was removed at reduced pressure. The residue was dissolved in H_2O , washed with ether, and the aqueous layer was acidified with 1 N HCl. The product was collected by filtration and dried to give a white powder. 0.7 g (44% yield).

- 15 (d) 4-(2-Cyanoethyl)-5-methyl-2-phenyloxazole (83).

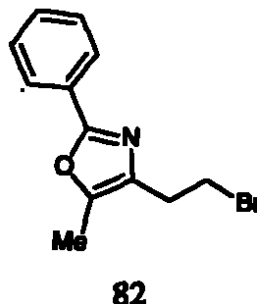


83

20 4-(2-bromoethyl)-5-methyl-2-phenyloxazole (84-1) (1.33 g, 5 mmole) was added to a suspension of KCN (0.65 g, 10 mmole) in 10 mL of DMSO at room temperature. The mixture was stirred for 17 hours, then diluted with water (100 mL), extracted with EtOAc, dried and evaporated, to give 1.1 g of the product which was used in the next step without further purification.

-149-

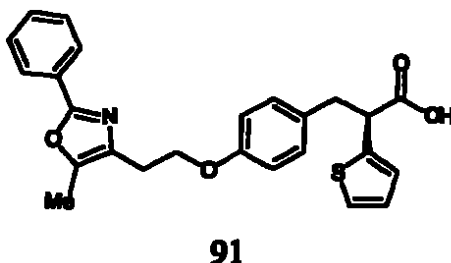
(e) 4-(2-bromoethyl)-5-methyl-2-phenyloxazole (82).



5 Triphenylphosphine (18 g, 68.9 mmole) and N-bromosuccinimide (12 g, 68.9 mmole) were added to a solution of 2-(5-methyl-2-phenyloxazol-4-yl)ethanol (11.16 g, 54.9 mmole) in 100 mL of THF. The mixture was stirred at room temperature for 2 hours. TLC and MS showed the reaction was completed. The reaction mixture was then distributed between EtOAc and saturated NaHCO₃.
10 The organic layer was washed with brine, dried and purified by column chromatography (3:1 = Hexanes:EtOAc). The product was isolated as a pale yellow powder (13.5 g, 92.5%).

Example 32

15 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-thiophen-2-yl-propionic acid (91).

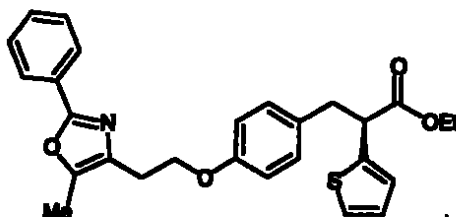


20 According to General Procedure A. The target compound was obtained by base (LiOH) hydrolysis of 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-thiophen-2-yl-propionic acid (90) in THF/H₂O. Mp: 146°C to 147°C, MS(M+1):434, Anal. Calcd for C₂₅H₂₃O₄NS: C, 69.26; H, 5.35, N, 3.23. Found: C, 68.90; H, 5.43, N, 3.06. ¹H NMR (DMSO-D₆) δ 7.95-6.75 (m, 14H), 4.1 (t, 2H), 4.05 (t, 2H), 3.1 (m, 1H), 2.85 (m, 2H), 2.3 (s, 3H).

-150-

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-thiophen-2-yl-propionic acid ethyl ester (90) was prepared in the following manner.

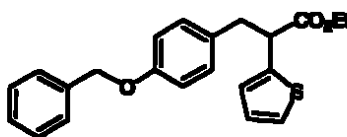
- 5 (a) 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-thiophen-2-yl-propionic acid ethyl ester (90).



90

- 10 The benzyl group in ethyl 3-(p-benzyloxyphenyl)-2-thiophenepropionate (89)) was removed with TMSI using acetonitrile as a solvent. General Procedure B was followed to prepare the title compound. To a 0 °C solution of 2-(5-methyl-2-phenyl-oxazol-4-yl)ethanol and the resulting phenol, and triphenyl phosphine in 10 mL THF was added DEAD (1.00 mL, 6.4 mmole). The mixture was then
- 15 stirred at ambient temperature for 20 hours. The solvent was removed and 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-thiophen-2-yl-propionic acid ethyl ester (90) was isolated by column chromatography (2.1 g, 84%).

- (b) Ethyl 3-(p-benzyloxyphenyl)-2-thiophenepropionate (89).



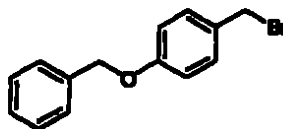
89

- 20 To a solution of ethyl 2-thiophene acetate (1.5 mL, 9.99 mmol) in 50 mL of THF under nitrogen was added LiHMDS (10 mL, 1.0M in THF) dropwise at -40°C. After the mixture was stirred for 30min., compound 3 in THF (50 mL) was
- 25 added. The resulting mixture was stirred at ambient temperature for another 20 hours. The solvent was removed and the product was collected by column chromatography (2.9 g, 81%).

168

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(c) p-Benzoyloxybenzyl bromide (88).



88

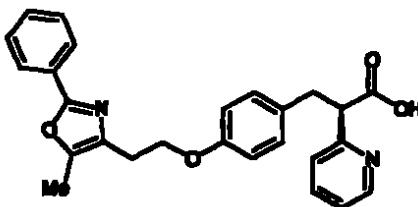
5

To a solution of 4.6 g of PBr_3 in 5 mL of dry THF at $-5^\circ C$ was added a solution 0.66 mL of pyridine in 1.3 mL of THF, followed by a solution of 2 in 75 mL of THF. The mixture was then stirred at ambient temperature for 20 hours, TLC and MS indicated the reaction was completed. The reaction was diluted with THF (100 mL) and filtered through celite, the product obtained (12 g, 87%) was used in the next step without further purification.

10

Example 33

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyridin-3-yl-propionic acid (92).



15

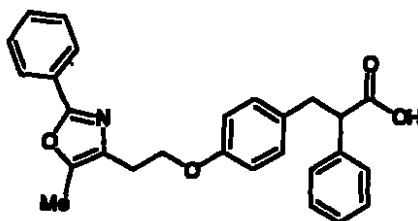
92

This compound was synthesized in the same manner as in Example 32 except ethyl 2-thiophene acetate was replaced by methyl 2-2-pyridin-3-yl acetate. Mp: 74.4-75.80 $^\circ C$, MS(M+1):471, Anal. Calcd for $C_{26}H_{24}O_4N_2$: C, 66.32; H, 5.49, N, 5.95. Found: C, 66.34; H, 5.86, N, 5.81. ^1H NMR(DMSO- D_6) δ 8.37-6.73 (m, 13H), 4.1 (t, 2H), 3.8 (t, 2H), 2.95 (m, 1H), 2.80 (m, 2H), 2.3 (s, 3H).

20

Example 34

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-propionic acid (93).



93

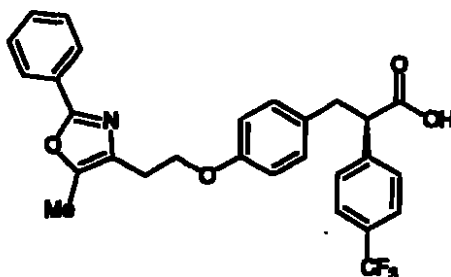
5

This compound was synthesized in the same manner as example 32 except ethyl 2-thiophene acetate was replaced by methyl 2-phenyl acetate. Mp: 177.9°C to 179.1°C, MS(M+1):417. Anal. Calcd for $C_{25}H_{24}O_4N_2$: C, 72.10; H, 5.81, N, 6.73. Found: C, 73.41; H, 6.04, N, 6.64. ^1H NMR($CDCl_3$) δ 6.6–7.9 (m, 15H), 4.3 (t, 2H), 3.7 (m, 2H), 3.41 (m, 1H), 3.2 (m, 2H), 2.3 (s, 3H).

10

Example 35

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-(3-triflorophenyl)-propionic acid (94).



94

15

This compound was synthesized in the same manner as example 32 except ethyl 2-thiophene acetate was replaced by methyl 2-(3-triflorophenyl) acetate. Mp: 118.8°C to 110°C, MS(M+1): 496.2; Anal. Calcd for $C_{28}H_{24}O_4NF_3$ HCl: C, 65.00; H, 4.79, N, 2.71. Found: C, 65.17; H, 4.37, N, 2.32. ^1H NMR(DMSO- D_6) δ 6.65–7.9 (m, 14H), 4.1 (t, 2H), 4.0 (m, 2H), 3.35 (m, 1H), 3.2 (m, 2H), 2.3 (s, 3H).

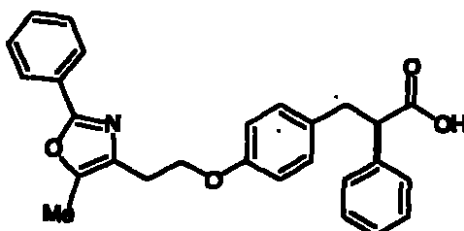
20

120

-153-

Example 36

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid (R) (95).



5

95

To a solution of 2-phenylacetic acid (10 g, 73.4 mmol) in oxalyl chloride (7 mL, 80.2 mmol) and 200 mL of CH_2Cl_2 , was added 2 drops of DMF and stirred at ambient temperature for 2 hours, the solvent was removed and the residue was redissolved in 50 mL of THF. To this solution was added dropwise a solution of lithium (R)-(+)-4-benzyl-2-oxazolidinone (6.58 g, 37.1 mmol) in THF (50 mL). The resulting mixture was stirred at ambient temperature for 17 hours. The solvent was removed and the residue was treated with saturated NH_4Cl and extracted into CH_2Cl_2 . The organic layer was washed with brine, and the solvent was removed to give 10.5 gm of oil (97%). Mp: 124.1°C to 125°C, MS(M+1): 428.1; Anal. Calcd for $\text{C}_{27}\text{H}_{25}\text{O}_4\text{N}$: C, 75.86; H, 5.89, N, 3.28. Found: C, 75.84; H, 5.91, N, 3.24. ^1H NMR(DMSO- D_6) δ 12.5 (br s, 1H), 7.05-6.75 (m, 14H), 4.1 (t, 2H), 3.72 (t, 2H), 3.15 (m, 1H), 2.7-2.88 (m, 2H), 2.3 (s, 3H).

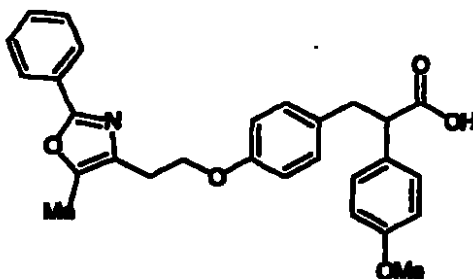
10

15

Example 37

2-(4-Methoxy-phenyl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (96).

20



96

121

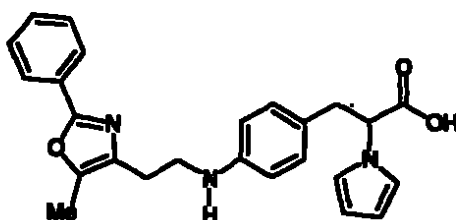
-154-

This compound was synthesized in the same manner as example 32 except that ethyl 2-thiopheneacetate was replaced by methyl p-methoxyphenylacetate.

Mp: 114.7°C to 116.6°C, MS(M+1): 458.1; Anal. Calcd for $C_{28}H_{27}O_3N$: C, 73.51; H, 5.95, N, 3.06. Found: C, 73.31; H, 5.76, N, 2.89. ^1H NMR (DMSO- D_6) δ 7.85-6.70 (m, 13H), 3.65 (s, 3H), 4.1 (t, 2H), 3.1 (m, 1H), 2.85 (m, 2H), 2.7-2.88 (m, 2H), 2.25 (s, 3H).

Example 38

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-phenyl}-2-pyrrol-1-yl-propionic acid (100).



100

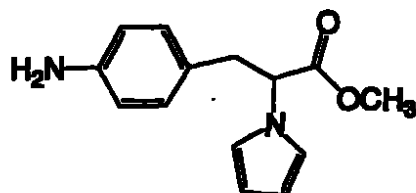
Compounds 99 (0.213 g, 1.06 mmol) and 97 (0.285 g, 1.17 mmol) were mixed in 20 mL of CH_2Cl_2 together with $NaBH(OAc)_3$ (0.337 mg, 1.6 mmol) and HOAc (0.7 mL) at 0 °C for 24 hours. The reaction was then diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was concentrated and purified by chromatography (4:1 EtOAc:Hexanes) to provide the product as a solid (0.15 g, 35%). Mp: 85.1°C to 87.4°C, MS(M+1): 416.1; Anal. Calcd for $C_{25}H_{25}O_3N_3$: C, 70.42; H, 5.98, N, 9.85. Found: C, 70.36; H, 5.97, N, 9.65. ^1H NMR(DMSO- D_6) δ 7.9-5.9 (m, 13H), 4.79 (t, 2H), 2.89-3.5 (m, 3H), 2.6 (t, 2H), 2.2 (s, 3H).

Compounds 99 and 98 were prepared in the following manner.

(a) 3-(4-aminophenyl)-2-pyrrolopropionic acid methyl ester (99).

172

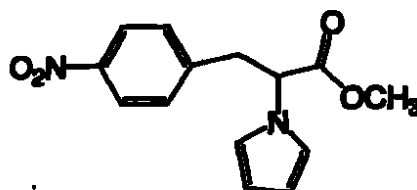
-155-



99

5 The nitro group in compound 98 was reduced to an amino group with Raney nickel in MeOH, which was used without further purification.

(b) 3-(4-nitrophenyl)-2-pyrrolopropionic acid methyl ester (98).



98

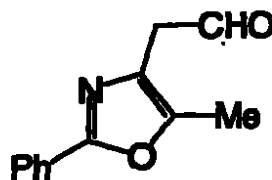
10

A mixture of 4-nitrophenylalanine (2.03 g, 9.66 mmol), 2,5-dimethoxytetrahydrofuran (2.15 mL, 16.6 mmol), and sodium acetate (1.603 g, 19.5 mmol) in 10 mL of water and 10 mL acetic acid was heated to 100 °C for 20 minutes. The black solid was partitioned between EtOAc and H₂O. The organic layer was dried and the solvent was removed. 0.6g of pure compound (3-(4-nitrophenyl)-2-pyrrolopropionic acid) was obtained by column chromatography (5% MeOH/CH₂Cl₂). The product was treated with TMSCHN₂ to provide the methyl ester (98).

15

20

(c) 2-(5-methyl-2-phenyl-oxazol-4-yl)acetaldehyde (97).



97

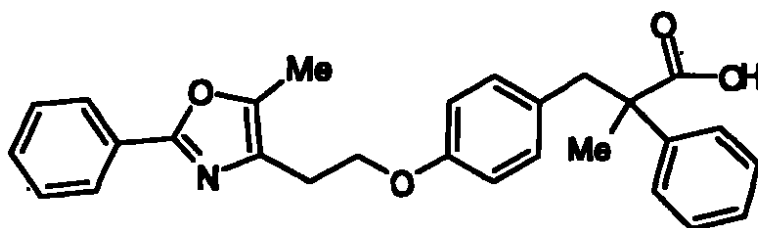
973

-156-

2-(5-methyl-2-phenyl-oxazol-4-yl)ethanol (0.5 g, 2.5 mmol) was added to a solution of ([1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin reagent) in 10 mL of CH₂Cl₂. The mixture was stirred at ambient temperature for one hr. TLC and MS showed the reaction was completed, and the aldehyde 97 was isolated as an oil.

Example 39

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid (101).



10

101

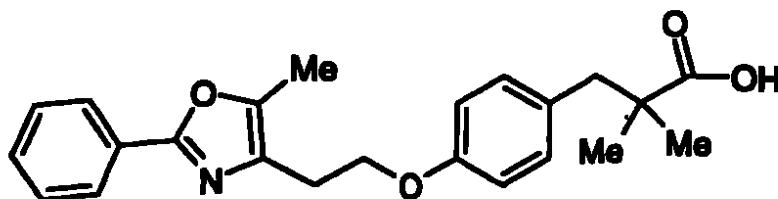
This compound was synthesized in the same manner as example 32 except that ethyl 2-thiopheneacetate was replaced by methyl 2,2-methylphenylacetate. Mp: 178°C to 179°C, MS(M+1): 442.1; Anal. Calcd for C₂₈H₂₇O₃N₁ 1/3 H₂O: C, 75.08; H, 6.18, N, 3.12. Found: C, 75.21; H, 6.34, N, 2.77. ¹H NMR(DMSO-D₆) δ 7.9-6.5 (m, 14H), 4.1 (t, 2H), 2.85 (t, 2H), 2.45 (s, 3H), 2.3 (s, 2H), 1.25 (s, 3H).

15

Example 40

2,2-Dimethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (102).

20



102

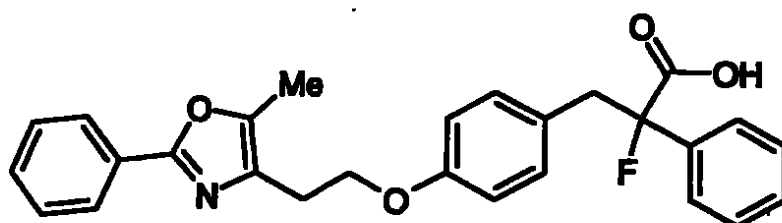
722

-157-

This compound was synthesized in the same manner as example 32 except that ethyl 2-thiopheneacetate was replaced by methyl 2,2-dimethylacetate. Mp: 133°C to 134°C, MS(M+1): 380.1; Anal. Calcd for C₂₃H₂₅O₄N: C, 72.80; H, 6.64, N, 3.69. Found: C, 72.60; H, 6.66, N, 3.50. ¹H NMR (DMSO-D₆) δ 7.85 (m, 2H), 7.45 (m, 3H), 6.95 (d, 2H), 4.15 (t, 2H), 2.85 (t, 2H), 2.65 (s, 2H), 2.3 (s, 3H), 0.99 (s, 3H).

Example 41

2-Fluoro-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid (103).

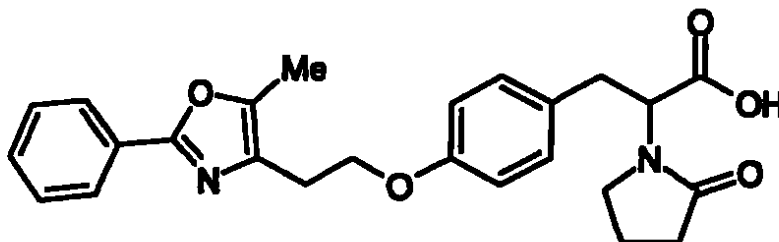


103

This compound was synthesized in the same manner as example 32 except that ethyl 2-thiopheneacetate was replaced by methyl 2,2-fluorophenylacetate. Mp: 163-165 °C, MS(M-1): 444.0; Anal. Calcd for C₂₇H₂₄O₄NF: C, 72.80; H, 5.43, N, 3.14. Found: C, 72.50; H, 5.56, N, 3.06. ¹H NMR(DMSO-D₆) δ 7.9-6.72 (m, 14H), 4.10 (t, 2H), 3.5 (t, 2H), 2.85 (t, 2H), 2.3 (s, 3H).

Example 42

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-oxo-pyrrolidin-1-yl)-propionic acid (104).



104

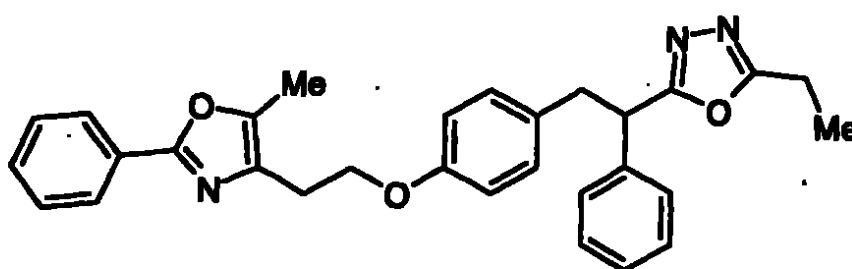
125

-158-

This compound was synthesized in the same manner as example 32 except that ethyl 2-thiopheneacetate was replaced by methyl 2-(2-oxo-pyrrolidin-1-ylphenyl) acetate. MS(M-1):435.1; Anal. Calcd for $C_{25}H_{26}O_3N_2 \cdot H_2O$: C, 66.30; H, 6.19, N, 6.19. Found: C, 66.26; H, 6.19, N, 6.19. ^1H NMR(DMSO- D_6) δ 7.88 (d, 2H), 7.4 (m, 3H), 7.05 (d, 2H), 6.75 (d, 2H), 4.60 (m, 1H), 4.1 (t, 2H), 3.1-2.75 (m, 4H), 2.3 (s, 3H), 2.1-1.65 (m, 6H).

Example 43

2-Ethyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1,3,4-oxadiazole (105).



105

To a 0°C of 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid (93) (0.197 g, 0.46 mmol) in 3 mL THF under N_2 was added 4-methylmorpholine (0.084 mL, 0.65 mmol), followed by isobutylchloroformate (0.084 mL, 0.65 mmol). The reaction mixture was stirred at 0 °C for 30 min., then filtered into a 0 °C solution of hydrazine (0.07 mL, 2.23 mmol) in 3 mL THF. The mixture was stirred for 50 min. at 0°C. EtOAc (10 mL), water, and NH_4Cl were then added. The organic portion was separated and evaporated to a white solid. The solid was redissolved in 4 mL dioxane. To the resulting solution was added triethylorthopropionate (0.28 mL, 1.39 mmol), and methanesulfonic acid (0.06 mL, 0.09 mmol). The mixture was heated at 105°C for 15 min, then cooled to ambient temperature. EtOAc was added, then washed with saturated $NaHCO_3$ and brine. The solvent was evaporated and the residue was triturated with Et_2O and hexanes. A white solid was obtained (105). Mp: 110°C, MS(M+1):480.2; Anal. Calcd for $C_{30}H_{29}O_3N_3 \cdot 1/2H_2O$: C, 73.97; H, 6.31, N, 8.40. Found: C, 73.68; H, 6.14, N, 8.59. ^1H NMR ($CDCl_3$) δ 7.95 (d, 2H), 7.45-7.2 (m,

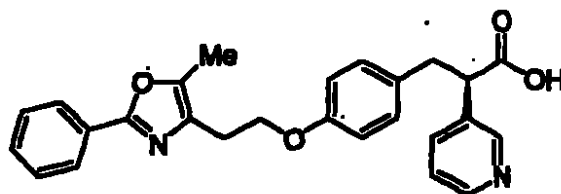
77

-160-

Ethyl 3-phenyl-2-pyrrolopropionate (See Example 31) was added then added, followed by AlCl_3 (0.77 g, 5.75 mmole), the mixture was stirred for 17 hours, water and EtOAc was added, the organic layer was washed with brine, sat. NaHCO_3 . The pure product was isolated by column chromatography (2/1 = hexane/EtOAc), it weight 0.62 g (45%).

Example 45

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyridin-3-yl-propionic acid (108).

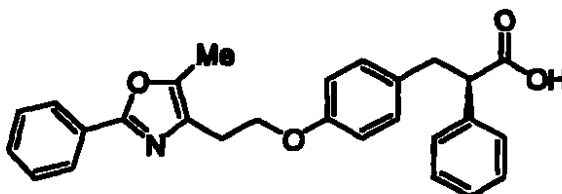


108

This compound was synthesized in the same manner as Example 32 except ethyl 2-thiophene acetate was replaced by methyl 2-2-pyridin-3-yl acetate. Mp: 74.4°C to 75.80°C, MS(M+1):471, Anal. Calcd for $\text{C}_{26}\text{H}_{24}\text{O}_4\text{N}_2$: C, 66.32; H, 5.49, N, 5.95. Found: C, 66.34; H, 5.86, N, 5.81. ^1H NMR(DMSO- D_6) δ 8.37-6.73 (m, 13 H), 4.1 (t, 2H), 3.8 (t, 2H), 2.95 (m, 1H), 2.80 (m, 2H), 2.3 (s, 3H).

Example 46

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid (110).



110

This compound was synthesized in the same manner as Example 32 from the corresponding methyl ester except compound 108 was used in the coupling

p28

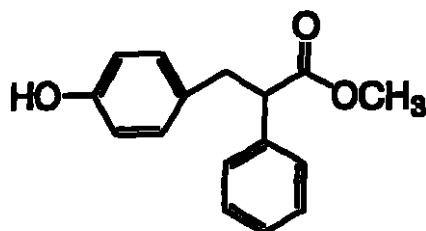
-161-

reaction. Mp: 177.9°C to 179.1°C, MS(M+1): 417. Anal. Calcd for $C_{25}H_{24}O_4N_2$: C, 72.10; H, 5.81, N, 6.73. Found: C, 73.41; H, 6.04, N, 6.64. ^1H NMR($CDCl_3$) δ 6.6–7.9 (m, 15H), 4.3 (t, 2H), 3.7 (m, 2H), 3.41 (m, 1H), 3.2 (m, 2H), 2.3 (s, 3H).

5

Methyl-2-phenyl-3-(p-hydroxy)phenyl propionate (109) was prepared in the following manner.

(a) Methyl-2-phenyl-3-(p-hydroxy)phenyl propionate (109).



10

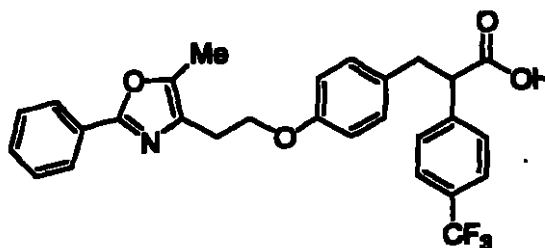
109

Prepared from 2-phenyl-3-(p-hydroxy) phenyl propionic acid using trimethylsilyl azide as the esterfying agent.

Example 47

15

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-triflorophenyl)-propionic acid (111).



111

20

This compound was synthesized in the same manner as Example 32 except ethyl 2-thiophene acetate was replaced by methyl 2-(3-triflorophenyl) acetate. Mp: 118.8°C to 110°C, MS(M+1): 496.2; Anal. Calcd for $C_{28}H_{24}O_4NF_3 \cdot 0.6HCl$: C, 65.00; H, 4.79, N, 2.71. Found: C, 65.17; H, 4.37, N, 2.32. ^1H NMR(DMSO-

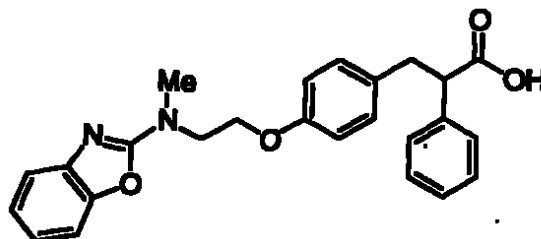
171

-162-

D₆) δ 6.65–7.9 (m, 14H), 4.1 (t, 2H), 4.0 (m, 2H), 3.35 (m, 1H), 3.2 (m, 2H), 2.3 (s, 3H).

Example 48

5 (R)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-propionic acid (113).



113

10 Synthesized in the same manner as example 32 except that ethyl 2-thiophene acetate was replaced by compound 112. Mp: 124.1°C to 125°C, MS(M+1): 428.1; Anal. Calcd for C₂₇H₂₅O₄N: C, 75.86; H, 5.89, N, 3.28. Found: C, 75.84; H, 5.91, N, 3.24. ¹H NMR(DMSO-D₆) δ 12.5 (b, 1H), 7.06–6.75 (m, 14H), 4.1 (t, 2H), 3.72 (t, 2H), 3.15 (m, 1H), 2.7–2.88 (m, 2H), 2.3 (s, 3H).

Compound 112 was prepared in the following manner.

15

(a) Compound (112).

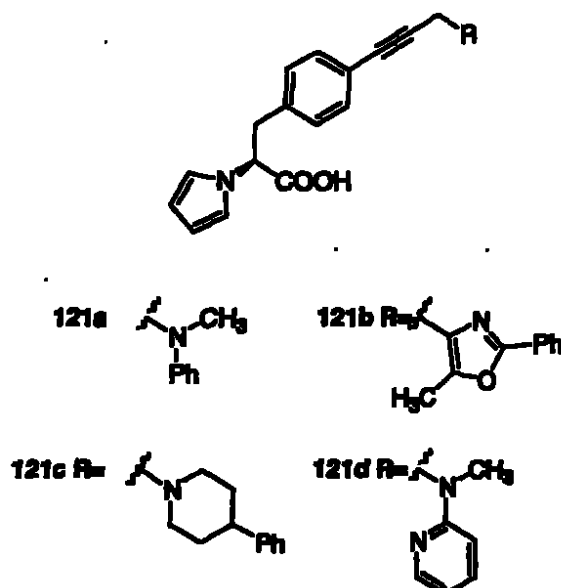
20

To a solution of 2-phenylacetic acid (10 g, 73.4 mmol) in oxalyl chloride (7 mL, 80.2 mmol) and 200 mL of CH₂Cl₂, was added 2 drops of DMF and stirred at ambient temperature for 2 hours. The solvent was removed and the residue was redissolved in 50 mL of THF. To this solution was added dropwise a solution of lithium (R)-(+)-4-benzyl-2-oxazolidinone (6.58 g, 37.1 mmol) in THF (50 mL). The mixture was again stirred at ambient temperature for 17 hours. The solvent was removed and the residue was treated with saturated NH₄Cl and extracted into CH₂Cl₂. The CH₂Cl₂ layer was washed with brine, dried over MgSO₄, and concentrated *in vacuo*, leaving 10.5g of oil (97% yield).

25

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Example 49**General procedure for the preparation of analogs 121 a-d.**

5 (S)-3-{4-[3-(Methyl-phenyl-amino)-prop-1-ynyl]-phenyl}-2-pyrrol-1-yl-propionic acid (121a). Ester 120a (0.82 g, 2.201 mmol) was dissolved in THF:H₂O (40:10 mL) and LiOH·H₂O (0.138 g, 3.301 mmol) was added and the mixture was stirred at room temperature for 3.5 hours. The solvent was removed and the residue was diluted with water, acidified with 10% HCl. The mixture was

10 extracted with CHCl₃ (3 × 50 mL). The combined organic extracts were dried over MgSO₄, filtered and the solvent removed. Purification by chromatography on silica gel eluting with 0-2% MeOH in CHCl₃ containing formic acid (0-0.1%) gave pure 129a as a light brown solid (0.727 g, 92%); Mp 55°C to 60°C; ¹H NMR (CDCl₃, 400 MHz) δ 7.29-7.25 (m, 2 H), 7.21 (d, J = 8.0 Hz, 2 H), 6.92 (d, J = 8.0 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 6.83 (t, J = 7.4 Hz, 1 H), 6.65 (t, J = 2.0 Hz, 2 H), 6.13 (t, J = 2.0 Hz, 2 H), 4.72 (dd, J = 9.2 and 6.0 Hz, 1 H), 4.23 (s, 2 H), 3.41-3.20 (m, 2 H), 3.00 (s, 3 H); CIMS m/z 359 (M + H)⁺; IR 3418, 2960, 1726, 1597, 1272 cm⁻¹. Anal. calcd for C₂₃H₂₂N₂O₂·0.3 H₂O: C, 75.93; H, 6.26; N, 7.74. Found: C, 75.73; H, 6.19; N, 7.53.

20

(S)-3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-2-pyrrol-1-yl-propionic acid (121b). Prepared from methyl ester 120b (0.337 g,

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0.794 mmol) by the general procedure described for 129a. Purification by chromatography on silica gel eluting with hexanes:ethyl acetate (2:1) followed by hexanes:ethyl acetate (2:1) containing 0.2% formic acid gave acid 128b as a pale yellow solid (0.231 g, 71%): mp 178°C to 180°C; ¹H NMR (CDCl₃, 400 MHz) δ 7.78-7.76 (m, 2 H), 7.22 (m, 3 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 6.72 (d, *J* = 8.4 Hz, 2 H), 6.46 (t, *J* = 2.0 Hz, 2 H), 5.86 (t, *J* = 2.0 Hz, 2 H), 4.48 (dd, *J* = 9.6 and 5.6 Hz, 1 H), 3.50 (s, 2 H), 3.27-2.97 (m, 2 H), 2.26 (s, 3 H); CIMS *m/z* 409 (M - H)⁺. Anal. calcd for C₂₆H₂₂N₂O₃: C, 76.08; H, 5.40; N, 6.82. Found: C, 75.77; H, 5.45; N, 6.70.

10

(*S*)-3-{4-[3-(4-Phenyl-piperidin-1-yl)-prop-1-ynyl]-phenyl}-2-pyrrol-1-yl-propionic acid (121c). Prepared from ester 120c (0.344 g, 0.806 mmol) following the general procedure described for 129a. Purification by chromatography eluting with 0-8% MeOH in CHCl₃ containing 0.1% formic acid gave pure 129c as a white solid (0.307 g, 92%): Mp 201°C-203°C; ¹H NMR (CDCl₃, 400 MHz) δ 7.33-7.21 (m, 5 H), 7.17 (d, *J* = 7.3 Hz, 2 H), 7.01 (d, *J* = 8.3 Hz, 2 H), 6.70 (t, *J* = 2.2 Hz, 2 H), 6.08 (t, *J* = 2.2 Hz, 2 H), 4.68 (dd, *J* = 8.8 and 6.1 Hz, 1 H), 3.91 (s, 2 H), 3.48-3.20 (m, 4 H), 2.98 (t, *J* = 11.5 Hz, 2 H), 2.61 (t, *J* = 11.9 Hz, 1 H), 2.25-2.13 (m, 2 H), 1.96 (d, *J* = 12.7 Hz, 2 H); CIMS *m/z* 413 (M + H)⁺. Anal. calcd for C₂₇H₂₈N₂O₂·0.9 H₂O: C, 75.64; H, 7.01; N, 6.53. Found: C, 75.29; H, 6.75; N, 6.44.

20

(*S*)-3-{4-[3-(Methyl-pyridin-2-yl-amino)-prop-1-ynyl]-phenyl}-2-pyrrol-1-yl-propionic acid (121d). Prepared from ester 120d (0.110 g, 0.294 mmol) by the general procedure described above. Acid 129d was obtained as a yellow solid (0.098 g, 93%): ¹H NMR (CDCl₃, 400 MHz) δ 8.02 (m, 1 H), 7.51-7.46 (m, 1 H), 7.14 (d, *J* = 8.3 Hz, 2 H), 6.82 (d, *J* = 8.0 Hz, 2 H), 6.62-6.54 (m, 2 H), 6.58 (t, *J* = 2.0 Hz, 2 H), 6.00 (t, *J* = 2.2 Hz, 2 H), 4.61 (dd, *J* = 9.4 and 5.6 Hz, 1 H), 4.37 (s, 2 H), 3.35-3.10 (m, 2 H), 3.05 (s, 3 H); CIMS *m/z* 360 (M + H)⁺. Anal. calcd for C₂₂H₂₁N₃O₂·0.5C₄H₈O₂: C, 71.44; H, 6.25; N, 10.41. Found: C, 71.14; H, 6.07; N, 10.20.

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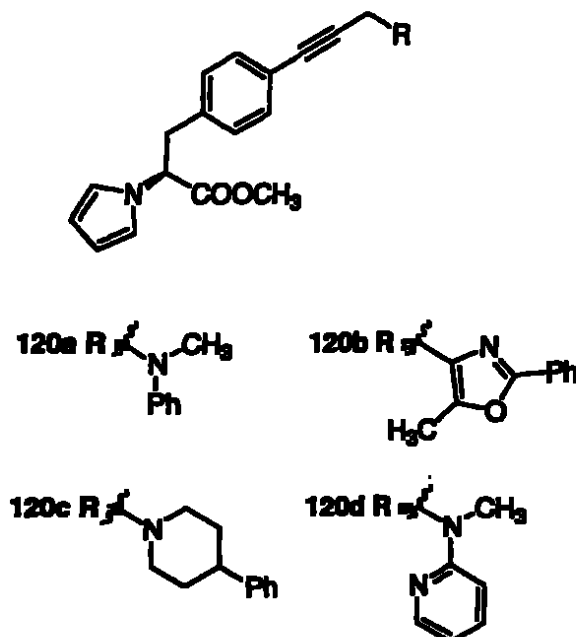
30

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The ester starting materials were prepared in the following manner.

(a) (120 a-d).



5 **General procedure for the synthesis of esters 120 a-d.**

(*S*)-3-[4-[3-(Methyl-phenyl-amino)-prop-1-ynyl]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (120a). Triflate 119 (1.66 g, 4.399 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.356 g, 0.308 mmol) were dissolved in dry DMF (10 mL). A solution of *N*-methyl-*N*-prop-2-ynyl aniline (Magnus, P.; Ladlow, M.; Elliot, J.; Sook Kim, C. *J. Chem. Soc. Chem. Comm.* 1989, 518-519) (1.27 g, 8.798 mmol) in DMF (2 mL) was added, followed by triethylamine (1.84 mL, 13.197 mmol). Nitrogen was passed through the reaction mixture for 0.5 hr. CuI (0.167 g, 0.880 mmol) was added and the mixture heated at 45-50 °C for 6 h under nitrogen. At this time additional $\text{Pd}(\text{PPh}_3)_4$ (0.356 g, 0.308 mmol) was incorporated. Heating was continued for 14 h and additional *N*-methyl-*N*-prop-2-ynyl aniline (0.635 g, 4.399 mmol) and catalyst (0.254 g, 0.220 mmol) were added. The mixture was heated for another 12 hr. At this time the mixture was allowed to cooled and diluted with water (150 mL) and Et_2O (100 mL). The phases were separated and the aqueous phase was extracted with Et_2O (4 × 80 mL). The combined organic extracts were washed with water and brine. Activated carbon was added and the

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mixture was boiled for 15-20 min. It was dried under MgSO_4 , filtered and the solvent removed. Purification by flash chromatography on silica gel eluting with 60%-0% petroleum ether in dichloromethane followed by a second chromatographic purification eluting with hexanes:ethyl acetate (7:1 to 5:1) gave pure 11 as a thick oil (1.256 g, 77%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.29-7.21 (m, 4 H), 7.23 (d, $J = 8.0$ Hz, 2 H), 6.92-6.66 (m, 1 H), 6.89 (d, $J = 8.4$ Hz, 2 H), 6.66 (t, $J = 2.4$ Hz, 2 H), 6.12 (t, $J = 2.4$ Hz, 2 H), 6.68 (dd, $J = 9.2$ and 6.4 Hz, 1 H), 4.24 (s, 2 H), 3.67 (s, 3 H), 3.39-3.18 (m, 2 H), 3.02 (s, 3 H); CIMS m/z 373 ($\text{M} + \text{H}$) $^+$.

(*S*)-3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (120b). This compound was prepared from triflate 119 (1.47 g, 3.9 mmol) and 5-methyl-2-phenyl-4-prop-2-ynyloxazole 125 (1.0 g, 5.070 mmol) following the general procedure described for 128a, except that no additional catalyst or 127 was added and the reaction was carried out at 90°C. Purification by chromatography eluting with hexanes:ethyl acetate (5:1 to 4:1) gave pure 128b as a thick oil (1.20, 73%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.99 (d, $J = 8.4$ Hz, 1 H), 7.98 (d, $J = 7.2$ Hz, 1 H), 7.45-7.39 (m, 3 H), 7.29 (d, $J = 8.0$ Hz, 2 H), 6.92 (d, $J = 8.4$ Hz, 2 H), 6.68 (t, $J = 2.0$ Hz, 2 H), 6.13 (t, $J = 2.0$ Hz, 2 H), 4.70 (dd, $J = 8.8$ and 6.4 Hz, 1 H), 3.71 (s, 2 H), 3.69 (s, 3 H), 3.40-3.20 (m, 2 H), 2.46 (s, 3 H); CIMS m/z 425 ($\text{M} + \text{H}$) $^+$.

(*S*)-3-[4-[3-(4-Phenyl-piperidin-1-yl)-prop-1-ynyl]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (120c). This compound was prepared from triflate 119 (0.500 g, 1.325 mmol) and *N*-prop-2-ynyl-4-phenylpiperidine (Lambert, S. J.; Kabalka, G. W.; Knapp, F. F. Jr.; Srivastava, P. C. *J. Org. Chem.* 1991, 56, 3707-3711) (0.396 g, 1.987 mmol) following the general procedure described for 128a with the exception that the reaction was carried out at 85°C. Additional catalyst (5 mol%) and *N*-prop-2-ynyl-4-phenylpiperidine (0.132 g, 0.662 mmol) were added after 20 hours. Purification by flash chromatography on silica gel eluting with 35%-45% ethyl acetate in hexanes afforded pure 128c as a thick oil (0.344 g,

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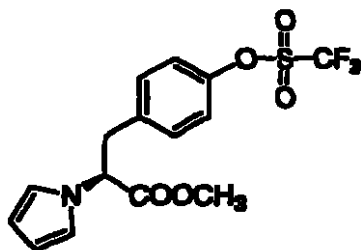
61%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.32-7.17 (m, 5 H), 7.31 (d, $J = 8.4$ Hz, 2 H), 6.93 (d, $J = 8.0$ Hz, 2 H), 6.69 (t, $J = 2.0$ Hz, 2 H), 6.14 (t, $J = 2.0$ Hz, 2 H), 4.71 (dd, $J = 9.2$ and 6.4 Hz, 1 H), 3.70 (s, 3 H), 3.53 (s, 2 H), 3.41-3.21 (m, 2 H), 3.08 (bd, $J = 11.6$ Hz, 2 H), 2.55-2.46 (m, 1 H), 2.36 (t, $J = 11.2$ Hz, 1 H), 2.35 (t, $J = 11.2$ Hz, 1 H), 1.91-1.79 (m, 4 H); CIMS m/z 427 ($M + \text{H}$) $^+$.

(*S*)-3-{4-[3-(Methyl-pyridin-2-yl-amino)-prop-1-ynyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (120d). This compound was prepared from triflate 119 (0.526 g, 1.394 mmol) and 2-(*N*-methyl-*N*-prop-2-ynyl)pyridine (see 126, below) (0.407 g, 2.788 mmol) following the general procedure described for 128a, with the exception that piperidine was used as solvent instead of DMF.

Purification by chromatography on silica gel eluting with hexanes:ethyl acetate (4:1) gave 128d as a yellowish thick oil (0.132 g, 25.3%): ^1H NMR (CDCl_3 , 400 MHz) δ 8.19-8.17 (m, 1 H), 7.48-7.43 (m, 1 H), 7.22 (d, $J = 8.0$ Hz, 2 H), 6.87 (d, $J = 8.0$ Hz, 2 H), 6.64 (t, $J = 2.0$ Hz, 2 H), 6.59 (d, $J = 7.6$ Hz, 1 H), 6.58 (d, $J = 6.4$ Hz, 1 H), 6.09 (t, $J = 2.0$ Hz, 2 H), 4.66 (dd, $J = 9.0$ and 6.4 Hz, 1 H), 4.54 (s, 2 H), 3.65 (s, 3 H), 3.36-3.16 (m, 2 H), 3.09 (s, 3 H); CIMS m/z 374 ($M + \text{H}$) $^+$.

(b) Triflate 119, used in the coupling action above, was prepared in the following manner.

(*S*)-2-Pyrrol-1-yl-3-[(4-trifluoromethanesulfonyloxy)phenyl]-propionic acid methyl ester (119).



119

A mixture of phenol 1 (See Example 1) (6.64 g, 27.088 mmol) and *N*-phenyltrifluoromethanesulfonimide (10.47 g, 27.9 mmol) in CH_2Cl_2 (70 mL)

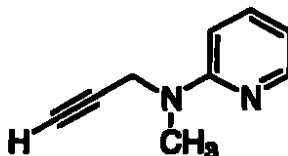
185

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under nitrogen was cooled at 0°C. Triethylamine (4.15 mL, 29.8 mmol) was added slowly. The mixture was stirred at 0°C for 1 hr. Then the temperature was allowed to reach room temperature slowly and stirred at this temperature for 2.5 hr. The mixture was diluted with Et₂O (70 mL) and washed with water, 1 N NaOH, and brine. The organic phase was dried over MgSO₄, filtered, and the solvent removed. Purification by flash chromatography on silica gel eluting with hexanes:ethyl acetate (5:1) afforded 127 as a thick oil (9.55 g, 93%) which solidified upon cooling and trituration to give a white solid: $[\alpha]_D^{25} -93.6^\circ$ ($c = 5$, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 7.13 (d, $J = 8.8$ Hz, 2 H), 7.02 (d, $J = 8.8$ Hz, 2 H), 6.66 (t, $J = 2.1$ Hz, 2 H), 6.14 (t, $J = 2.1$ Hz, 2 H), 4.69 (dd, $J = 9.3$ and 5.9 Hz, 1 H), 3.72 (s, 3 H), 3.43-3.25 (m, 2 H); IR 1731, 1426, 1203, 1136 cm⁻¹; CIMS m/z 378 ($M + H$)⁺. Anal. calcd for C₁₅H₁₄F₃NO₅S: C, 47.75; H, 3.74; N, 3.71. Found: C, 47.83; H, 3.64; N, 3.54.

(c) The alkynes that were used in the coupling reaction above were prepared in the following manner.

2-(*N*-Methyl-*N*-prop-2-ynyl)pyridine (118).



118

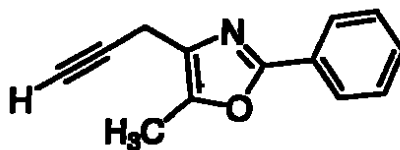
Sodium hydride (0.467 g, 11.673 mmol) was suspended in DMF (10 mL) under nitrogen and stirred in an ice bath. 2-(Methylamino)pyridine (1 mL, 9.728 mmol) was added and the mixture stirred at 0°C for 45 min. An 80% solution of propargyl bromide in toluene (1.19 mL, 10.7 mmol) was then incorporated. The mixture was allowed to reach room temperature and stirred overnight. The mixture was diluted with water and extracted with Et₂O. The combined organic extracts were washed with water and brine, dried over MgSO₄, filtered, and the solvent removed. Purification by flash chromatography on silica gel eluting with

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hexanes:ethyl acetate (8:1) afforded 126 as an oil (0.867 g, 61%): ^1H NMR (CDCl_3 , 400 MHz) δ 8.17 (dd, $J = 4.6$ and 1.7 Hz, 1 H), 7.46 (dt, $J = 8.5$ and 2.0 Hz, 1 H), 6.58 (m, 2 H), 4.35 (d, $J = 2.4$ Hz, 2 H), 3.04 (s, 3 H), 2.11 (t, $J = 2.4$ Hz, 1 H); CIMS m/z 147 ($M + H$) $^+$.

5 5-Methyl-2-phenyl-4-prop-2-ynylloxazole (117).



117

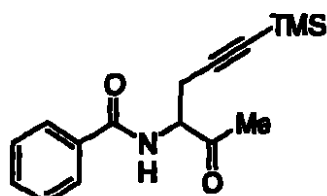
According to the procedure of Hulin (Hulin, B.; Newton, L. S.; Lewis,
10 D. M.; Genereux, P. E.; Gibbs, M.; Clark, D. A. *J. Med. Chem.* 1996, 39, 3897-3907). Alkyne 7 (3.01 g, 10.472 mmol) was dissolved in MeOH (150 mL) and treated with 10% KOH (10 mL). The mixture was stirred at room temperature for 4.5 hours. At this time the solvents were removed and the residue diluted with water and acidified to pH~2 with 6 M HCl. The solid that precipitated was
15 separated by vacuum filtration and dried. The filtrate was extracted with ethyl acetate (3 $\times$ 40 mL) and the combined organic extracts were dried over MgSO_4 , filtered, and the solvent removed. The solid obtained from the previous steps (2.19 g) was treated with TFA (16 mL) and TFAA (8 mL) at 35-40 $^\circ\text{C}$ overnight, as previously described by Hulin and collaborators, to give oxazole 125 after
20 purification by flash chromatography over silica gel eluting with hexanes:ethyl acetate (10:1 to 9:1). Oxazole 125 was obtained as an off-white solid (1.89 g, 94%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.96-7.99 (m, 2 H), 7.37-7.44 (m, 3 H), 3.50 (d, $J = 2.8$ Hz, 2 H), 2.41 (s, 3 H), 2.12 (t, $J = 2.8$ Hz, 1 H); CIMS m/z 198 ($M + H$) $^+$.

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N-[(1-acetyl-4-(trimethylsilyl)but-3-ynyl]benzamide (116).

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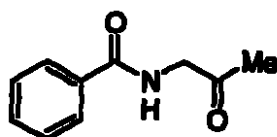
-170-



116

Amide 123 (2.55 g, 14.4 mmol) was dissolved in THF (150 mL) and cooled to -78 °C under nitrogen. A 1.0 M solution of LHMDS in THF (14.4 mL, 14.4 mmol) was added and the mixture stirred for 0.5 hr. A solution of 3-bromo-1-(trimethylsilyl)-1-propyne (2.6 mL, 18.7 mmol) in THF (15 mL) was added. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with water and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were dried over MgSO₄, filtered, and the solvent removed. Purification by flash chromatography on silica gel eluting with hexanes:ethyl acetate (3:1) gave amide 124 as white solid (3.01 g, 73%): ¹H NMR (CDCl₃, 400 MHz) δ 7.68 (d, *J* = 7.2 Hz, 2 H), 7.40 (t, *J* = 7.2 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 2 H), 7.02 (bd, *J* = 6.4 Hz, 1 H), 4.71 (q, *J* = 5.2 Hz, 1 H), 2.78 (d, *J* = 5.6 Hz, 2 H), 2.20 (s, 3 H), 0.01 (s, 9 H); CIMS *m/z* 288 (*M* + *H*)⁺; IR 3396, 2961, 2174, 1722, 1644, 1481, 1250 cm⁻¹. Anal. calcd for C₁₆H₂₁NO₂Si: C, 66.86; H, 7.36; N, 4.87. Found: C, 67.15; H, 7.49; N, 4.72.

20 Benzamidoacetone (115).



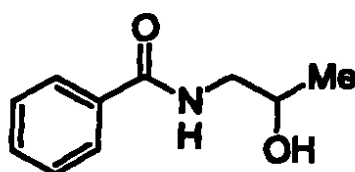
115

According to the procedure of Ellinger (Ellinger, L. P.; Goldberg, A. A. *J. Chem. Soc.* 1949, 263). *N*-(2-Hydroxypropyl)benzamide (123) (3.0 g, 16.7 mmol) was dissolved in CH₂Cl₂ (60 mL) and PDC (9.42 g, 25.0 mmol) was added. The mixture was stirred at room temperature for 24 and more PDC (9.42 g, 25.0

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mmol) was added. Stirring was continued for 24 hours. The mixture was diluted with ethyl acetate and filtered through a celite pad. The residue was then passed through a shoroom temperature silica gel column eluting with ethyl acetate. The solvent was removed and the residue was purified by flash chromatography on silica gel eluting with hexanes:ethyl acetate (1:1) containing MeOH (0 to 4%). This purification afforded amide 122 as a white solid (2.21 g, 75%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.76 (dd, $J = 7.0$ and 1.5 Hz, 2 H), 7.48-7.36 (m, 3 H), 6.96 (bs, 1 H), 4.30 (d, $J = 4.6$ Hz, 2 H), 2.21 (s, 3 H); CIMS m/z 178 ($\text{M} + \text{H}$) $^+$.

N-(2-Hydroxypropyl)benzamide (114).

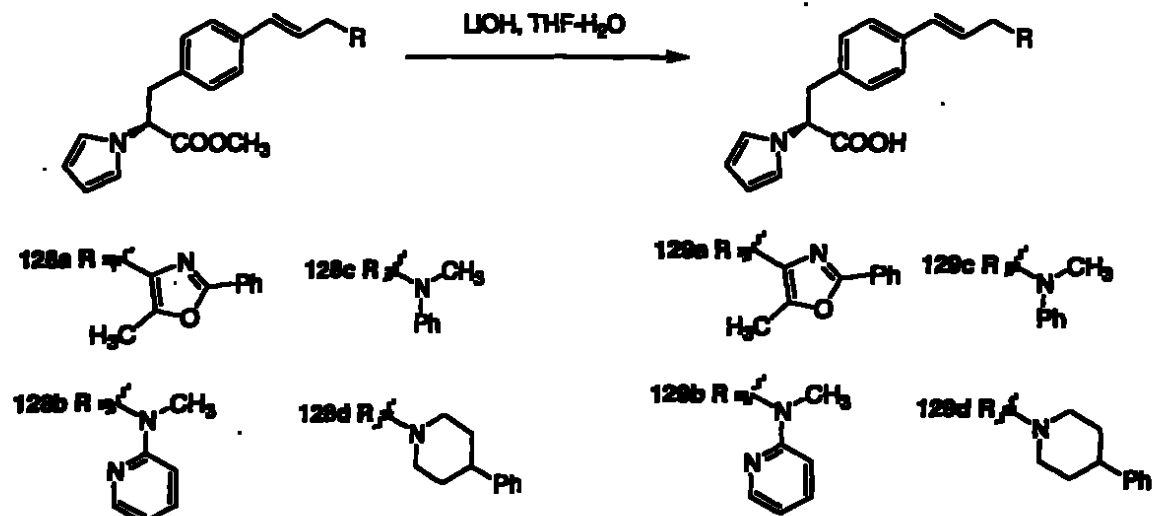


114

According to the procedure of Arai (Arai, K.; Tamura, S.; Masumizu, T.; Kawai, K.-I.; Nakajima, S.; Ueda, A. *Can. J. Chem.* 1990, 68, 903-907). A solution of DL-1-amino-2-propanol (3.4 mL, 43.2 mmol) and triethylamine (16.4 mL, 117.9 mmol) in CH_2Cl_2 (60 mL) under nitrogen was cooled at -78°C . Benzoyl chloride (4.6 mL, 39.3 mmol) was added dropwise. The mixture was allowed to warm slowly and stirred at room temperature overnight. It was then diluted with CH_2Cl_2 (100 mL) and washed with cold 5% HCl and brine. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried over MgSO_4 , filtered, and the solvent removed. The residue was dried under vacuum to give amide 5 as a pale yellow solid (6.21 g, 88%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.75 (d, $J = 6.8$ Hz, 2 H), 7.49-7.39 (m, 3 H), 6.57 (bs, 1 H), 4.00 (m, 1 H), 3.67-3.61 (m, 1 H), 3.31-3.24 (m, 1 H), 1.22 (d, $J = 6.3$ Hz, 3 H).

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Example 50*General procedure for the preparation of analogs 129a-d.*

- 5 (S)-3-(4-[(E)-3-(5-Methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl)-2-pyrrol-1-yl-propionic acid (129a). Prepared from ester 128a (0.140 g, 0.328 mmol) following the general procedure. Purification by chromatography on silica gel eluting with hexanes:ethyl acetate (2:1) containing formic acid (0-0.2%) gave acid 129a as an off-white solid (0.085 g, 63%): Mp 132°C-133°C; ¹H NMR (CDCl₃, 400 MHz) δ 7.95-7.92 (m, 2 H), 7.41-7.39 (m, 3 H), 7.19 (d, J = 8.0 Hz, 2 H), 6.90 (d, J = 8.4 Hz, 2 H), 6.65 (t, J = 2.0 Hz, 2 H), 6.37 (d, J = 15.6 Hz, 1 H), 6.25 (dt, J = 16.0 and 6.4 Hz, 1 H), 6.13 (t, J = 2.0 Hz, 2 H), 4.57 (dd, J = 8.8 and 6.0 Hz, 1 H), 3.39 (d, J = 6.8 Hz, 2 H), 3.38-3.15 (m, 2 H), 2.33 (s, 3 H); CIMS m/z 413 (M + H)⁺. Anal. calcd for C₂₆H₂₄N₂O₃·0.1 H₂O: C, 75.38; H, 5.89; N, 6.76. Found: C, 75.58; H, 6.21; N, 6.37.

- 20 (S)-3-(4-[(E)-3-(Methyl-pyridin-2-yl-amino)-propenyl]-phenyl)-2-pyrrol-1-yl-propionic acid (129b). Prepared from ester 128b (0.481 g, 1.281 mmol) following the general procedure described above. Purification by chromatography on silica gel eluting with 0-15% MeOH in CHCl₃ followed by THF gave pure 129b (0.123 g, 26%): Mp 155°C-165°C; ¹H NMR (CD₃OD, 400 MHz) δ 7.98 (dd, J = 5.2 and 1.0 Hz, 1 H), 7.52-7.47 (m, 1 H), 7.13 (d, J = 8.4 Hz, 2 H), 6.91 (d, J = 8.4 Hz, 2 H), 6.66 (t, J = 2.0 Hz, 2 H), 6.56 (dd, J = 6.4 and 5.2 Hz, 1 H), 6.38 (d,

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$J = 15.6$ Hz, 1 H), 6.14 (dt, $J = 16.0$ and 5.6 Hz, 1 H), 5.92 (t, $J = 2.0$ Hz, 2 H), 4.58 (dd, $J = 9.6$ and 5.6 Hz, 1 H), 4.22 (dd, $J = 5.6$ and 1.2 Hz, 2 H), 3.34-3.08 (m, 2 H), 3.02 (s, 3 H); CIMS m/z 362 ($M + H$)⁺.

5 (S)-3-{4-[(E)-3-(Methyl-phenyl-amino)-propenyl]-phenyl}-2-pyrrol-1-yl-propionic acid (129c). Ester 128c (0.877 g, 2.342 mmol) was dissolved in THF:H₂O (40:10 mL) and LiOH·H₂O (0.147 g, 3.513 mmol) was added and the mixture was stirred at room temperature for 3.5 hours. The solvent was removed and the residue was diluted with water, acidified with 10% HCl. The mixture was
10 extracted with CHCl₃ (3 × 50 mL). The combined organic extracts were dried over MgSO₄, filtered and the solvent removed. Purification by chromatography on silica gel eluting with 0-3% MeOH in CHCl₃ containing 0.1% formic acid gave pure 138c as brownish solid (0.280 g, 33%); mp 85°C-90°C; ¹H NMR (CDCl₃, 400 MHz) δ *E*-isomer: 7.26-7.18 (m, 3 H), 6.92 (d, $J = 8.4$ Hz, 2 H), 6.81-6.69 (m, 4 H), 6.68 (t, $J = 2$ Hz, 2 H), 2 H), 6.44 (d, $J = 15.6$ Hz, 1 H), 6.14 (t, $J = 2.0$ Hz, 2 H), 4.73 (dd, $J = 9.2$ and 6.0 Hz, 1 H), 4.03 (dd, $J = 5.6$ and 1.2 Hz, 2 H), 3.48-3.24 (m, 2 H), 2.97 (s, 3 H); CIMS m/z 361 ($M + H$)⁺. Anal. calcd for C₂₃H₂₄N₂O₂·0.9 H₂O: C, 74.41; H, 6.84; N, 7.55. Found: C, 74.03; H, 6.62; N, 7.36.

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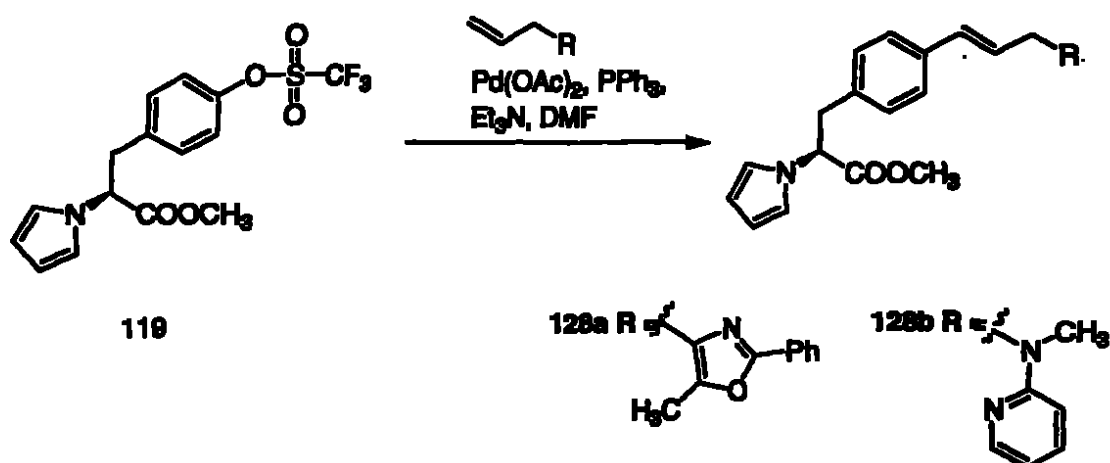
(S)-3-{4-[(E)-3-(4-Phenyl-piperidin-1-yl)-propenyl]-phenyl}-2-pyrrol-1-yl-propionic acid (129d). Prepared from ester 128d (1.772 g, 4.135 mmol) following the general procedure. Purification by chromatography on silica gel eluting with 0-12% MeOH in CHCl₃ containing formic acid (0%-0.1%) gave acid
25 138d as a pale yellow foam (1.38 g, 80%); Mp 126°C-130°C; ¹H NMR (CDCl₃, 400 MHz) δ 7.30-7.18 (m, 5 H), 7.17 (d, $J = 7.1$ Hz, 2 H), 6.95 (d, $J = 8.1$ Hz, 2 H), 6.57 (d, $J = 16.0$ Hz, 1 H), 6.55 (t, $J = 2.0$ Hz, 2 H), 6.26 (dt, $J = 15.6$ and 7.3 Hz, 1 H), 6.02 (t, $J = 2.0$ Hz, 2 H), 4.56 (dd, $J = 8.8$ and 6.1 Hz, 1 H), 3.69-3.49 (m, 4 H), 3.42-3.12 (m, 2 H), 2.70-2.62 (m, 3 H), 2.33-2.26 (m, 2 H), 1.91 (m, 2
30 H); CIMS m/z 415 ($M + H$)⁺. Anal. calcd for C₂₇H₃₀N₂O₂·1.0CH₂O₂: C, 73.02; H, 7.00; N, 6.08. Found: C, 72.85; H, 7.05; N, 6.06.

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The ester starting materials were prepared in the following manner.

Esters 128a-b.



5

(S)-3-(4-[(E)-3-(5-Methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (128a). A mixture of triflate 119

(Example 49) (1.5 g, 3.975 mmol), 5-methyl-2-phenyl-4-prop-2-enyloxazole 135 (1.19 g, 5.962 mmol), Pd(OAc)₂ (0.045 g, 0.199 mmol), PPh₃ (0.114 g, 0.437

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mmol), triethylamine (1.10 mL, 7.95 mmol) was dissolved in DMF (15 mL). Nitrogen was passed through the mixture for 20-25 min. The reaction mixture was heated at 90°C under nitrogen for 44 hours. The mixture was allowed to cool and filtered through a celite pad, washing with ethyl ether. Water was added and the phases were separated. The aqueous phase was extracted with ethyl ether (4 × 60

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mL). The combined organic extracts were washed with water, brine, dried over MgSO₄, filtered and the solvent removed. Purification by chromatography on silica gel eluting with 20%-25% ethyl acetate in hexanes afforded 137a as a thick oil (0.668, 39%): ¹H NMR (CDCl₃, 400 MHz) δ 8.00-7.97 (m, 2 H), 7.44-7.39 (m, 3 H), 7.22 (d, J = 8.0 Hz, 2 H), 6.91 (d, J = 8.0 Hz, 2 H), 6.69 (t, J = 2.0 Hz, 2 H), 6.42 (d, J = 14.8 Hz, 1 H), 6.32 (dt, J = 15.6 and 6.4 Hz, 1 H), 6.13 (t, J = 2.0 Hz, 2 H), 4.71 (dd, J = 8.8 and 6.4 Hz, 1 H), 3.68 (s, 3 H), 3.42 (d, J = 6.4 Hz, 2 H), 3.39-3.18 (m, 2 H), 2.34 (s, 3 H); CIMS m/z 427 (M + H)⁺.

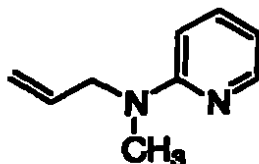
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(S)-3-[4-[(E)-3-(Methyl-pyridin-2-yl-amino)-propenyl]-phenyl]-2-pyrrol-
1-yl-propionic acid methyl ester (128b). This compound was prepared from
triflate 119 (1.0 g, 5.30 mmol) and 2-(N-methyl-N-prop-2-enyl)pyridine 136
(0.785 g, 5.300 mmol) following the procedure described for 137a. Additional
5 Pd(OAc)₂ (5 mol%) was added after 16 hr. The reaction was completed after 24
hours. Purification by chromatography eluting with 20%-25% ethyl acetate in
hexanes gave 137b as a thick oil (0.600, 60%): ¹H NMR (CDCl₃, 400 MHz) δ
8.18-8.16 (m, 1 H), 7.47-7.42 (m, 1 H), 7.21 (d, J = 8.4 Hz, 2 H), 6.92 (d, J = 8.0
Hz, 2 H), 6.69 (t, J = 2.0 Hz, 2 H), 6.67-6.51 (m, 2 H), 6.42 (d, J = 15.6 Hz, 1 H),
10 6.18 (dt, J = 16.0 and 5.6 Hz, 1 H), 6.13 (t, J = 2.0 Hz, 2 H), 4.71 (dd, J = 8.6 and
6.0 Hz, 1 H), 4.30 (dd, J = 5.6 and 1.2 Hz, 2 H), 3.66 (s, 3 H), 3.39-3.19 (m, 2 H),
3.05 (s, 3 H); CIMS m/z 376 (M + H)⁺.

2-(N-Methyl-N-prop-2-enyl)pyridine (127).



127

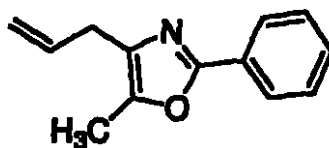
Sodium hydride (0.82 g, 20.4 mmol) was suspended in DMF (10 mL)
under nitrogen and stirred in an ice bath. 2-(Methylamino)pyridine (1.5 mL, 14.6
20 mmol) was added. The ice bath was removed and the mixture stirred at room
temperature for 0.5 hr. The mixture was cooled back in an ice bath and allyl
bromide (1.9 mL, 21.9 mmol) was added. The mixture was allowed to reach room
temperature and stirred overnight. The mixture was diluted with water and
extracted with Et₂O. The combined organic extracts were washed with water and
25 brine, dried over MgSO₄, filtered, and the solvent removed. Purification by flash
chromatography on silica gel eluting with hexanes:ethyl acetate (20:1) afforded
127 as an oil (1.74 g, 80%): ¹H NMR (CDCl₃, 400 MHz) δ 8.15 (m, 1 H), 7.42 (m,
1 H), 6.53 (dd, J = 6.8 and 4.8 Hz, 1 H), 6.48 (d, J = 8.4 Hz, 1 H), 5.89-5.79 (m, 1

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H), 5.14 (m, 1 H), 4.14 (d, $J = 5.1$ Hz, 2 H), 3.03 (s, 3 H); CIMS m/z 149 ($M + H$)⁺.

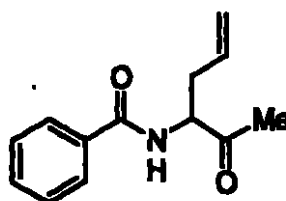
5-Methyl-2-phenyl-4-prop-2-enyloxazole (126).



126

Amide 125 (2.00 g, 9.205 mmol) was dissolved in TFA (16 mL) and TFAA (8 mL) was added. The mixture was heated at 35°C–40°C for 16 hours. The mixture was allowed to cool and the solvents removed under reduced pressure. The residue was diluted with saturated NaHCO₃ (50 mL) and solid NaHCO₃ was added to neutralize the mixture. It then was extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and the solvent removed. Purification by flash chromatography on silica gel eluting with hexanes:ethyl acetate (15:1) gave 135 (1.751 g, 95.5%): ¹H NMR (CDCl₃, 400 MHz) δ 7.98 (d, $J = 7.8$ Hz, 2 H), 7.43–7.35 (m, 3 H), 6.03–5.93 (m, 1 H), 5.13 (dq, $J = 16.9$ and 1.7 Hz, 1 H), 5.09 (dq, $J = 10.0$ and 1.5 Hz, 1 H), 3.29 (d, $J = 6.3$ Hz, 2 H), 2.32 (s, 3 H); CIMS m/z 200 ($M + H$)⁺; IR 3070, 2924, 1638, 1450 cm⁻¹.

N-(1-Acetylbut-3-enyl)benzamide (125).



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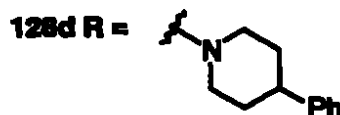
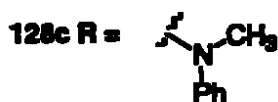
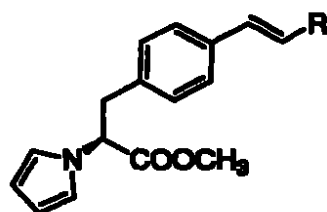
Benzamidoacetone (See Example 49) (2.098 g, 11.839 mmol) was dissolved in THF (120 mL) and cooled to -78°C under nitrogen. A 1.0 M solution of LHMDS in THF (11.9 mL, 11.9 mmol) was added and the mixture stirred for

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40 minutes. A solution of allyl bromide (1.33 mL, 15.39 mmol) in THF (10 mL) was added. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with brine and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were dried over MgSO₄, filtered, and the solvent removed. Purification by flash chromatography on silica gel eluting with hexanes:ethyl acetate (2:1 to 1:1) gave amide 9 (2.019 g, 78.5%): ¹H NMR (CDCl₃, 400 MHz) δ 7.79 (d, *J* = 7.1 Hz, 2 H), 7.51-7.41 (m, 3 H), 6.95 (bd, *J* = 5.4 Hz, 1 H), 5.74-5.64 (m, 1 H), 5.17-5.12 (m, 2 H), 4.88 (dt, *J* = 6.8 and 5.4 Hz, 1 H), 2.85-2.78 (m, 1 H), 2.61-2.54 (m, 1 H), 2.28 (s, 3 H); CIMS *m/z* 218 (*M* + H)⁺; IR 3263, 3081, 1719, 1632, 1556 cm⁻¹. Anal. calcd for C₁₃H₁₃NO₂: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.91; H, 7.03; N, 6.52.

(a-2) Esters 128c-d were prepared in the following manner.



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(*S*)-3-{4-[(*E*)-3-(Methyl-phenyl-amino)-propenyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (128c). Triflate 127 (0.98 g, 2.592 mmol), boronate ester 124 (0.850 g, 3.111 mmol), K₂CO₃ (0.716 g, 5.184 mmol) were stirred in dry toluene (25 mL). Nitrogen was passed through the mixture for 0.5 hr. Pd(PPh₃)₄ (0.149 g, 0.129 mmol) was added and the reaction mixture was heated at 85°C-90°C for 24 hours. The mixture was allowed to cool, diluted with ethyl acetate (70 mL) and washed with sat NaHCO₃, water and brine. The organic extracts were dried over MgSO₄, filtered and the solvent removed. Purification by flash chromatography on silica gel eluting with 50-0% petroleum ether in

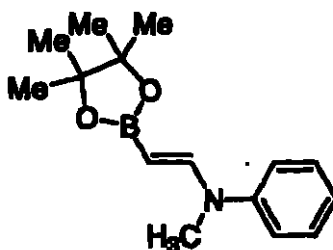
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dichloromethane followed by a second chromatographic purification eluting with hexanes:ethyl acetate (8:1 to 5:1) gave ester 137c as a 94:6 *E:Z* mixture of isomers (0.819 g, 84%). *E*-isomer: ^1H NMR (CDCl_3 , 400 MHz) δ 7.23-7.20 (m, 2 H), 7.21 (d, $J = 8.0$ Hz, 2 H), 6.92 (d, $J = 8.0$ Hz, 2 H), 6.77-6.70 (m, 3 H), 6.69 (t, $J = 2.0$ Hz, 2 H), 6.44 (d, $J = 16.0$ Hz, 1 H), 6.19 (dt, $J = 15.6$ and 5.6 Hz, 1 H), 6.13 (t, $J = 2.0$ Hz, 2 H), 4.71 (dd, $J = 9.2$ and 6.4 Hz, 1 H), 4.05 (dd, $J = 5.6$ and 1.2 Hz, 2 H), 3.69 (s, 3 H), 3.40-3.19 (m, 2 H), 2.95 (s, 3 H); CIMS m/z 375 ($M + \text{H}$) $^+$.

(*S*)-3-[4-[(*E*)-3-(4-Phenyl-piperidin-1-yl)-propenyl]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (128d). This compound was prepared from triflate 127 (2.0 g, 5.296 mmol), and boronate ester 124 (2.6 g, 7.944 mmol) following the procedure described for 128c. Purification by flash chromatography eluting with 33-45% ethyl acetate in hexanes containing 1% Et_3N gave 128d (*E*-isomer, 1.801 g, 79%) and *E:Z* mixture (0.217 g, 9.9%) as oils. *E*-isomer: ^1H NMR (CDCl_3 , 400 MHz) δ 7.50-7.15 (m, 7 H), 6.95 (d, $J = 8.4$ Hz, 2 H), 6.69 (t, $J = 2.0$ Hz, 2 H), 6.45 (d, $J = 16.0$ Hz, 1 H), 6.27 (dt, $J = 15.6$ and 6.8 Hz, 1 H), 6.13 (t, $J = 2.0$ Hz, 2 H), 4.71 (dd, $J = 8.8$ and 6.4 Hz, 1 H), 3.68 (s, 3 H), 3.40-3.19 (m, 2 H), 3.16 (d, $J = 6.8$ Hz, 2 H), 3.08 (d, $J = 11.6$ Hz, 2 H), 2.51-2.46 (m, 1 H), 2.07 (t, $J = 11.2$ Hz, 1 H), 2.06 (t, $J = 11.2$ Hz, 1 H), 1.84-1.77 (m, 4 H); CIMS m/z 429 ($M + \text{H}$) $^+$.

Methyl-phenyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-vinyl]-amine (124).



124

A mixture of *N*-methyl-*N*-prop-2-ynyl aniline (1.0 mL, 6.873 mmol) and pinacolborane (1.2 mL, 8.247 mmol) in CH_2Cl_2 (5 mL) was added to Cp_2ZrHCl

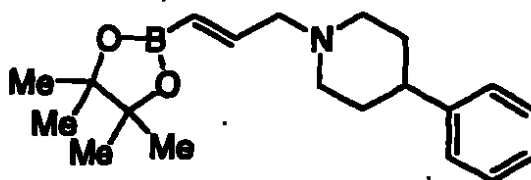
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-179-

(0.088 g, 0.343 mmol), at 0°C. The mixture was allowed to warm at room temperature and stirred for 8 days under nitrogen. At this time, the mixture was diluted with Et₂O (50 mL) and washed with water (30 mL). The phases were separated and the aqueous phase was extracted with Et₂O (2 × 30 mL). The combined organic extracts were dried over MgSO₄, filtered and the solvent removed. Purification by chromatography on silica gel eluting with hexanes: ethyl acetate (20:1 to 10:1) afforded 124 as an off-white solid (0.99 g, 53%): ¹H NMR (CDCl₃, 400 MHz) δ 7.21-7.17 (m, 2 H), 6.69-6.64 (m, 3 H), 6.60 (dt, *J* = 18.0 and 4.4 Hz, 1 H), 5.55 (dt, *J* = 18.0 and 1.6 Hz, 1 H), 3.99 (dd, *J* = 4.4 and 1.6 Hz, 2 H), 2.94 (s, 3 H), 1.25 (s, 12 H); CIMS *m/z* 274 (M + H)⁺.

(*S*)-3-[4-[(*E*)-3-(Methyl-phenyl-amino)-propenyl]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (123). This compound was prepared from triflate 119 (2.0 g, 5.296 mmol), and boronate ester 124 (2.6 g, 7.944 mmol) following the procedure described for 137c. Purification by flash chromatography eluting with 33-45% ethyl acetate in hexanes containing 1% Et₃N gave 123 (*E*-isomer, 1.801 g, 79%) and *E:Z* mixture (0.217 g, 9.9%) as oils. *E*-Isomer: ¹H NMR (CDCl₃, 400 MHz) δ 7.50-7.15 (m, 7 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 6.69 (t, *J* = 2.0 Hz, 2 H), 6.45 (d, *J* = 16.0 Hz, 1 H), 6.27 (dt, *J* = 15.6 and 6.8 Hz, 1 H), 6.13 (t, *J* = 2.0 Hz, 2 H), 4.71 (dd, *J* = 8.8 and 6.4 Hz, 1 H), 3.68 (s, 3 H), 3.40-3.19 (m, 2 H), 3.16 (d, *J* = 6.8 Hz, 2 H), 3.08 (d, *J* = 11.6 Hz, 2 H), 2.51-2.46 (m, 1 H), 2.07 (t, *J* = 11.2 Hz, 1 H), 2.06 (t, *J* = 11.2 Hz, 1 H), 1.84-1.77 (m, 4 H); CIMS *m/z* 429 (M + H)⁺.

4-Phenyl-1-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-vinyl]-piperidine (130).

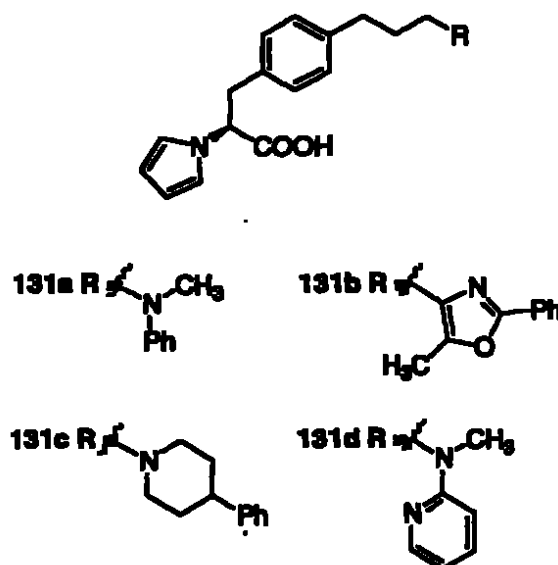


122

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-180-

A mixture of *N*-prop-2-ynyl-4-phenylpiperidine (1.5 g, 7.526 mmol) and pinacolborane (1.64 mL, 11.289 mmol) in CH_2Cl_2 (8 mL) was added to Cp_2ZrHCl (0.194 g, 0.753 mmol) at 0°C . The mixture was allowed to warm at room temperature and stirred for 48 hours under nitrogen. At this time, the mixture was diluted with Et_2O (50 mL) and water (30 mL) was added carefully. The phases were separated and the organic extracts were dried over MgSO_4 , filtered and the solvent removed to give 18 as a solid (2.46 g, 100%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.29-7.18 (m, 5 H), 6.68 (dt, $J = 17.6$ and 6.0 Hz, 1 H), 5.62 (dt, $J = 18.0$ and 1.6 Hz, 1 H), 3.11 (dd, $J = 6.4$ and 1.6 Hz, 2 H), 3.04 (d, $J = 12.0$ Hz, 2 H), 2.51-2.44 (m, 1 H), 2.10-2.03 (m, 2 H), 1.84-1.79 (m, 4 H), 1.26 (s, 12 H); CIMS m/z 328 ($\text{M} + \text{H}$) $^+$.

Example 51**General procedure for the preparation of analogs 131a-d.**

(*S*)-3-[4-[3-(Methyl-phenyl-amino)-propyl]-phenyl]-2-pyrrol-1-yl-propionic acid (131a). Ester 130a (0.223 g, 0.592 mmol) was dissolved in $\text{THF}:\text{H}_2\text{O}$ (10:4 mL) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.037 g, 0.888 mmol) was added and the mixture was stirred at room temperature for 3.5 hours. The solvent was removed and the residue was diluted with water, acidified with 10% HCl . The mixture was

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-181-

extracted with CHCl_3 ($3 \times 50 \text{ mL}$). The combined organic extracts were dried over MgSO_4 , filtered and the solvent removed. Purification by chromatography on silica gel eluting with 0-5% MeOH in CHCl_3 containing formic acid (0-0.1%) gave pure 140a as pale brown solid (0.190 g, 88%): $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.33 (m, 2 H), 7.12-7.06 (m, 3 H), 6.95 (d, $J = 8.3 \text{ Hz}$, 2 H), 6.91 (d, $J = 8.3 \text{ Hz}$, 2 H), 6.69 (t, $J = 2.0 \text{ Hz}$, 2 H), 6.10 (t, $J = 2.0 \text{ Hz}$, 2 H), 4.73 (dd, $J = 9.1$ and 6.3 Hz , 1 H), 3.42-3.18 (m, 4 H), 2.52 (t, $J = 7.3 \text{ Hz}$, 2 H), 1.88-1.81 (m, 2 H). Anal. calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2 \cdot 0.1 \text{ H}_2\text{O}$: C, 75.84; H, 7.25; N, 7.69. Found: C, 75.73; H, 7.40; N, 7.50.

10

(*S*)-3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-pyrrol-1-yl-propionic acid (131b). Prepared from ester 130b (0.243 g, 0.567 mmol) following the general procedure. Purification by flash chromatography eluting with 33-50% ethyl acetate in hexanes containing formic acid (0-0.2%) gave pure 140b as a light yellow solid (0.206 g, 88%): mp 167°C - 168°C ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.94 (m, 2 H), 7.40 (m, 3 H), 7.04 (d, $J = 7.8 \text{ Hz}$, 2 H), 6.93 (d, $J = 7.8 \text{ Hz}$, 2 H), 6.71 (bs, 2 H), 6.14 (bs, 2 H), 4.72 (m, 1 H), 3.39-3.16 (m, 2 H), 2.58 (t, $J = 7.3 \text{ Hz}$, 2 H), 2.47 (t, $J = 7.3 \text{ Hz}$, 2 H), 2.26 (s, 3 H), 1.92 (qn, $J = 7.3 \text{ Hz}$, 2 H); CIMS m/z 415 ($\text{M} + \text{H}$) $^+$.

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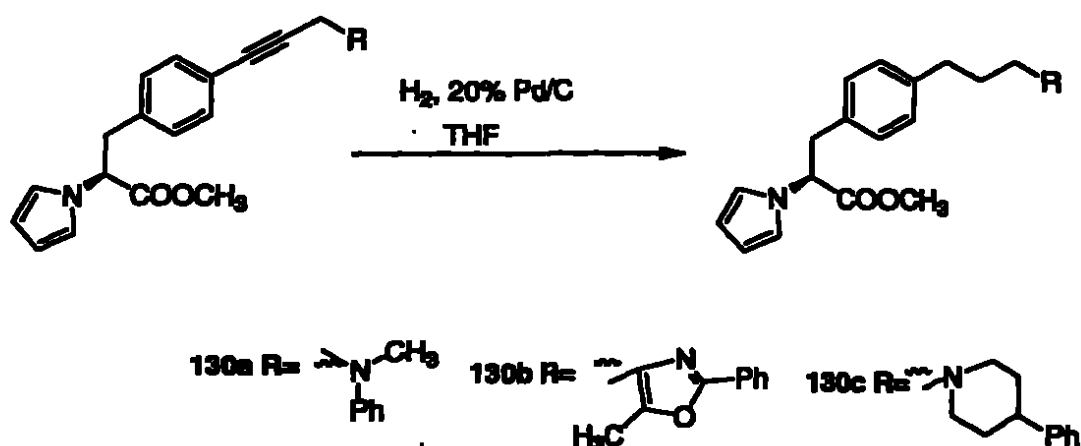
(*S*)-3-[4-[3-(4-Phenyl-piperidin-1-yl)-propyl]-phenyl]-2-pyrrol-1-yl-propionic acid (131c). Prepared from ester 131c (0.248 g, 0.576 mmol) by the general procedure described above. Purification by chromatography on silica gel eluting with 0-9% MeOH in CHCl_3 containing formic acid (0-0.1%) gave pure 139c as a white foam (0.137 g, 57%): mp 95°C - 100°C ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.29-7.16 (m, 3 H), 7.14 (d, $J = 8.3 \text{ Hz}$, 2 H), 6.98 (d, $J = 8.3 \text{ Hz}$, 2 H), 6.95 (d, $J = 8.0 \text{ Hz}$, 2 H), 6.67 (t, $J = 2.0 \text{ Hz}$, 2 H), 6.04 (t, $J = 2.0 \text{ Hz}$, 2 H), 4.64 (t, $J = 7.5 \text{ Hz}$, 1 H), 3.50 (m, 1 H), 3.45 (m, 1 H), 3.41-3.09 (m, 2 H), 2.82-2.78 (m, 2 H), 2.57-2.33 (m, 4 H), 2.21 (m, 2 H), 2.03-1.99 (m, 2 H), 1.84 (m, 2 H); CIMS m/z 417 ($\text{M} + \text{H}$) $^+$. Anal. calcd for $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_2 \cdot 1.0 \text{ H}_2\text{O}$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.23; H, 7.63; N, 6.25.

30

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(*S*)-3-[4-[3-(Methyl-pyridin-2-yl-amino)-propyl]-phenyl]-2-pyrrol-1-yl-propionic acid (131d). Prepared from ester 131d (0.378 g, 1.001 mmol) by the general procedure. Purification by flash chromatography eluting with 0-15% MeOH in CHCl₃ gave 142d as a white solid (0.280 g, 77%): mp 66°C-68°C; ¹H NMR (CD₃OD, 400 MHz) δ 7.90-7.85 (m, 1 H), 7.82 (d, *J* = 6.0 Hz, 1 H), 7.01 (t, *J* = 8.0 Hz, 3 H), 6.94 (d, *J* = 8.0 Hz, 2 H), 6.87 (t, *J* = 6.8 Hz, 1 H), 6.66 (t, *J* = 2.0 Hz, 2 H), 5.96 (t, *J* = 2.0 Hz, 2 H), 4.80 (dd, *J* = 10.0 and 5.6 Hz, 1 H), 3.55 (t, *J* = 7.6 Hz, 2 H); 3.37-3.15 (m, 2 H), 3.12 (s, 3 H), 2.62 (t, *J* = 7.6 Hz, 2 H), 1.94 (qn, *J* = 7.2 Hz, 2 H); CIMS *m/z* 364 (*M* + H)⁺. Anal. calcd for C₂₂H₂₅N₃O₂·0.3 CHCl₃: C, 67.08; N, 6.39; N, 10.52. Found: C, 67.30; H, 6.39; N, 10.21.

(a) The esters 130a-c were prepared in the following manner.



15

(*S*)-3-[4-[3-(Methyl-phenyl-amino)-propyl]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (130a). Alkyne 120a (0.648 g, 1.739 mmol) was dissolved in MeOH (50 mL) and 20% Pd/C (0.050 g) was added. The mixture was hydrogenated at room temperature for 18 hr. The mixture was filtered through celite and the solvent removed. Purification by flash chromatography eluting with hexanes:ethyl acetate (6:1) gave 130a as an oil (0.439 g, 67%): ¹H NMR (CDCl₃, 400 MHz) δ 7.20 (t, *J* = 8.0 Hz, 2 H), 7.05 (d, *J* = 7.6 Hz, 2 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 6.71 (t, *J* = 2.0 Hz, 2 H), 6.65 (t, *J* = 7.8 Hz, 3 H), 6.14 (t, *J* = 2.0 Hz, 2 H), 4.73 (dd, *J* = 8.8 and 6.4 Hz, 1 H), 3.69 (s, 3 H), 3.41-3.20 (m, 2 H), 3.30 (t, *J*

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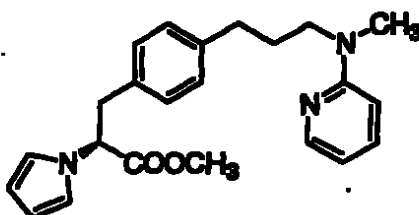
= 7.4 Hz, 2 H), 2.90 (s, 3 H), 2.59 (t, $J = 7.6$ Hz, 2 H), 1.86 (qn, $J = 7.6$ Hz, 2 H); CIMS m/z 377 ($M + H$)⁺.

5 (S)-3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (130b). This compound was prepared from alkyne 120b (0.249 g, 0.586 mmol) following the general procedure described for 130a with the exception that the reaction was carried out in THF. The crude product was used for subsequent transformations. Ester 130b was obtained as an oil (0.243, 96.8%): ¹H NMR (CDCl₃, 400 MHz) δ 7.91 (dd, $J = 8.0$ and 1.6 Hz, 2 H), 7.37-7.32 (m, 3 H), 6.99 (d, $J = 8.4$ Hz, 2 H), 6.85 (d, $J = 8.0$ Hz, 2 H), 6.64 (t, $J = 2.0$ Hz, 2 H), 6.07 (t, $J = 2.0$ Hz, 2 H), 4.65 (dd, $J = 8.8$ and 6.8 Hz, 1 H), 3.62 (s, 3 H), 3.33-3.11 (m, 2 H), 2.54 (t, $J = 7.6$ Hz, 2 H), 2.41 (t, $J = 7.6$ Hz, 2 H), 2.19 (s, 3 H), 1.89 (qn, $J = 7.6$ Hz, 2 H); CIMS m/z 429 ($M + H$)⁺.

15 (S)-3-{4-[3-(4-Phenyl-piperidin-1-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (130c). This compound was prepared from alkyne 120c (0.408 g, 0.956 mmol) following the procedure described for 130a. The reaction was carried out in THF. Purification was achieved by chromatography eluting with 33-45% ethyl acetate in hexanes containing 1.0% Et₃N to give 130c as an oil (0.262 g, 64%): ¹H NMR (CDCl₃, 400 MHz) δ 7.24-7.10 (m, 5 H), 7.00 (d, $J = 8.0$ Hz, 2 H), 6.85 (d, $J = 8.0$ Hz, 2 H), 6.65 (t, $J = 2.0$ Hz, 2 H), 6.08 (t, $J = 2.0$ Hz, 2 H), 4.66 (dd, $J = 8.8$ and 6.4 Hz, 1 H), 3.62 (s, 3 H), 3.34-3.12 (m, 2 H), 2.98 (d, $J = 11.6$ Hz, 2 H), 2.52 (t, $J = 7.6$ Hz, 2 H), 2.42 (m, 1 H), 2.31 (t, $J = 7.6$ Hz, 2 H), 1.99-1.93 (m, 2 H), 1.80-1.72 (m, 6 H); CIMS m/z 431 ($M + H$)⁺.

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(S)-3-{4-[3-(Methyl-pyridin-2-yl-amino)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (130d).



130d

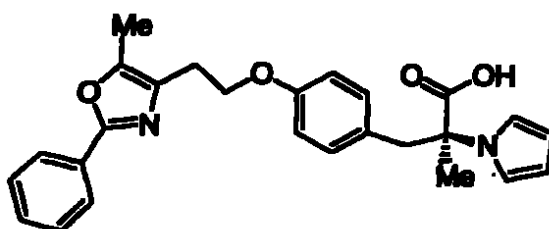
201

-184-

Alkene 128b (0.430 g, 1.145 mmol) was dissolved in THF (16 mL). 5% Pd/C (0.050 g) was added and the mixture was hydrogenated at room temperature for 24 hours. Additional catalyst (0.050 g) was added and the reaction was continued for another 24 hours. The catalyst was filtered off and the solvent removed to give ester 130d as a thick oil (0.378 g, 87%): ¹H NMR (CDCl₃, 400 MHz) δ 8.08-8.06 (m, 1 H), 7.36-7.31 (m, 1 H), 6.99 (d, *J* = 8.0 Hz, 2 H), 6.85 (d, *J* = 8.0 Hz, 2 H), 6.64 (t, *J* = 2.0 Hz, 2 H), 6.43 (dd, *J* = 6.4 and 5.4 Hz, 1 H), 6.33 (d, *J* = 8.8 Hz, 6.07 (t, *J* = 2.0 Hz, 2 H), 6.65 (dd, *J* = 8.8 and 6.8 Hz, 1 H), 3.62 (s, 3 H), 3.45 (t, *J* = 7.4 Hz, 2 H), 3.33-3.12 (m, 2 H), 2.94 (s, 3 H), 2.53 (t, *J* = 7.6 Hz, 2 H), 1.81 (qn, *J* = 7.6 Hz, 2 H); CIMS *m/z* 378 (M + H)⁺.

Example 52

(S)-2-Methyl-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (134).



134

To a stirred solution of (S)-2-Methyl-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (3.33 g, 7.5mmol) in 2-methoxyethanol (20 mL) and water (5 mL) was added Lithium Hydroxide (180 mg, 7.5 mmol) The reaction was stirred at room temperature overnight. The reaction mixture was poured into water and acidified with dilute Hydrochloric acid. The reaction was extracted with ethyl acetate and the organic layer dried (MgSO₄) and purified by chromatography. Recrystallisation from ethyl acetate and hexane gave the product as white crystals. Yield = 1.3g, 40% Mp 149.5°C-150.5°C. 500 MHz ¹H NMR (CDCl₃) δ 7.94 (m, 2H), 7.41 (m, 3H), 6.76 (m, 2H), 6.70 (d, *J* = 9 Hz) 6.65 (d, *J* = 9 Hz) 6.18 (m, 2H) 4.15 (t, 2H, *J* = 6.8 Hz),

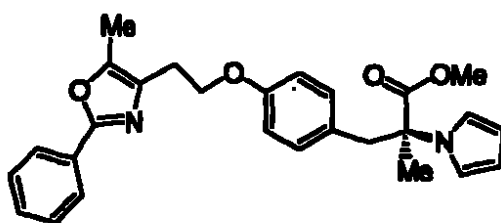
202

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3.36 (d, 1H, $J=13.9$) 3.29 (d, 1H $J=13.9$) 2.96 (t, 2H $J=6.8\text{Hz}$) , 2.36 (s, 3H), 1.62 (s, 3H); MS m/z 431 (M+1), 429 (M-1) Anal. Calc'd for $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_4$ C, 72.54; H 6.09; N 6.51 found: C, 72.17; H, 6.15; N 6.50

5 (S)-2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester was prepared in the following manner.

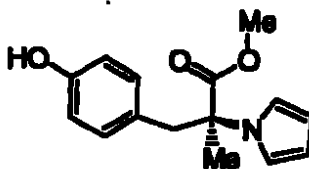
(a) (S)-2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (133).



133

10 To a stirred solution of of (S)-3-(4-Hydroxy-phenyl)-2-methyl-2-pyrrol-1-yl-propionic acid methyl ester described in example 1 (2.44g, 9.4mmol) in
15 anhydrous THF (25mL) was added triphenyl phosphine (2.47g, 9.4mmol) and 2-(5-methyl-2-phenyloxazol-4-yl) ethanol (1.911g, 9.4mmol). A solution of DIAD (1.85mL, 9.4mmol) in anhydrous THF (10mL) was added dropwise and the
20 reaction mixture stirred at room temperature for 48hr. The solvent was then removed under reduced pressure to give a yellow oil. The reaction mixture was purified by chromatography eluting with 1:10 to 1:1 EtOAc: Hexane. To give the
desired ester as an opaque oil (3.33g, 80%). MS m/z 445 (M+1).

(b) (S)-3-(4-Hydroxy-phenyl)-2-methyl-2-pyrrol-1-yl-propionic acid methyl ester (132).



132

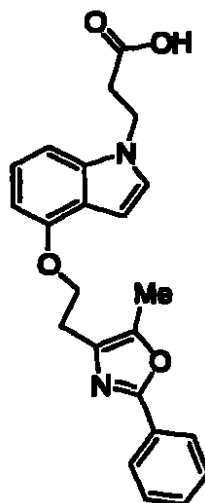
203

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To a stirred, cooled (0°C) solution of methanol (20mL) was added dropwise thionyl chloride (2.06mL, 28.2mmol) and the reaction stirred for 5 minutes. α -methyl-L-tyrosine (5g, 25.6mmol) was added and the reaction mixture warmed to room temperature. The reaction was then heated at reflux for 6 hours and cooled to room temperature. The solvent was removed in vacuo. The crude methyl ester was dissolved in water (50mL) acetic acid (50mL) and sodium acetate (3.36g, 40.9mmol), 2,5 dimethoxy tetrahydrofuran (5.29mL, 40.9mmol) added. The reaction mixture was heated at 90°C for 15 minutes, poured into water (200mL) and extracted with ethyl acetate (3x100mL). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by chromatography (using ethyl acetate hexanes 1:10 to 1:1) to give the desired pyrrole (5.38g, 81% g) as a clear oil. 500 MHz ¹NMR (CDCl₃) δ 6.71 (m, 2H), 6.63 (d, 2H J = 8.4Hz), 6.57 (d, 2H J = 8.4Hz), 6.17 (m, 2H) 3.34 (s, 3H), 3.36 (d, 1H, J = 13.9,) 3.25 (d, 1H, J = 13.9) 1.6 (s, 3H); MS m/z 258 (M-1).

Example 53

3-(5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl)-propionic acid (140).



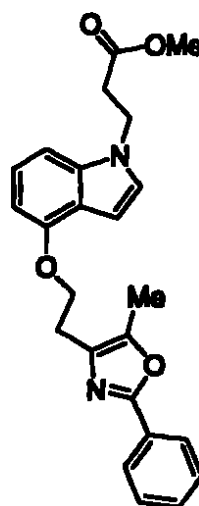
204

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A mixture of 4-[5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl]-propionic acid methyl ester (136, 0.81 g, 2.00 mmol) and LiOH (240 mg, 10.0 mmol) in DME (16 mL) and water (4 mL) was stirred at room temperature overnight. The reaction was diluted with water, acidified with 2N HCl, extracted with ethyl acetate, dried over MgSO₄, and concentrated under reduced pressure. The solid was recrystallized from EtOAc/hexanes to yield the desired propionic acid (560 mg, 72%). 400 MHz ¹H NMR (DMSO-*d*₆) δ 7.86 (m, 2H), 7.43 (m, 3H), 7.31 (d, 1H, *J* = 8.8 Hz), 7.23 (d, 1H, *J* = 2.9 Hz), 7.01 (d, 1H, *J* = 2.4 Hz), 6.71 (dd, 1H, *J* = 8.8, 2.4 Hz), 6.24 (d, 1H, *J* = 2.9 Hz), 4.28 (t, 2H, *J* = 6.8 Hz), 4.14 (t, 2H, *J* = 6.6 Hz), 2.88 (t, 2H, *J* = 6.6 Hz), 2.65 (t, 2H, *J* = 6.8 Hz), 2.32 (s, 3H). MS *m/z* 391 (M+1).

4-[5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl]-propionic acid methyl ester was prepared in the following manner.

- (a) 4-[5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl]-propionic acid methyl ester (139).



139

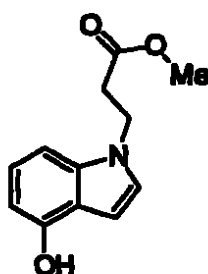
A mixture of 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl]-propionic acid methyl ester (0.88g, 2.18 mmol) and LiOH (260 mg, 10.9 mmol) in 2-methoxyethanol (16 mL) and water (4 mL) was stirred at room

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temperature overnight. The reaction was diluted with water, acidified with 2N HCl, extracted with ethyl acetate, dried over MgSO_4 , and concentrated under reduced pressure. The solid was recrystallized from EtOAc/hexanes to yield the desired propionic acid (400 mg, 47%). 400 MHz ^1H NMR ($\text{DMSO}-d_6$) δ 7.86 (m, 2H), 7.43 (m, 3H), 7.16 (d, 1H, $J = 3.2$ Hz), 6.99 (m, 2H), 6.50 (d, 1H, $J = 7.3$ Hz), 6.30 (d, 1H, $J = 2.7$ Hz), 4.29 (t, 2H, $J = 6.8$ Hz), 4.24 (t, 2H, $J = 6.4$ Hz), 2.94 (t, 2H, $J = 6.4$ Hz), 2.65 (t, 2H, $J = 6.8$ Hz), 2.35 (s, 3H). MS m/z 391 (M+1).

10 (b) 3-(4-Hydroxy-indol-1-yl)-propionic acid methyl ester (138)



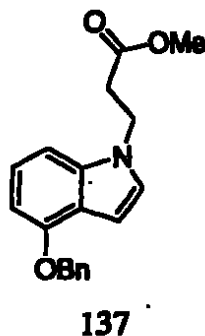
138

A mixture of 3-(4-Hydroxy-indol-1-yl)-propionic acid methyl ester (0.56g, 2.55 mmol), cesium carbonate (1.66g, 5.11 mmol) and toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl ester (1.63g, 4.57 mmol) in DMF (25 mL) was heated to 50°C overnight. The reaction was diluted with water, acidified with 2N HCl, extracted with ethyl acetate, dried over MgSO_4 , and concentrated under reduced pressure. The crude oil was chromatographed eluting with 20%-25% EtOAc (with 20% HOAc) in hexanes to yield the desired propionic acid (0.88g, 85%). 400 MHz ^1H NMR ($\text{DMSO}-d_6$) δ 7.86 (m, 2H), 7.44 (m, 3H), 7.14 (d, 1H, $J = 3.2$ Hz), 6.99 (m, 2H), 6.50 (dd, 1H, $J = 7.1, 1.0$ Hz), 6.30 (d, $J = 3.2$ Hz), 4.33 (t, 2H, $J = 6.8$ Hz), 4.24 (t, 2H, $J = 6.4$ Hz), 3.49 (s, 3H), 2.94 (t, 2H, $J = 6.4$ Hz), 2.74 (t, 2H, $J = 6.8$ Hz), 2.35 (s, 3H). MS m/z 405 (M+1).

25 (c) 3-(4-Benzoyloxy-indol-1-yl)-propionic acid methyl ester (137).

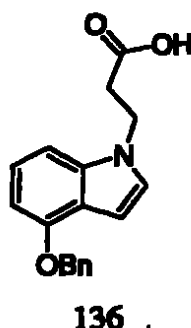
206

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5 A mixture of 3-(4-Benzyloxy-indol-1-yl)-propionic acid methyl ester (1.52g, 4.91 mmol) and 20% Pd/C (160mg) in methanol (25 mL) and THF (25 mL) was stirred under an H₂ atmosphere for 3 days. The reaction was filtered and concentrated to yield the crude deprotected product. MS *m/z* 220 (M+1).

(d) 3-(4-Benzyloxy-indol-1-yl)-propionic acid (136).



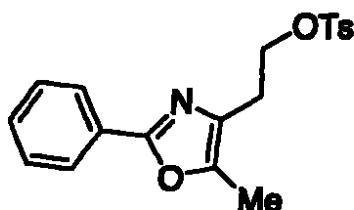
10

15 A solution of 4-Benzyloxyindole (1.61g, 7.21 mmol) and potassium hydroxide (2.02g, 36.1 mmol) in DMSO (12 mL) was stirred at room temperature for 1.5 hours. Ethyl 3-bromopropionate (1.11 mL, 8.65 mmol) was added and the mixture stirred overnight. The reaction was diluted with water, acidified with 2N HCl, extracted with ethyl acetate, dried over MgSO₄, and concentrated under reduced pressure. The crude oil was chromatographed eluting with 25%-30% EtOAc (with 20% HOAc) in hexanes to yield the desired
20 propionic acid (1.65g, 77%). 400 MHz ¹H NMR (DMSO-*d*₆) δ 7.44 (m, 2H), 7.35 (m, 2H), 7.27 (m, 1H), 7.18 (d, 1H, *J* = 3.2 Hz), 7.04 (d, 1H, *J* = 8.3 Hz), 6.97 (m, 1H), 6.55 (d, 1H, *J* = 7.3 Hz), 6.39 (m, 1H), 5.16 (s, 2H), 4.30 (t, 2H, *J* = 6.8 Hz), 2.67 (t, 2H, *J* = 6.8 Hz). MS *m/z* 296 (M+1).

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- (e) Toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl ester (135).

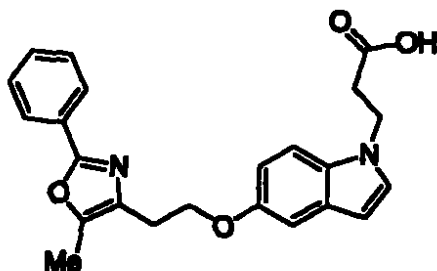


135

A solution of 2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethanol (2g, 9.84 mmol), *p*-toluenesulfonyl chloride (2.25g, 11.8 mmol) and DMAP (10 mg) in dichloromethane (40 mL) was cooled to 0°C. Triethylamine (2.75 mL, 19.7 mmol) was added dropwise. The reaction was stirred at 0°C for 3 hours, then warmed to room temperature overnight. The solution was cooled to 0°C, diluted with water (25 mL) and neutralized with 1N HCl. The mixture was extracted with dichloromethane, washed with saturated NaHCO₃ and brine, dried with MgSO₄, and concentrated to yield a brown solid in near quantitative yield. 400 MHz ¹H NMR (DMSO-*d*₆) δ 6.83 (m, 2H), 6.66 (m, 4H), 6.11 (m, 2H), 4.65 (dd, 1H, *J* = 8.8, 6.6 Hz), 3.66 (s, 3H), 3.30 (dd, 1H, *J* = 13.9, 6.6 Hz), 3.15 (dd, 1H, *J* = 13.9, 8.8 Hz). MS *m/z* 246 (*M*+1).

Example 53a

4-{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-propionic acid (140a).



140a

Prepared as in Example 53 from the corresponding 3-(5-Benzoyloxy-indol-1-yl)-propionic acid. Thus, a mixture of 3-{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester (0.81g, 2.00 mmol) and LiOH (240 mg, 10.0 mmol) in 2-methoxyethanol (16 mL) and water (4 mL) was stirred at room temperature overnight. The reaction was diluted with water, acidified with 2N HCl, extracted with ethyl acetate, dried over MgSO₄, and concentrated under reduced pressure. The solid was recrystallized from EtOAc/hexanes to yield the desired propionic acid (560 mg, 72%). 400 MHz ¹H NMR (DMSO-*d*₆) δ 7.86 (m, 2H), 7.43 (m, 3H), 7.31 (d, 1H, *J* = 8.8 Hz), 7.23 (d, 1H, *J* = 2.9 Hz), 7.01 (d, 1H, *J* = 2.4 Hz), 6.71 (dd, 1H, *J* = 8.8, 2.4 Hz), 6.24 (d, 1H, *J* = 2.9 Hz), 4.28 (t, 2H, *J* = 6.8 Hz), 4.14 (t, 2H, *J* = 6.6 Hz), 2.88 (t, 2H, *J* = 6.6 Hz), 2.65 (t, 2H, *J* = 6.8 Hz), 2.32 (s, 3H). MS *m/z* 391 (M+1).

4-{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-propionic acid (139a). A mixture of 3-(5-Hydroxy-indol-1-yl)-propionic acid methyl ester (1.14g, 5.20 mmol), cesium carbonate (3.39g, 10.4 mmol) and toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl ester (3.27g, 9.14 mmol) in DMF (50 mL) was heated to 50°C overnight. The reaction was diluted with water, acidified with 2N HCl, extracted with ethyl acetate, dried over MgSO₄, and concentrated under reduced pressure. The crude oil was chromatographed eluting with 25%-30% EtOAc (with 20% HOAc) in hexanes to yield the desired propionic acid (0.81g, 39%). 400 MHz ¹H NMR (DMSO-*d*₆) δ 7.86 (m, 2H), 7.44 (m, 3H), 7.31 (d, 1H, 9.0 Hz), 7.21 (d, 1H, 2.9 Hz), 7.01 (d, 1H, 2.2 Hz), 6.71 (dd, 1H, 9.0, 2.2 Hz), 6.24 (m, 1H), 4.32 (t, 2H, *J* = 6.8 Hz), 4.14 (t, 2H, *J* = 6.8 Hz), 3.50 (s, 3H), 2.88 (t, 2H, *J* = 6.8 Hz), 2.75 (t, 2H, *J* = 6.8 Hz), 2.32 (s, 3H). MS *m/z* 405 (M+1).

3-(5-Hydroxy-indol-1-yl)-propionic acid methyl ester (138a). A mixture of 3-(5-Benzoyloxy-indol-1-yl)-propionic acid methyl ester (2.38g, 7.69 mmol) and 20% Pd/C (145mg) in methanol (25 mL) and THF (25 mL) was stirred under an H₂ atmosphere for 18 hours. The reaction was filtered and concentrated to yield the deprotected product in near quantitative yield. 400 MHz ¹H NMR

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(DMSO- d_6) δ 7.19 (d, 1H, $J = 8.8$ Hz), 7.15 (d, 1H, $J = 2.6$ Hz), 6.78 (1H, d, $J = 2.6$ Hz), 6.58 (dd, 1H, $J = 8.8, 2.4$ Hz), 6.15 (d, 1H, $J = 2.4$ Hz), 4.28 (t, 2H, $J = 6.8$ Hz), 3.51 (s, 3H), 2.74 (t, 2H, $J = 6.8$ Hz). MS m/z 220 ($M+1$).

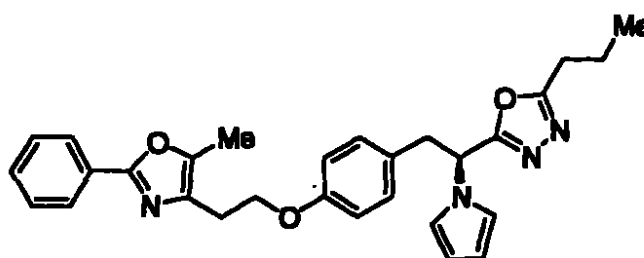
5 3-(5-Benzoyloxy-indol-1-yl)-propionic acid methyl ester (137a). TMS-diazomethane (6.65 mL, 13.3 mmol, 2.0 M in hexanes) was added to a solution of 3-(5-Benzoyloxy-indol-1-yl)-propionic acid (2.27g, 8.87 mmol) in toluene (72 mL) and methanol (18 mL). The reaction stirred at room temperature for 30 minutes, quenched with acetic acid and concentrated. The desired ester as a brown oil was
10 obtained in near quantitative yield. 400 MHz ^1H NMR (DMSO- d_6) δ 7.41 (m, 2H), 7.33 (m, 3H), 7.25 (m, 2H), 7.06 (d, 1H, $J = 2.4$ Hz), 6.80 (dd, 1H, $J = 9.0, 2.4$ Hz), 6.25 (d, 1H, $J = 2.4$ Hz), 5.03 (s, 2H), 4.33 (t, 2H, $J = 6.7$ Hz), 3.50 (s, 3H), 2.75 (t, 2H, $J = 6.7$ Hz). MS m/z 310 ($M+1$).

15 3-(5-Benzoyloxy-indol-1-yl)-propionic acid (136a). A solution of 5-Benzoyloxyindole (4g, 17.9 mmol) and potassium hydroxide (5.03g, 89.6 mmol) in DMSO (30 mL) was stirred at room temperature for 1.5 hours. Ethyl 3-bromopropionate (2.75 mL, 21.5 mmol) was added and the mixture stirred for 3 hours. The reaction was diluted with water, acidified with 2N HCl, extracted with
20 ethyl acetate, dried over MgSO_4 , and concentrated under reduced pressure. The crude oil was chromatographed eluting with 25%-30% EtOAc (with 20% HOAc) in hexanes to yield the desired propionic acid (2.56g, 49%). 400 MHz ^1H NMR (DMSO- d_6) δ 7.40 (m, 2H), 7.33 (m, 3H), 7.25 (m, 2H), 7.06 (d, 1H, $J = 2.4$ Hz), 6.80 (dd, 1H, $J = 8.8, 2.4$ Hz), 6.24 (dd, 1H, $J = 2.9, 0.7$ Hz), 5.03 (s, 2H), 4.29 (t,
25 2H, $J = 6.7$ Hz), 2.66 (t, 2H, $J = 6.7$ Hz). MS m/z 324 ($M+1$).

Example 54

(S)-2-(2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole (147).

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147

5 (S)-3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid hydrazide (147, 2.95g, 6.85mmol) was dissolved in dioxane (20ml) and trimethyl orthobutyrate (3.29mL, 20.5mmol), and methane sulfonic acid (100μL, 1.37mmol) were added. The reaction mixture was heated at 105°C for 15 minutes then poured into water and extracted with ethyl acetate (2x100ml). The organic layer was washed with sodium bicarbonate, brine and dried over
 10 MgSO₄. The solvent was removed under vacuum and the residual oil purified by chromatography using 1:10 to 1:1 ethyl acetate: hexane. (S)-2-(2-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole was isolated as a clear oil. Yield = 0.80g, 24% ¹H NMR (400MHz) δ (CDCl₃) 7.97 (2H, m), 7.41 (3H, m), 6.88 (2H dd, J=2.2, 5.85) 6.74 (2H, dd, J=1.95, 6.59 Hz), 6.69 (2H, t, J=2.2Hz), 6.13 (2H, t, J=2.2Hz), 5.33 (1H, dd, J = 6.83, 8.78Hz), 4.18 (2H, t, J=6.83), 3.52 (1H, dd, J=6.59, 14.16Hz,), 3.45 (1H, dd, J = 8.78, 14.16Hz). 2.95 (2H, t, J=6.59Hz) 2.77 (2H, m) 2.35 (3H, s), 1.76 (2H, sex, J=7.32), 0.97 (3H, t, J=7.32), MS m/z 483 (M+1).
 15

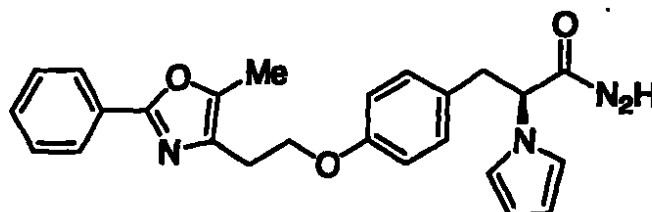
20 (S)-3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid hydrazide (146) was prepared in the following manner.

(a) (S)-3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid hydrazide (146).

25

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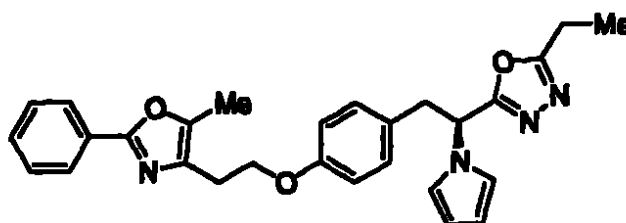


146

(S)-3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid prepared as described in example 1 (5g, 12 mmol) was dissolved in THF (60mL) and 4-methyl morpholine (1.70mL, 15.5 mmol) was added followed by isobutyl chloroformate (2.22mL, 17.2mmol). The resulting suspension was stirred for 30 minutes at 10°C and then filtered into a cooled (0°C) solution of hydrazine (1.88mL, 60mmol) in THF (40mL). After stirring for 45 minutes the mixture was poured into ethyl acetate and, washed with water, followed by a saturated solution of ammonium chloride and then brine. The organic layer was separated and dried over MgSO₄. Removal of the solvent under reduced pressure provided the desired monoacyl hydrazide as a clear oil used without further purification. ¹H NMR (400MHz) δ (CDCl₃) 7.96 (2H, m), 7.40 (3H, m), 6.88 (2H d, J=8.78) 6.73 (2H, dd, J=1.95, 6.59 Hz), 6.62 (2H, t, J=2.2Hz), 6.16 (2H, t, J=2.2Hz), 5.59 (1H, dd, J = 4.63, 10.49Hz), 4.16 (2H, t, J=6.59), 3.57 (1H, dd, J=4.63, 6.59, 14.4Hz,), 3.15 (1H, dd, J = 14.40, 10.49Hz). 2.93 (2H, t, J=6.59Hz) 2.33 (3H, s) MS m/z 431 (M+1).

Example 55

(S)-2-Ethyl-5-(2-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole (148)



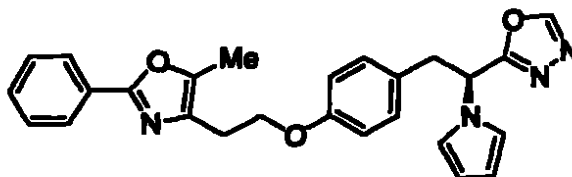
148

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(S)-3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid hydrazide (146, 2.89 g, 6.72 mmol) was dissolved in dioxane (20 ml) and triethyl propionate (4.06 mL, 20.2 mmol), and methane sulfonic acid (98 μ L, 1.34 mmol) were added. The reaction mixture was heated at 105°C for 15 minutes then poured into water and extracted with ethyl acetate (2x100 mL). The organic layer was washed with sodium bicarbonate, brine and dried over MgSO₄. The solvent was removed under vacuum and the residual oil purified by chromatography using 1:10 to 1:1 ethyl acetate: hexane. 2-Ethyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole was isolated as a clear oil. Yield = 0.82g, 26% some of the oil was dissolved in ethyl ether and evaporated slowly to give clear crystals Yield = 58mg, m.p. 96.5-98°C, C₂₈H₂₈N₄O₃ required C71.78, H6.02, N11.96 found C71.68, H6.15, N11.89. 73431x34 mw= 468.54

Example 56

(S)-2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole (149).



149

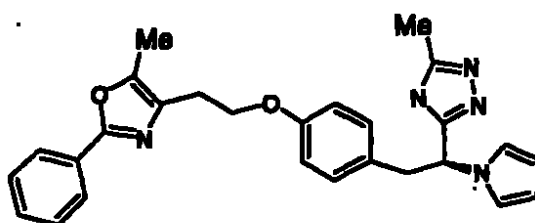
(S)-3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid hydrazide (146, 1.22g, 2.85mmol) was dissolved in dioxane (20ml) and trimethyl orthoformate (1.42mL, 8.56 mmol) and methane sulfonic acid (42, 0.57 mmol) added. The reaction mixture was heated at 105°C for 15 minutes then poured into water and extracted with ethyl acetate (2x100ml). The organic layer was washed with sodium bicarbonate, brine and dried over MgSO₄. The solvent was removed under vacuum and the residual oil purified by chromatography using 1:10 to 1:1 ethyl acetate: hexane. (S)-2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole was

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isolated as a clear tacky oil. Yield = 401mg, 32% ^1H NMR (400MHz) δ (CDCl_3) 8.34 (1H, s), 7.96 (2H, m), 7.41 (3H, m), 6.88 (2H d, $J=8.79$) 6.73 (2H, m), 6.62 (2H, t, $J=2.2\text{Hz}$), 6.16 (2H, t, $J=2.2\text{Hz}$), 5.42 (1H, dd, $J = 6.83, 8.78 \text{ Hz}$), 4.18 (2H, t, $J=6.59$), 3.57 (1H, dd, $J=6.6, 13.9\text{Hz}$), 3.15 (1H, dd, $J = 8.54, 13.9\text{Hz}$), 2.95 (2H, t, $J=6.59\text{Hz}$) 2.35 (3H, s) MS m/z 431 (M+1)

Example 57

(S)-3-Methyl-5-(2-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole (151).



151

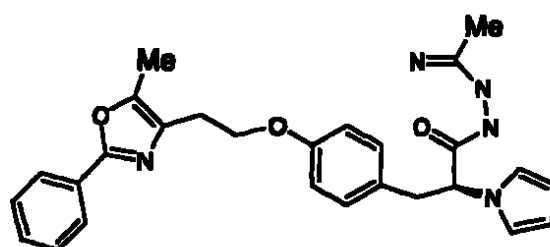
(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid N'-(1-imino-ethyl)-hydrazide (150, 0.860g, 1.82mmol) was suspended in para xylene (15ml) and heated to 120°C in a sealed tube for 24h. The product was isolated by chromatography 1:1 ethyl acetate:hexane to give the desired product as a white foam. Yield = 684mg, 76%. ^1H NMR (400MHz) δ (CDCl_3) 7.96 (2H, m), 7.40 (3H, m), 6.87 (2H d, $J=8.54$) 6.77 (2H, t, $J=1.95$), 6.11 (2H, d, $J=8.54\text{Hz}$), 6.11 (2H, t, $J=1.95\text{Hz}$), 5.25 (1H, dd, $J = 6.34, 9.27 \text{ Hz}$), 4.16 (2H, t, $J=6.83$), 3.51 (1H, dd, $J=6.1, 14.16\text{Hz}$), 3.38 (1H, dd, $J = 9.27, 14.16\text{Hz}$) 2.93 (2H, t, $J=6.59\text{Hz}$) 2.42 (3H, s) 2.34 (3H, s) MS m/z 454 (M+1)

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid N'-(1-imino-ethyl)-hydrazide (150) was prepared in the following manner.

- (a) (S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid N'-(1-imino-ethyl)-hydrazide (150)

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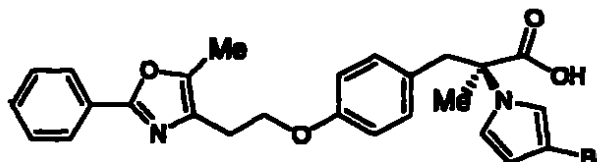


150

(S)-3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid hydrazide (146, 1.22 g, 2.83 mmol) was dissolved in THF (20ml) and cooled to 0°C. Ethyl acetimidate hydrochloride (420 mg, 3.40 mmol) and triethyl amine (513 μ L, 3.68 mmol) were added and the reaction mixture stirred at 0°C for 1.5 hours followed by stirring at room temperature overnight. The reaction mixture was purified by chromatography 1:20 to 1:4 methanol to dichloromethane. The desired product was obtained as a pink solid. Yield = 860mg, 64% ^1H NMR (400MHz) δ (D₆DMSO) 7.85 (2H, m), 7.42 (3H, m), 6.95 (2H d, J=8.54), 6.90 (2H, t, J=8.30), 6.73 (4H, m), 5.85 (1H, m), 4.08 (2H, t, J=6.83), 3.11-2.93 (4H, m) 2.83 (2H, m) 2.43 (3H, s) MS m/z 472 (M+1)

Example 58

2-(3-Bromo-pyrrol-1-yl)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (154)



154

(S)-2-(3-Bromo-pyrrol-1-yl)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (153, 1.46g, 2.79mmol) was hydrolysed as described in procedure A. The desired product was isolated by chromatography 1:1 ethyl acetate : hexane. Yield = 0.633, 45% mp 158-159°C ^1H NMR (400MHz) δ (CDCl₃) 8.06 (2H, m), 7.46 (3H, m), 6.75-6.61 (6H, m), 6.15

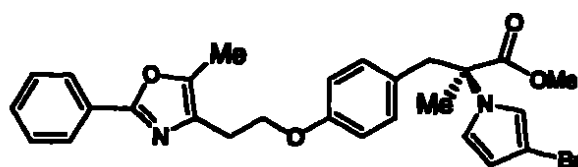
215

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(1H, m), 4.21 (2H, t, J=6.1), 3.25 (2H, m) 3.05 (2H, t, J=6.1) 2.41 (3H, s), 1.58 (3H, s) MS m/z 511 (M+1).

(S)-2-(3-Bromo-pyrrol-1-yl)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (153) was prepared in the following manner.

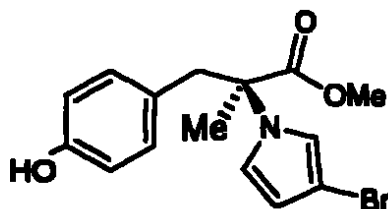
(a) (S)-2-(3-Bromo-pyrrol-1-yl)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (153).



153

(S)-2-(3-Bromo-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid methyl ester (152, 4.01g, 11.8 mmol) was coupled as described in procedure B. The ester was isolated via chromatography 1:10 to 1:1 ethyl acetate:hexanes as an oil Yield = 1.46g, 24% ^1H NMR (400MHz) δ (CDCl_3) 7.96 (2H, m), 7.40 (3H, m), 6.75-6.57 (6H, m), 6.15 (1H, m), 4.18 (2H, m), 3.73 (3H, s) 3.21 (2H, m), 2.35 (3H, s), 1.54 (3H, s) MS m/z 525 (M+1),

(b) (S)-2-(3-Bromo-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid methyl ester (152).



152

25

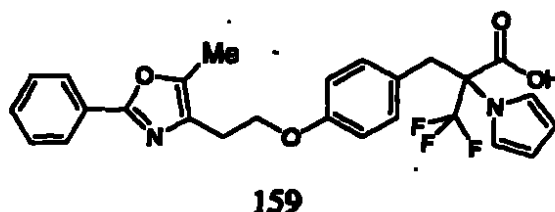
216

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(S)-3-(4-Hydroxy-phenyl)-2-methyl-2-pyrrol-1-yl-propionic acid methyl ester (5.4g 20.8mmol) was dissolved in dichloromethane, (50mL) and cooled to -78°C. N-Bromosuccinimide (4.08g, 22.9mmol) was added and the reaction warmed to room temperature and stirred for 3h. The solvent was removed *in vacuo* and the residue adsorbed onto silica gel. Chromatography using 1:10 to 1:1 ethyl acetate:hexane gave the desired product as a gum. Yield = 6.44g, 91%, ¹H NMR (400MHz) δ (CDCl₃) 6.71-6.58 (6H, m), 6.16 (1H, m), 3.75 (3H, s) 3.31-3.18 (2H, m), 1.55 (3H, s) MS *m/z* 525 (M+1).

Example 59

3,3,3-Trifluoro-2-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl]-2-pyrrol-1-yl-propionic acid (159).



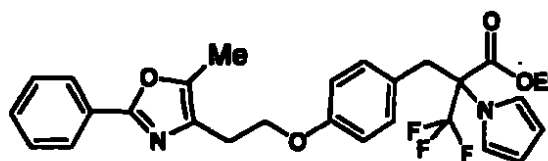
3,3,3-Trifluoro-2-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl]-2-pyrrol-1-yl-propionic acid ethyl ester (158, 0.83g, 13.3mmol) was hydrolysed as described in procedure B. the product was recrystallised from hot ethyl acetate to give 2.03g, 31% m.p. 201-203°C ¹H NMR (400MHz) δ (D₆DMSO) 7.85 (2H, m), 7.42 (3H, m), 7.71 (2H, d J=8.78), 6.93 (2H, br s), 6.79 (2H, d, J=8.78), 6.06 (2H, t, J=2.19) 4.12 (2H, t, J=6.59), 3.74 (1H, d, J=14.39Hz), 3.62 (1H, d, J=14.64) 2.85 (2H, t, J=6.58Hz) 2.29 (3H, s) MS *m/z* 485 (M+1)

3,3,3-Trifluoro-2-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl]-2-pyrrol-1-yl-propionic acid ethyl ester (158) was prepared in the following manner.

(a) 3,3,3-Trifluoro-2-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl]-2-pyrrol-1-yl-propionic acid ethyl ester (158)

217

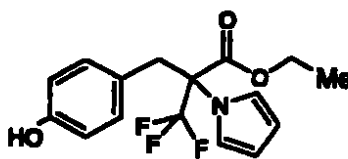
-200-



158

5 3,3,3-Trifluoro-2-(4-hydroxy-benzyl)-2-pyrrol-1-yl-propionic acid ethyl ester (157, 4.92g, 15mmol) was coupled as described in procedure B. The product was purified using chromatography to give the desired product. Yield=6.83g, 88%
¹H NMR (400MHz) (CDCl₃) 8.05 (2H, m), 7.44 (3H, m), 6.98 (2H, d J=8.54), 6.81 (2H, br s), 6.75 (2H, dd, J=2.19, 6.06), 6.23 (2H, t, J=2.19) 4.22 (4H, m), 3.67 (2H, 2d, J=14.39, Hz), 3.01 (2H, t, J=6.58Hz) 2.38 (3H, s) 1.21 (3H, m) MS
 10 m/z 513 (M+1)

(b) 3,3,3-Trifluoro-2-(4-hydroxy-benzyl)-2-pyrrol-1-yl-propionic acid ethyl ester (157).



157

15

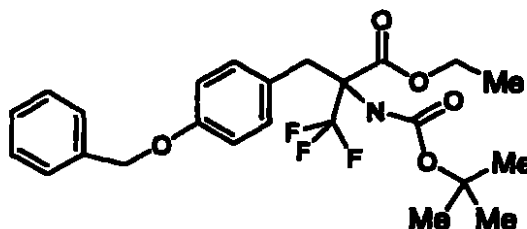
2-(4-Benzyloxy-benzyl)-2-tert-butoxycarbonylamino-3,3,3-trifluoro-propionic acid ethyl ester (156, 10.72g) was dissolved in THF and Hydrogenated using Palladium on Carbon. The product 2-tert-Butoxycarbonylamino-3,3,3-trifluoro-2-(4-hydroxy-benzyl)-propionic acid ethyl ester (156a) was used crude in
 20 the next step.

Thionyl Chloride (3.46mL, 47.4mmol) was added to methanol (100mL) at 0°C. 2-tert-Butoxycarbonylamino-3,3,3-trifluoro-2-(4-hydroxy-benzyl)-propionic acid ethyl ester (8.94g, 23.7mmol) was added and the reaction mixture allowed to reach room temperature and stirred for 24h.. The solvent was removed in vacuo and the crude product 2-Amino-3,3,3-trifluoro-2-(4-hydroxy-benzyl)-propionic acid ethyl ester hydrochloride used directly in the next step. MS m/z 278 (M+1)
 25

-201-

2-Amino-3,3,3-trifluoro-2-(4-hydroxy-benzyl)-propionic acid ethyl ester hydrochloride (156a, 7.13g, 22.7 mmol) was dissolved in water (40ml) and acetic acid (40mL). Sodium acetate (2.98g, 36.3mmol) and 2,5 dimethoxy tetrahydrofuran (4.7mL, 36.3 mmol) were added and the reaction mixture heated at 90°C for 20minutes until no starting material was observed by mass spectrum analysis. The reaction mixture was poured into water, extracted with ethyl acetate and neutralized using sodium carbonate. The organic layer was dried MgSO₄ and the solvent removed in vacuo. The residue was purified by Chromatography 1:10 to 1:1 ethyl acetate:hexane to give the desired product 3,3,3-Trifluoro-2-(4-hydroxy-benzyl)-2-pyrrol-1-yl-propionic acid ethyl ester as a white solid. Yield = 4.95g, 66%, ¹H NMR (400MHz) (CDCl₃) 6.98 (2H, m), 6.83 (2H, br s), 6.75 (2H, m), 6.24 (2H, t, J=2.44) 4.24 (2H, m), 3.70 (1H, d, J=14.64 Hz), 3.66 (1H, d, J=14.64) 1.21 (3H, t, J=7.32) MS m/z 328 (M+1)

(c) 2-(4-Benzyloxy-benzyl)-2-tert-butoxycarbonylamino-3,3,3-trifluoro-propionic acid ethyl ester (156).



156

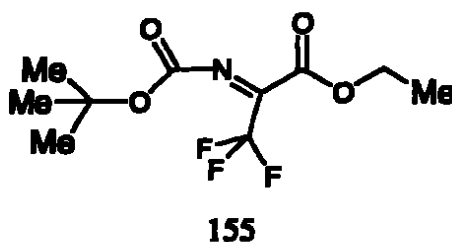
Magnesium turnings (2.82g, 0.16mol) in toluene (5ml) was stirred at room temperature. 4-Benzyloxy benzyl chloride (11.3g, 48.5mmol) in THF (100ml) was added dropwise with careful control of the Grignard formation. Once all the chloride had been added the reaction was stirred until no more color change was observed. The Grignard reagent was transferred via cannular to a solution of 2-tert-Butoxycarbonylimino-3,3,3-trifluoro-propionic acid ethyl ester (155, 29.4mmol) in THF (50ml) at -78°C. The reaction was then warmed to 0°C and stirred for 10minutes. This was quenched with saturated aqueous ammonium chloride and the product extracted with ethyl acetate. The organic layer was dried

2A

-202-

MgSO₄ and the solvent removed in vacuo. The desired product was isolated using chromatography 1:10 to 1:1 ethyl acetate:hexane. 2-(4-Benzyloxy-benzyl)-2-tert-butoxycarbonylamino-3,3,3-trifluoro-propionic acid ethyl ester was obtained as a white solid. Yield = 10.72g, 78% (3 steps) ¹H NMR (400MHz) (CDCl₃) 7.43-7.32 (5H, m), 7.11 (2H, d, J=8.78), 6.87 (2H, d, J=8.78), 5.52 (1H br s), 5.02 (2H, s), 4.30 (2H, m), 3.70 (2H, d, J=13.9Hz), 1.46, (9H, s), 1.33 (3H, t, J=7.32) MS m/z 466 (M-1)

(d) 2-tert-Butoxycarbonylimino-3,3,3-trifluoro-propionic acid ethyl ester (155).



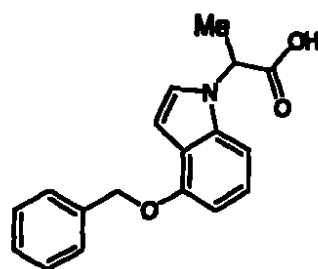
Ethyl 3,3,3 trifluoropyruvate (5g, 29.4mmol) was dissolved in dichloromethane and t-Butyl carbamate added (3.44g, 29.4mmol). The reaction mixture was stirred at room temperature for 16h. The solvent was removed under vacuum to give a white solid. The solid was dissolved in ether (50mL) and trifluoroacetic anhydride (4.57mL, 32.34mmol) was added dropwise over 30 minutes with vigorous stirring. After stirring for an additional 30 minutes Pyridine (5.23mL, 64.7mmol) was added dropwise and the reaction stirred for an additional 2h. Hexane (100ml) was added and the reaction filtered rapidly after cooling to -78°C. The isolated product 2-tert-Butoxycarbonylimino-3,3,3-trifluoro-propionic acid ethyl ester was stored under vacuum and used without further purification. ¹H NMR (400MHz) (CDCl₃) 4.30 (2H, q, J=7.32), 1.57, (9H, s), 1.37 (3H, t, J=7.32) MS m/z 269 (M)

Example 60

2-(4-Benzyloxy-indol-1-yl)-propionic acid (160).

220

-203-

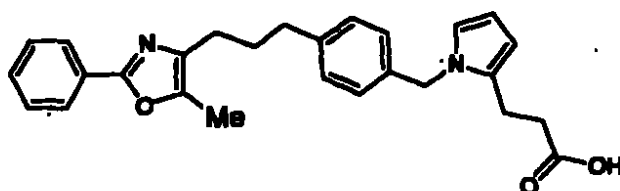


160

Prepared as in Example 53 using methyl 2-bromopropionate. Mp 143°C-146°C, CHN; CALC'D: C, 73.20; H, 5.80; N, 4.74; FOUND: C, 72.95; H, 5.86; N, 4.62

Example 61

3-(1-(4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-benzyl)-1H-pyrrol-2-yl)-propionic acid (165).



165

A mixture of 3-(1-(4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-benzyl)-1H-pyrrol-2-yl)-propionic acid methyl ester (164, 0.44g, 1.48 mmol) and Lithium hydroxide (175 mg, 7.39 mmol) in 2-methoxyethanol (12 mL) and water (3 mL) was stirred at room temperature overnight. The reaction was diluted with water, acidified, extracted with ethyl acetate, dried over MgSO₄, and concentrated under reduced pressure. The crude solid was recrystallized from EtOAc/hexanes to yield the desired acid. 400 MHz ¹H NMR (DMSO-*d*₆) δ 7.84 (m, 2H), 7.43 (m, 3H), 7.11 (d, 2H, *J* = 8.1 Hz), 6.88 (d, 2H, *J* = 8.1 Hz), 6.67 (m, 1H), 5.88 (m, 1H), 5.75 (dd, 1H, *J* = 3.4, 2.7 Hz), 5.00 (s, 2H), 2.55 (m, 4H), 2.38 (m, 4H), 2.23 (s, 3H), 1.82 (m, 2H). mp 139-141.

221

-204-

3-(1-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-benzyl}-1H-pyrrol-2-yl)-propionic acid methyl ester (164) was prepared in the following manner.

5 (a) 3-(1-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-benzyl}-1H-pyrrol-2-yl)-propionic acid methyl ester (164).

10 A mixture of 3-(1-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-benzyl}-1H-pyrrol-2-yl)-acrylic acid methyl ester (163, 0.47g, 1.07 mmol) and 10% Pd/C (59 mg) in methanol (40 mL) and THF (10 mL) was stirred under an H₂ atmosphere for 17 hours. The reaction was filtered and concentrated to yield the desired product.

15 (b) 3-(1-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-benzyl}-1H-pyrrol-2-yl)-acrylic acid methyl ester (163).

20 Sodium hydride (60%, 85 mg, 2.10 mmol) was added to a solution of 3-(1H-Pyrrol-2-yl)-acrylic acid methyl ester (162, 265 mg, 1.75 mmol) in dimethylformamide (15 mL) and the mixture was stirred at room temperature for 15 minutes. 4-[3-(4-Chloromethyl-phenyl)-propyl]-5-methyl-2-phenyl-oxazole (161, 1.14g, 3.50 mmol) was added and the reaction heated to 60°C overnight. The reaction was diluted with water, acidified, extracted with ethyl acetate, dried over MgSO₄s, and concentrated under reduced pressure. A mixture of the product and starting material was taken on to the next step.

25 (c) 3-(1H-Pyrrol-2-yl)-acrylic acid methyl ester (162).

30 A solution of pyrrole-2-carboxaldehyde (2.5g, 26.3 mmol) and methyl (triphenylphosphoranylidene)-acetate (9.23g, 27.6 mmol) in toluene (250 mL) was heated to 45°C overnight. The reaction was concentrated under reduced pressure. The crude oil was chromatographed eluting with 20%-30% EtOAc in hexanes to yield the desired product (2.70g, 68%).

222

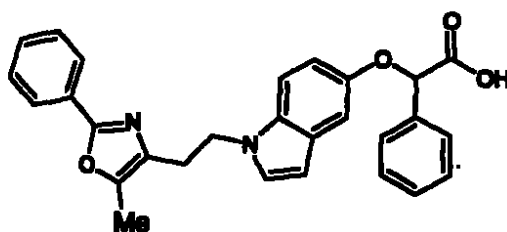
-205-

(d) 4-[3-(4-Chloromethyl-phenyl)-propyl]-5-methyl-2-phenyl-oxazole
(161).

5 A solution of {4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-
methanol (2.0g, 6.51 mmol) in dichloromethane (25 mL) was cooled to 0°C.
Methanesulfonyl chloride (550μL, 7.16 mmol) and triethylamine (1.81 mL, 13.0
mmol) were added and the mixture warmed to room temperature overnight. The
reaction was diluted with saturated NH₄Cl solution, extracted with CH₂Cl₂,
washed with brine, dried over MgSO₄, and concentrated under reduced pressure to
10 yield the desired product.

Example 62

(1-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl]-1H-indol-5-yloxy)-phenyl-
acetic acid (169).



15

169

A mixture of {1-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl]-1H-indol-5-
yloxy}-phenyl-acetic acid methyl ester (168, 1.44g, 3.09 mmol) and LiOH (370
mg, 15.4 mmol) in 2-methoxyethanol (24 mL) and water (6 mL) was stirred at
20 room temperature overnight. The reaction was diluted with water, acidified with
2N HCl, extracted with ethyl acetate, dried over MgSO₄, and concentrated under
reduced pressure. The crude oil was chromatographed eluting with 30% EtOAc
(with 20% HOAc) in hexanes. The resulting solid was recrystallized from
EtOAc/hexanes to yield the desired acid (140 mg). 400 MHz ¹H NMR (DMSO-
d₆) δ 7.88 (m, 2H), 7.49 (m, 5H), 7.35 (m, 3H), 7.26 (d, 1H, J = 9.0 Hz), 7.17 (d,
25 1H, J = 2.9 Hz), 7.00 (d, 1H, J = 2.4 Hz), 6.77 (dd, 1H, J = 9.0, 2.4 Hz), 6.25 (d,

223

-206-

1H, $J = 2.9$ Hz), 5.68 (s, 1H), 4.34 (t, 2H, $J = 6.6$ Hz), 2.87 (t, 2H, $J = 6.6$ Hz), 1.87 (s, 3H). mp 176-178.

5 {1-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl]-1H-indol-5-yloxy}-phenyl-acetic acid methyl ester (168) was prepared in the following manner.

(a) {1-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl]-1H-indol-5-yloxy}-phenyl-acetic acid methyl ester (168).

10 A mixture of 1-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl]-1H-indol-5-ol (167, 1.16g, 3.64 mmol), cesium carbonate (2.37g, 7.29 mmol) and methyl α -bromophenylacetate (1.15 mL, 7.29 mmol) in DMF (35 mL) was heated to 55°C overnight. The reaction was diluted with water, acidified with 2N HCl, extracted with ethyl acetate, dried over MgSO₄s, and concentrated under reduced pressure. .
15 The crude oil was chromatographed eluting with 15%-25% EtOAc (with 20% HOAc) in hexanes to yield the desired product (1.44g, 85%).

(b) 1-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl]-1H-indol-5-ol (167).

20 A mixture of 3-(5-Benzyloxy-indol-1-yl)-propionic acid methyl ester (166, 1.93g, 4.72 mmol) and 20%-Pd/C (360 mg) in ethanol (40 mL) and THF (10 mL) was stirred under an H₂ atmosphere for 18 hours. The reaction was filtered and concentrated. Purified by chromatography to yield the deprotected product in near quantitative yield.

25

(c) 5-Benzyloxy-1-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-1H-indole (166).

30 5-Benzyloxyindole (2.0 g, 8.96 mmol) was dissolved in dimethylformamide (90 mL) and 60% sodium hydride (540 mg, 13.4 mmol) was added. Toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl ester (600 μ L, 5.37 mmol) was added. The reaction was stirred at room temperature

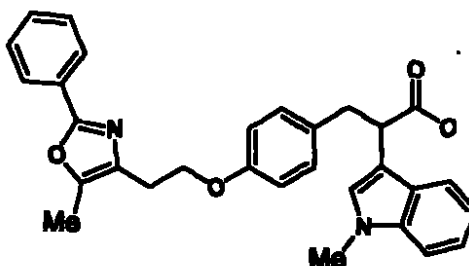
224

-207-

overnight. The reaction was diluted with water, acidified, extracted with ethyl acetate, dried over MgSO₄s, and concentrated under reduced pressure. Purified using chromatography. Yield 1.93 g (60%).

Example 63

5 2-(1-Methyl-1H-indol-3-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (173)



173

10 2-(1-Methyl-1H-indol-3-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (172, 250 mg, 0.51 mmol) was dissolved in 2-methoxyethanol (4 mL) and H₂O (1 mL). LiOH monohydrate (60 mg, 2.53 mmol) was added in one portion and the suspension stirred overnight. The reaction was diluted with water, extracted with ethyl acetate, dried over
15 MgSO₄, and concentrated under reduced pressure to yield the desired product. Near quantitative yield. 400 MHz ¹H NMR (DMSO-*d*₆) δ 7.85 (m, 2H), 7.58 (d, 1H, *J* = 7.8 Hz), 7.44 (m, 3H), 7.32 (t, 1H, *J* = 6.6 Hz), 7.17 (s, 1H), 7.08 (m, 3H), 6.96 (m, 1H), 6.75 (dd, 2H, *J* = 8.5, 6.6 Hz), 4.10 (m, 2H), 3.97 (m, 1H), 3.67 (s, 3H), 2.95 (m, 2H), 2.84 (t, 2H, *J* = 6.3 Hz), 2.29 (s, 3H). MS *m/z* 481 (M+1).

20

2-(1-Methyl-1H-indol-3-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (172) was prepared in the following manner.

25 (a) 2-(1-Methyl-1H-indol-3-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (172).

925

-208-

A solution of (1-Methyl-1H-indol-3-yl)-acetic acid methyl ester (171, 450 mg, 2.21 mmol) in tetrahydrofuran (14 mL) was cooled to 0°C. Lithium bis(trimethylsilyl)amide (1.0 M in THF, 2.32 mL, 2.32 mmol) was added and the mixture stirred at 0°C for 1 hour. A solution of 4-[2-(4-Chloromethyl-phenoxy)-ethyl]-5-methyl-2-phenyl-oxazole (835 mg, 2.55 mmol) in THF (4 mL) was added and the reaction warmed to room temperature and stirred for 6 hours. The reaction was diluted with water, extracted with ethyl acetate, dried over MgSO₄, and concentrated under reduced pressure. The crude oil was chromatographed eluting with 15%-20% EtOAc (with 20% HOAc) in hexanes to yield the desired product (250mg, 23%).

(b) 4-[2-(4-Chloromethyl-phenoxy)-ethyl]-5-methyl-2-phenyl-oxazole (171).

A solution of {4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-methanol (170, 2.0g, 6.46 mmol) in dichloromethane (25 mL) was cooled to 0°C. Methanesulfanyl chloride (550µL, 7.16 mmol) and triethylamine (1.80 mL, 12.9 mmol) were added and the mixture warmed to room temperature overnight. The reaction was diluted with saturated NH₄Cl solution, extracted with CH₂Cl₂, washed with brine, dried over MgSO₄, and concentrated under reduced pressure to yield the desired product.

(c) (1-Methyl-1H-indol-3-yl)-acetic acid methyl ester (170).

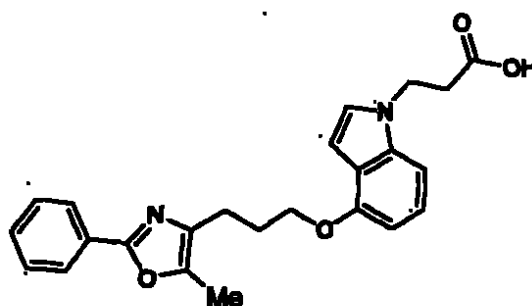
TMS-diazomethane (7.93 mL, 15.9 mmol, 2.0 M in hexanes) was added to a solution of 1-methyl-3-indoleacetic acid (2.0g, 10.6 mmol) in toluene (80 mL) and methanol (20 mL). The reaction stirred at room temperature for 30 minutes, quenched with acetic acid and concentrated. The desired ester was obtained in near quantitative yield.

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Example 64

3-(4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propoxy]-indol-1-yl)-propionic acid (174).



5

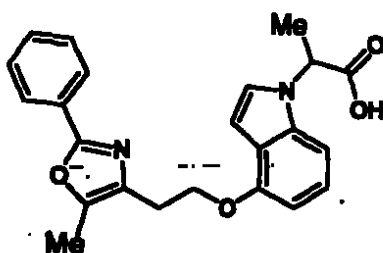
174

Prepared as described for Example 53 using 4-(3-Bromo-propyl)-5-methyl-2-phenyl-oxazole. m.p. 133-134, CHN (theor): 71.27% C, 5.98% H, 6.93% N. Found: 71.19% C, 5.92% H, 6.93% N.

10

Example 65

2-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl)-propionic acid (175).



175

15

Prepared as described for Example 53 using methyl 2-bromopropionate. Mp 157°C-159°C, CHN (theor.): 70.75% C, 5.68% H, 7.17% N. Found: 70.82% C, 5.74% H, 7.13% N.

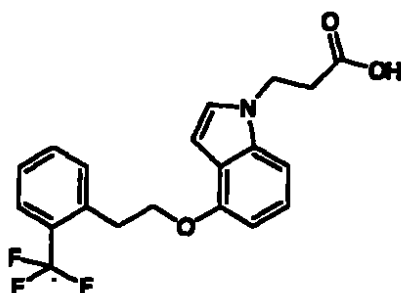
Example 67

3-(4-[2-(2-Trifluoromethyl-phenyl)-ethoxy]-indol-1-yl)-propionic acid (176)

20

228

-210-

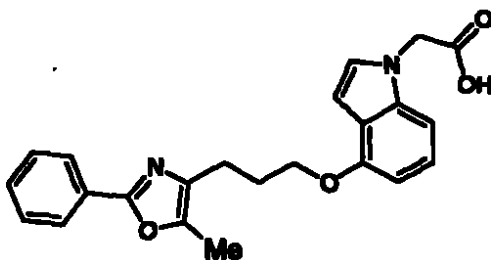


176

Prepared as described for Example 53 except the alkylation on the indole oxygen was completed in the following manner. 3-(4-Hydroxy-indol-1-yl)-propionic acid methyl ester (1.73g, 7.89 mmol), triphenylphosphine (2.07g, 7.89 mmol), and 2-(2-Trifluoromethyl-phenyl)-ethanol (1.25 mL, 7.89 mmol) were dissolved in tetrahydrofuran (35 mL). Diethyl azodicarboxylate (1.28 mL in 5 mL THF, 7.89 mmol) was added dropwise and the reaction stirred at room temperature overnight. The mixture was concentrated and purified by chromatography. Yield = 290 mg, 10%. m.p.=126-129, THEORY: 63.66% C, 4.81% H, 3.71% N. ACTUAL: 63.68% C, 4.97% H, 3.71% N.

Example 67

(4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propoxy]-indol-1-yl)-acetic acid (177).



177

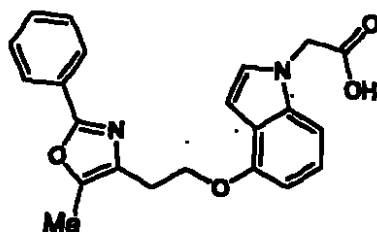
Prepared from 4-(3-Bromo-propyl)-5-methyl-2-phenyl-oxazole as described in Example 69. CHN: THEORY: 70.75% C, 5.68% H, 7.17% N. ACTUAL: 69.37% C, 5.59% H, 6.82% N. MS m/z 391 (M+1).

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Example 68

4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl]-acetic acid
(178).



5

178

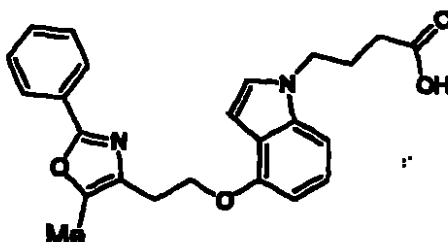
4-Benzylxyindole (1.0 g, 4.48 mmol) was dissolved in dimethylformamide (45 mL) and 60% sodium hydride 180 mg, 4.48 mmol) was added. Ethyl bromoacetate (600 μ L, 5.37 mmol) was added. The reaction was stirred at room temperature overnight. The reaction was diluted with water, extracted with ethyl acetate, dried over $MgSO_4$ s, and concentrated under reduced pressure. Near quantitative yield. The compound was then prepared as described for Example 53. MW=376.41, mp. 193-196, CHN: THEORY: 70.20% C, 5.36% H, 7.44% N. ACTUAL: 69.89% C, 5.33% H, 7.39% N.

10

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Example 69

4-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl]-butyric acid
(179).



179

20

4-Benzylxyindole (2.0 g, 8.96 mmol) was dissolved in toluene (5 mL) and 60% sodium hydride (360 mg, 8.96 mmol) was added. The mixture was heated to 100°C for 20 minutes. The residue was taken up in dimethylformamide (20 mL) and γ -butyrolactone (1.38 mL, 17.9 mmol) was added. The reaction was

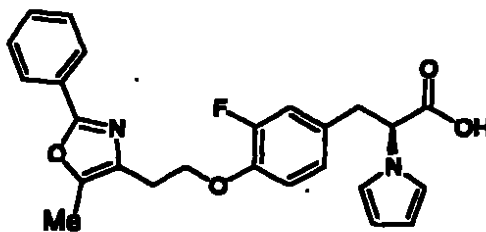
229

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heated to 150°C for 72 hours. The reaction was diluted with water, acidified with 2N HCl, extracted with ethyl acetate, dried over MgSO₄, and concentrated under reduced pressure. The compound was then prepared as described for PD#0333941-0000. 73140x27, mw=404.4, mp 151-154; CHN; THEORY: 71.27% C, 5.98% H, 6.93% N; ACTUAL: 71.01% C, 6.02% H, 6.83% N.

Example 70

3-(3-Fluoro-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-(S)-pyrrol-1-yl-propionic acid (180).



180

Prepared as described for Example 1 using 5-fluoro-L-tyrosine. 73140x37 MW=434.4, mp=154-155, CHN; THEORY: 69.11% C, 5.34% H, 6.45% N; ACTUAL: 69.09% C, 5.25% H, 6.26% N

Example 71

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyridin-4-yl-propionic acid (181).

The title compound was synthesized as described in Example 12 using ethyl 4-pyridyl acetate as starting material (45 mg, 7%). ¹H NMR *d*₆-DMSO δ 2.30 (s, 3H) 2.85 (m, 3H) 3.02 (m, 2H) 4.11 (t, 2H) 6.80 (d, 2H) 7.06 (d, 2H) 7.44 (m, 3H) 7.65 (d, 2H) 7.84 (d, 2H) 8.63 (s, 2H)...MS(M-44)(minus carboxylate): 385.1. Anal. Calcd for C₂₆H₂₄O₄N₂ · 1.67 H₂O: C, 68.05; H, 5.82; N, 6.11. Found: C, 68.03; H, 6.00; N, 6.11.

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Example 72

2-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-2H-tetrazole (186a) and 1-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1H-tetrazole (186b).

5

A mixture of 5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1H-tetrazole (185a) and 5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-2H-tetrazole (185b) (0.23 g, 0.51 mmol), methyl iodide (0.20 mL, 3.2 mmol), TEA (0.22 mL, 1.6 mmol) was refluxed in acetonitrile for 1 hour. The reaction was cooled and concentrated. The residue was dissolved in EtOAc, washed with water, dried (MgSO₄). The products were isolated by column chromatography (25% to 35% EtOAc/hex)

10

2-methyl tetrazole (186a): front running spot (13%). C₂₈H₂₇N₅O₂ Mass
Calc. = 465.555; M+1(obs) = 466.2. HPLC: c-18 column, 87%, 20/80
(CH₃CN/H₂O) to 90/10 over 20 min, rt=18.876 min, 254 nm. Lack of NOE
between H35/H23 confirmed regiochemistry.

15

1-methyl tetrazole (186b): bottom running spot (24%). C₂₈H₂₇N₅O₂ Mass
Calc. = 465.555; M+1(obs) = 466.2. HPLC: c-18 column, 85%, 20/80
(CH₃CN/H₂O) to 90/10 over 20 min, rt=17.438 min, 254 nm. Presence of NOE
between H35/H23 confirmed regiochemistry.

20

5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1H-tetrazole (185a) and 5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-2H-tetrazole (185b) were prepared in the following manner.

25

(a) 5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1H-tetrazole (185a) and 5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-2H-tetrazole (185b).

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3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionitrile (184, 1.81 g, 4.47 mmol) was refluxed with azidotributyltin (2.3 mL, 8.4 mmol) in 20 mL dioxane for 25 hours. The reaction was concentrated and the residue dissolved in Et₂O. HCl gas was bubbled through the solution. The solution was concentrated and triturated with hexanes and the hexanes layer decanted. The remaining residue was purified by column chromatography (25% to 100% EtOAc/hex) to obtain a mixture of 5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1H-tetrazole (185a) and 5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-2H-tetrazole (185b) (23% recovered starting material, 14% product).

(b) 3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionitrile (184).

The title compound was prepared according to General Procedure B using 3-(4-hydroxy-phenyl)-2-phenyl-propionitrile (183) and 2-(5-methyl-2-phenyloxazol-4-yl) ethanol as starting materials.

(c) 3-(4-Hydroxy-phenyl)-2-phenyl-propionitrile (183).

The benzyl group in 3-(4-Benzoyloxy-phenyl)-2-phenyl-propionitrile (182) was removed by hydrogenolysis using 10% Pd/C as a catalyst.

(d) 3-(4-Benzoyloxy-phenyl)-2-phenyl-propionitrile (182).

This compound was synthesized in the same manner as Compound 89 using benzyl cyanide (2.4 mL, 21 mmol) and compound 88 (5.85 g, 21 mmol) as starting materials.

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Example 73

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-2-yl-propionic acid (189).

5 This compound was prepared as described in Example 32 using 2-thiophen-3-yl-propionic acid ethyl ester (188) and compound 88 as the starting materials. Mp: 165-166°C. Anal. Calcd for $C_{26}H_{25}O_4NS$: C, 69.78; H, 5.63; N, 3.13. Found: C, 69.65; H, 5.88; N, 3.00.

10 2-Thiophen-2-yl-propionic acid ethyl ester was prepared in the following manner.

(a) 2-Thiophen-2-yl-propionic acid ethyl ester (188).

15 This compound was prepared as described for compound 89, using ethyl 2-thiophene acetate and methyl iodide as starting materials.

Example 74

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-3-yl-propionic acid (191).

20 This compound was prepared as described in Example 32 using 2-thiophen-3-yl-propionic acid ethyl ester (191) and compound 88 as the starting materials. Mp: 165-166°C. Anal. Calcd for $C_{26}H_{25}O_4NS$: C, 69.78; H, 5.63; N, 3.13. Found: C, 69.65; H, 5.88; N, 3.00.

25 2-Thiophen-3-yl-propionic acid ethyl ester (190) was prepared in the following manner.

(a) 2-Thiophen-3-yl-propionic acid ethyl ester (190).

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-216-

This compound was prepared as described for compound 89, using ethyl 3-thiophene acetate and methyl iodide as starting materials.

Example 75

5 N-(2,2-Dimethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionyl)-methanesulfonamide (192).

10 Compound 102 (0.493 g, 1.3 mmol), 4-DMAP (0.169 g, 1.4 mmol), EDC (0.266 g, 1.4 mmol) and methanesulfonamide (0.132g, 1.4 mmol) were combined in 10 mL CH₂Cl₂ and stirred at ambient temperature overnight. The reaction was washed with 1N HCl and H₂O, dried (MgSO₄). Column chromatography (25% to 40% EtOAc/Hex) was used to isolate the pure compound which was recrystallized from Et₂O/hex (73 mg, 12%). Mp: 112-113°C. Anal. Calcd for C₂₄H₂₈O₅N₂S: C, 63.14; H, 6.18; N, 6.14. Found: C, 63.46; H, 6.20; N, 6.09.

Example 76

15 N-(2-Fluoro-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionyl)-methanesulfonamide (193).

20 Compound 103 (1.003 g, 2.3 mmol) was subjected to the same conditions as above for PD 0333437. (32 mg, 2%). Mp: 118-120°C. Anal. Calcd for C₂₈H₂₇O₅N₂SF: C, 64.35; H, 5.21; N, 5.36. Found: C, 64.02; H, 5.00; N, 5.15.

Example 77

3-{3-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-isoxazol-5-yl}-2-pyrrol-1-yl-propionic acid (199).

25 3-{3-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-isoxazol-5-yl}-2-pyrrol-1-yl-propionic acid methyl ester (198, 0.2 g, 0.5 mmol) was hydrolyzed by using General Procedure A. (0.16 g, 81%). Mp: 143-144°C. Anal. Calcd for C₂₂H₂₁O₅N₃ · 0.17 H₂O: C, 64.32; H, 5.20; N, 10.23. Found: C, 64.37; H, 5.24; N, 9.79. C₂₂H₂₁N₃O₅ Mass Calc. = 407.426; M+1(obs) = 408.2.

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-217-

3-{3-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-isoxazol-5-yl}-2-pyrrol-1-yl-propionic acid methyl ester (198) was prepared in the following manner.

- 5 (a) 3-{3-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-isoxazol-5-yl}-2-pyrrol-1-yl-propionic acid methyl ester (198).

10 The title compound was synthesized as described for Compound 89 using Pyrrol-2-yl-acetic acid methyl ester (197, 0.139 g, 1 mmol) and 5-Bromomethyl-3-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-isoxazole (196, 0.359 g, 0.99 mmol) as starting materials. (0.20 g, 48%).

- (b) Pyrrol-2-yl-acetic acid methyl ester (197).

15 General procedure C (for synthesis of compound 1) was used to synthesize pyrrol-2-yl-acetic acid methyl ester using glycine methyl ester hydrochloride (1.26 g, 10 mmol) as the starting material, heating only until the reaction starts to yellow (7-10 min). (1.01 g, 73%)

- 20 (c) 5-Bromomethyl-3-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-isoxazole (196).

25 Carbon tetrabromide (1.99 g, 6 mmol) was added to a 0°C solution of {3-[2-(195, 5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-oxazol-5-yl}-methanol (0.91 g, 3 mmol) and Ph₃P (1.99 g, 7.6 mmol) in 15 mL THF. The reaction was stirred at 0°C for 1 hour. The reaction was concentrated and isolated by column chromatography (15% to 20% EtOAc/hex). (0.62 g, 57%)

- 30 (d) {3-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-oxazol-5-yl}-methanol (195).

25

-218-

Sodium borohydride (0.20 g, 5.3mmol) was added in portions to a suspension of 3-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-oxazole-5-carboxylic acid methyl ester (194, 0.57 g, 1.7 mmol) in 15 mL MeOH at 0°C. The reaction was allowed to warm to ambient temperature for 2 hours. The reaction was quenched with water and the solvent removed. The residue was dissolved in Et₂O, washed with water and brine, dried (MgSO₄) and concentrated to give a white solid. (0.47 g, 90%)

(e) 3-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-oxazole-5-carboxylic acid methyl ester (194).

General Procedure B was used to synthesize this compound using methyl 3-hydroxy-5-isoxazole carboxylate (1.423 g, 10 mmol) and 2-(5-methyl-2-phenyl-oxazol-4-yl)ethanol (2.141 g, 10.5 mmol) as starting materials. (2.71 g, 83%)

Example 78

2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid (204).

General Procedure A was used to hydrolyze 3-{4-[3-(5-Methyl-2-phenyl-oxazol-r-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (203) to provide the final product, (0.54 g, 80%). C₃₂H₃₀N₂O₄ Mass Calc. = 506.601; M+1(obs) = 507.3. Anal. Calc'd for C₃₂H₃₀O₄N₂ 0.17 H₂O: C, 75.35; H, 5.95; N, 5.49. Found: C, 75.19; H, 6.06; N, 5.28.

3-{4-[3-(5-Methyl-2-phenyl-oxazol-r-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (203) was prepared in the following manner.

(a) 3-{4-[3-(5-Methyl-2-phenyl-oxazol-r-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (203).

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The title compound was synthesized as described for compound 89 using methyl 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetate (0.55 g, 2.3 mmol) and 4-[3-(4-Bromomethyl-phenyl)-propyl]-5-methyl-2-phenyl-oxazole (202, 0.78 g, 2.1 mmol) as starting materials.

5

(b) 4-[3-(4-Bromomethyl-phenyl)-propyl]-5-methyl-2-phenyl-oxazole (202).

10

Carbon tetrabromide (2.65 g, 8 mmol) was added to a 0°C solution of {4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-methanol (202, 1.25 g, 4 mmol) and Ph₃P (2.67 g, 10 mmol) in 40 mL THF. The reaction was stirred at 0°C for 1 hour. The reaction was concentrated and isolated by column chromatography (5% EtOAc/hex). (0.83 g, 53%).

15

(c) {4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-methanol (202).

20

{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-methanol (201, 6.63 g, 21.8 mmol) is reduced using Raney nickel in 1:1 MeOH/THF. The catalyst is filtered off and the filtrate concentrated to obtain a pale yellow solid. (6.45 g, 100%).

25

(d) {4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-methanol (201).

30

5-Methyl-2-phenyl-4-prop-2-ynyloxazole (compound 117, 11.74 g, 60 mmol) in 50 mL pyrrolidine was added to a suspension of 4-iodobenzyl alcohol (10.71 g, 46 mmol), tetrakis(triphenylphosphine) palladium (0) (5.30 g, 4.6 mmol) and copper (I) iodide (0.431 g, 2.3 mmol) in 50 mL pyrrolidine. The reaction was complete after alkyne addition. The reaction was concentrated and the residue dissolved in EtOAc. The organic layer was washed with sat'd NH₄Cl and brine, filtered, dried (MgSO₄). The crude material was triturated with CH₂Cl₂ and

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-220-

filtered. This process is repeated twice to obtain two crops of desired material which was recrystallized from EtOAc/hex. (6.63 g, 48%)

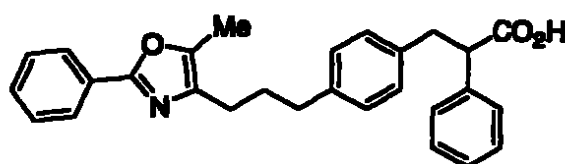
Example 79

2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (205).

This compound was synthesized as described for Example 32 using methyl 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetate and compound 88 as starting materials. Mp: 120°C. MS(M+1):509.2.

Example 80

3-{4-[3-(5-Methyl-2-phenyloxazol-4-yl)-propyl]-phenyl}-2-phenylpropionic acid (211).



211

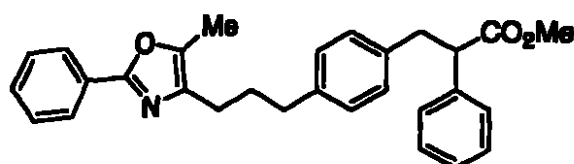
A solution of 3-{4-[3-(5-Methyl-2-phenyloxazol-4-yl)-propyl]-phenyl}-2-phenylpropionic acid (210, 0.86 g, 1.96 mmol) in MeOH was treated with excess LiOH (1.0 M) and stirred at ambient temperature. After completion, the reaction was diluted with sat. NH₄Cl and extracted with EtOAc. The combined organic extracts were dried with brine followed by Na₂SO₄ and chromatographed (5 to 60 % EtOAc in hexanes) to provide 120 mg of the title compound. MS *m/z* 426 (M+H)⁺.

3-{4-[3-(5-Methyl-2-phenyloxazol-4-yl)-propyl]-phenyl}-2-phenylpropionic acid methyl ester (210) was prepared in the following manner.

(a) 3-{4-[3-(5-Methyl-2-phenyloxazol-4-yl)-propyl]-phenyl}-2-phenylpropionic acid methyl ester (210).

928

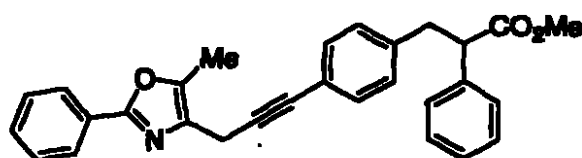
-221-



210

5 A solution of 3-[4-[3-(5-methyl-2-phenyloxazol-4-yl)-prop-1-ynyl]-phenyl]-2-phenylpropionic acid methyl ester (209, 0.89 g, 2.0 mmol) in MeOH (50 mL) with 20 % Pd/C (0.13 g) was stirred under an atmosphere of H₂ for 13.5 h. Filtration provided the desired compound in 96 % yield.

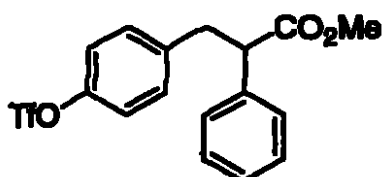
10 (b) 3-[4-[3-(5-Methyl-2-phenyloxazol-4-yl)-prop-1-ynyl]-phenyl]-2-phenylpropionic acid methyl ester (208).



208

15 A mixture of 5-methyl-2-phenyl-4-prop-ynyloxazole (1.0, 5.07 mmol), 2-phenyl-3-(4-trifluoromethanesulfonylphenyl)-propionic acid methyl ester (207, 1.52 g, 3.9 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.32 g, 0.27 mmol) were combined in 3 mL DMF. The mixture was purged with nitrogen before adding TEA (0.163 mL, 1.17 mmol) and CuI (15 mg, 0.078 mmol). After stirring at 80 °C for 18 h, the mixture was diluted with EtOAc and washed with
20 water and brine, dried over Na₂SO₄, and chromatographed (5 % EtOAc in hexanes) to give 0.89 g of the title compound.

(c) 2-Phenyl-3-(4-trifluoromethanesulfonylphenyl)-propionic acid methyl ester (207).



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-222-

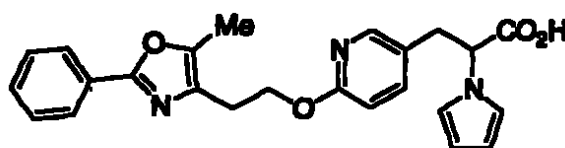
207

A solution of 2-phenyl-3-(4-hydroxyphenyl)-propionic acid methyl ester (2.0 g, 7.8 mmol) in CH₂Cl₂ (25 mL) was purged with nitrogen. TEA (1.2 mL, 8.6 mmol) was added, and the mixture was cooled to 0 °C.

Trifluoromethanesulfonic anhydride (1.38 mL, 8.2 mmol) was added, and the reaction was allowed to warm to ambient temperature. After 18 h, the reaction was diluted with EtOAc, washed with 5 % NaHCO₃, water, and brine, dried over Na₂SO₄, and chromatographed (10 % EtOAc in hexanes) to provide 2.84 g of the title compound.

Example 81

3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-pyrrol-1-yl-propionic acid (216).



15

216

A solution of 5-bromomethyl-2-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridine (215, 0.73 g, 1.96 mmol) and pyrrole-1-yl-acetic acid methyl ester (0.54 g, 3.91 mmol) in 20 mL anhydrous THF was purged with dry nitrogen and treated with lithium bis(trimethylsilyl)amide (1.0 M in THF, 3.9 mL). After stirring at room temperature for 18 h, the reaction was diluted with EtOAc and washed with sat. NH₄Cl. TLC and MS of the organic layer indicate hydrolysis of some of the methyl ester. The organic layer was washed with brine and evaporated to dryness. The resultant oil was dissolved in MeOH and treated with excess LiOH (1 M in water). After stirring 18 h at room temperature, the mixture was evaporated to dryness and partitioned between EtOAc and pH 7 buffer. Upon washing the organic layer with brine, the product precipitated. The solid was

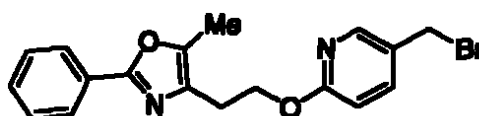
240

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collected, washed with water and ether, and dried under vacuum to constant weight to provide 287 mg (34 %) of the title compound. MS m/z 465 (M+H)⁺.

5-Bromomethyl-2-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridine (215) was prepared in the following manner.

(a) 5-Bromomethyl-2-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridine (215).



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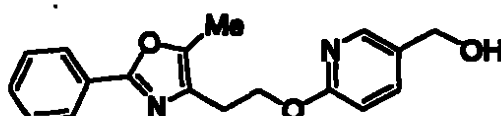
10

{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-methanol (214, 1.50 g, 4.83 mmol) was dissolved in anhydrous CH₂Cl₂ (40 mL) and purged with dry nitrogen and cooled to 0 °C. Triphenylphosphine (1.34 g, 5.12 mmol) was added, followed by N-bromosuccinimide (0.95 g, 5.36 mmol). After 30 min, the reaction mixture was concentrated and chromatographed (5 to 25 % EtOAc in hexanes) to give 1.19g (66 %) of the bromide.

15

(b) {6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-methanol (214).

20



214

To a nitrogen-purged solution of 6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-nicotinic acid methyl ester (213, 1.87 g, 5.53 mmol) in anhydrous ether (50 mL) was added lithium aluminum hydride (1.0 M in THF, 11.1 mL) over about 5 min. The bath was removed, and the reaction was allowed to stir at ambient temperature for 4 h. HCl (1.0 M) was added, and the reaction was stirred at room temperature overnight. Na₂CO₃ (5) was added to pH 8. The mixture

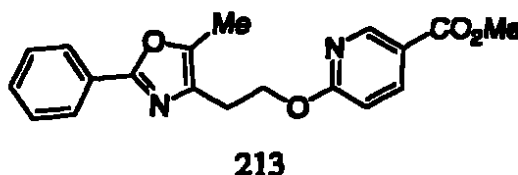
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-224-

was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4 , and evaporated to provide the title compound in 62 % yield.

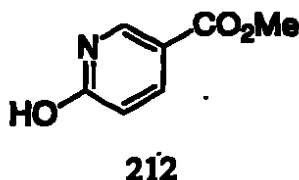
- 5 (c) 6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-nicotinic acid methyl ester (213).



- 10 6-Hydroxynicotinic acid methyl ester (212, 3.47 g, 22.7 mmol), 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethanol (5.53 g, 27.2 mmol), and triphenylphosphine (7.1 g, 27.2 mmol) were combined in anhydrous THF (100 mL), purged with dry nitrogen, and cooled to 0 °C. DEAD (5.9 g, 34.0 mmol) was added over 5 min, and the mixture was allowed to slowly warm to ambient temperature overnight. The THF was removed under reduced pressure, and the residue was partitioned between EtOAc and 5 % NaHCO_3 . The organic layer was washed with 5 % NaHCO_3 , water, and brine, dried over anhydrous Na_2SO_4 , and chromatographed (5 to 40 % EtOAc in hexanes) to provide 2.98 g (39 %) of the title compound.

20

- (d) 6-Hydroxynicotinic acid methyl ester (212).



- 25 A suspension of 6-hydroxynicotinic acid (10.0 g, 71.9 mmol) in anhydrous CH_2Cl_2 (80 mL, plus 3 drops of DMF) was purged with nitrogen, cooled to 0 °C, and treated with oxalyl chloride (7.53 mL, 86.3 mmol). After 18 h at room temperature, excess methanol was cautiously added. The reaction was evaporated

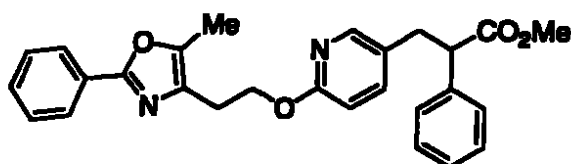
242

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and chromatographed (20 % EtOAc in hexanes) to provide 2.74 g (25 %) of the title compound.

Example 82

3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-phenylpropionic acid methyl ester (217).

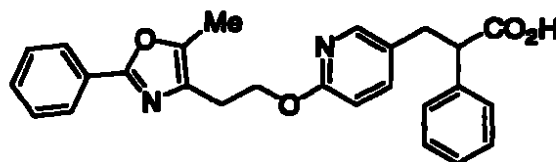


217

The title compound was prepared in a manner analogous to PD-341440-0000 utilizing methyl phenylacetate in 79 % yield. MS m/z 443 (M+H)⁺.

Example 83

3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-phenylpropionic acid (218).



218

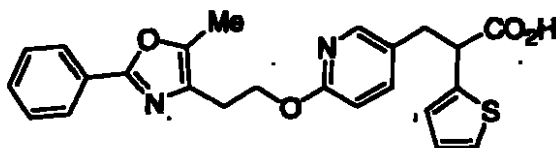
A solution of 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-phenylpropionic acid methyl ester (0.52 g, 1.18 mmol) in 10 mL MeOH was treated with excess 1 M LiOH. After completion, the reaction was diluted with sat. NH₄Cl and extracted with EtOAc. The combined organic extracts were dried with brine followed by Na₂SO₄ and chromatographed (5 to 60 % EtOAc in hexanes) to provide 323 mg of the title compound. MS m/z 429 (M+H)⁺.

Example 84

3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-thiophen-2-yl-propionic acid (219).

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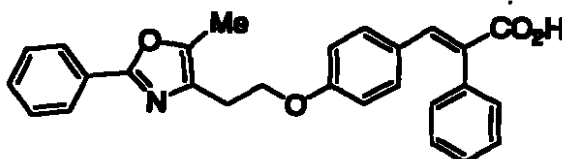


219

5 The title compound (155 mg) was prepared in a manner analogous to PD-341440-0000 utilizing methyl thiophen-2-ylacetate. MS m/z 435 (M+H)⁺.

Example 85

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-acrylic acid (222).



10

222

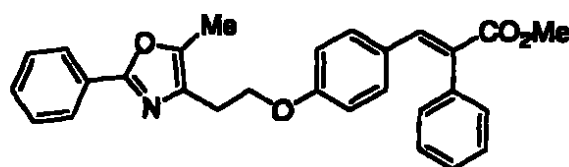
15 A solution of 3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-acrylic acid methyl ester (221, 0.31 g, 0.71 mmol) in 10 mL MeOH was treated with excess 1 M LiOH. After completion, the reaction was diluted with sat. NH₄Cl and extracted with EtOAc. The combined organic extracts were dried with brine followed by Na₂SO₄ and chromatographed (5 to 60 % EtOAc in hexanes) to provide 241 mg of the title compound. MS m/z 426 (M+H)⁺.

20 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-acrylic acid methyl ester (221) was prepared in the following manner.

(a) 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-acrylic acid methyl ester (221)

244

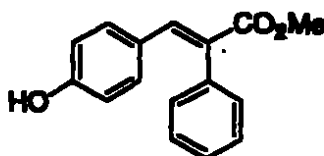
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221

Triphenylphosphine (0.57 g, 2.17 mmol), 3-(4-hydroxyphenyl)-2-phenylacrylic acid methyl ester (220, 0.46g, 1.81 mmol), and 2-(5-methyl-2-phenyloxazol-4-yl)-ethanol (0.44 g, 2.17 mmol) were combined in THF (10 mL), purged with nitrogen, and cooled to 0 °C. DEAD (0.43 mL, 2.71 mmol) was added, and the mixture was allowed to warm to ambient temperature overnight. The reaction was diluted with EtOAc and washed with 5 % NaHCO₃, water, and brine, dried over Na₂SO₄, and chromatographed (0 to 60 % EtOAc in hexanes) to provide 0.31 g of the title compound.

(b) 3-(4-Hydroxyphenyl)-2-phenylacrylic acid methyl ester (220).



220

15

A suspension of 3-(4-hydroxyphenyl)-2-phenylacrylic acid (2.5 g, 10.4 mmol) in MeOH (50 mL) was treated with H₂SO₄ (1 mL) and refluxed 72 h. Most of the solvent was removed under reduced pressure, and the residue was diluted with EtOAc and washed with 5 % NaHCO₃, water, and brine. Chromatography (5 to 60 % EtOAc in hexanes) provided 0.46 g of the title compound as a white solid.

20

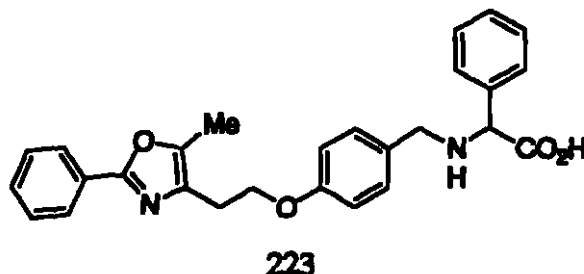
Example 87

{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid (223).

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245

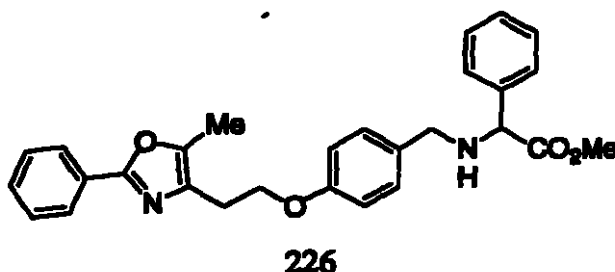
-228-



A solution of {4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester (0.30 g, 0.66 mmol) in 10 mL MeOH was treated with excess 1 M LiOH. After completion, the reaction was diluted with sat. NH₄Cl and extracted with EtOAc. The combined organic extracts were dried with brine followed by Na₂SO₄ and chromatographed (5 to 60 % EtOAc in hexanes) to provide the title compound in 71 % yield. MS *m/z* 443 (M+H)⁺.

Example 87

{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester (226).



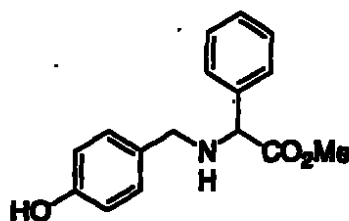
Triphenylphosphine (2.00 g, 7.65 mmol), (4-hydroxybenzylamino)-phenylacetic acid methyl ester (225, 1.73 g, 6.38 mmol), and 2-(5-methyl-2-phenyloxazol-4-yl)-ethanol (1.56 g, 7.65 mmol) were combined in THF (25 mL), purged with nitrogen, and cooled to 0 °C. DEAD (1.20 mL, 7.65 mmol) was added, and the mixture was allowed to warm to ambient temperature overnight. The reaction was diluted with EtOAc and washed with 5 % NaHCO₃, water, and brine, dried over Na₂SO₄, and chromatographed (0 to 60 % EtOAc in hexanes) to provide 1.52 g of the title compound. MS *m/z* 457 (M+H)⁺.

246

-229-

(4-Hydroxybenzylamino)-phenylacetic acid methyl ester (225) was prepared in the following manner.

5 (a) (4-Hydroxybenzylamino)-phenylacetic acid methyl ester (225).

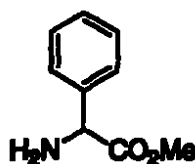


225

Phenylglycine methyl ester (224, 1.63 g, 9.87 mmol) and 4-hydroxybenzaldehyde (0.80 g, 6.58 mmol) were combined in 1 % HOAc in MeOH (100 mL). Sodium cyanoborohydride (0.62 g, 9.87 mmol) was added, and the mixture was allowed to stir at room temperature. After 18 hours, the reaction was concentrated under reduced pressure and partitioned between EtOAc and 5 % NaHCO₃. The organic layer was washed with water and brine, dried over Na₂SO₄, and chromatographed (0 to 50 % EtOAc in hexanes) to provide the title compound in 97 % yield.

15

(b) Phenylglycine methyl ester (224).



224

20

Phenylglycine (10.0 g, 66.2 mmol) was dissolved in 100 mL MeOH with 2 mL H₂SO₄ and refluxed overnight. The reaction was concentrated under reduced pressure and partitioned between ether and water. Solid NaHCO₃ was added to pH 7. The aqueous layer was extracted with ether and EtOAc. The combined

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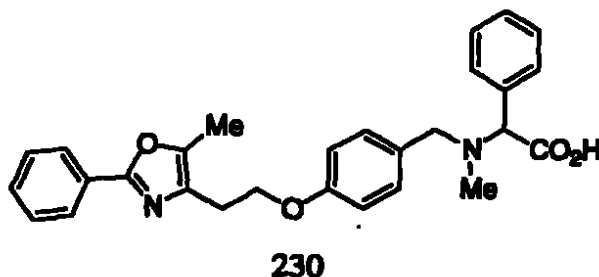
247

-230-

organic extracts were washed with water and brine, and dried over Na_2SO_4 to provide 1.63 g of the title compound.

Example 88

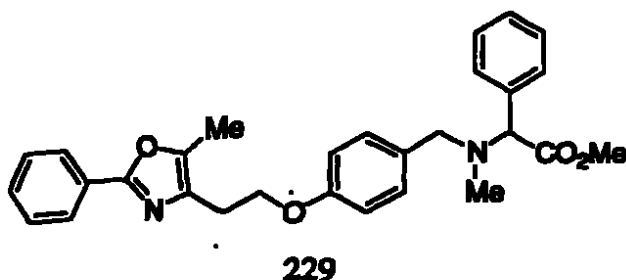
5 Methyl-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid (230).



10 A solution of methyl-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester (229, 0.18 g, 0.38 mmol) in 5 mL MeOH was treated with excess 1 M LiOH. After completion, the reaction was diluted with sat. NH_4Cl and extracted with EtOAc. The combined organic
15 extracts were dried with brine followed by Na_2SO_4 and chromatographed (5 to 60 % EtOAc in hexanes) to provide the title compound in 62 % yield. MS m/z 457 ($\text{M}+\text{H}$)⁺.

Methyl-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester (229) was prepared in the following manner.

20 (a) Methyl-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester (229).

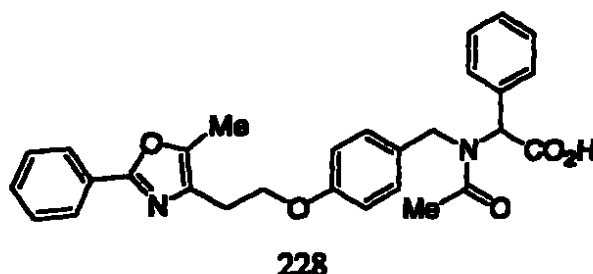


248

-231-

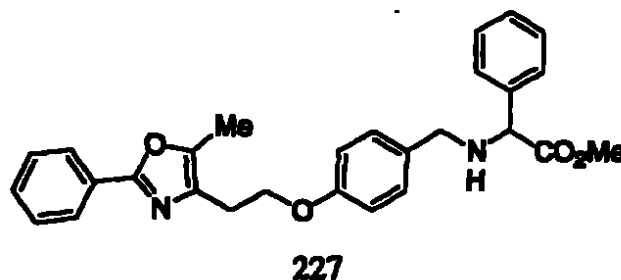
A solution of {4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester (228, 0.30 g, 0.66 μ mol), formaldehyde (37 % in water, 0.26 mL, 3.10 mmol), and HOAc (0.056 mL, 0.99 mmol) in CH₃CN (5 mL) was treated with sodium cyanoborohydride (45 mg, 0.72 mmol). After 18 h, the product was purified as in the preparation of (4-hydroxybenzylamino)-phenylacetic acid methyl ester to give the title compound in 65 % yield. MS m/z 471 (M+H)⁺.

(b) Acetyl-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid (228).



A solution of acetyl-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester (227, 0.25 g, 0.50 mmol) in 5 mL MeOH was treated with excess 1 M LiOH. After completion, the reaction was diluted with sat. NH₄Cl and extracted with EtOAc. The combined organic extracts were dried with brine followed by Na₂SO₄ and chromatographed (5 to 60 % EtOAc in hexanes) to provide the title compound in 55 % yield. MS m/z 485 (M+H)⁺.

(c) Acetyl-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester (227).



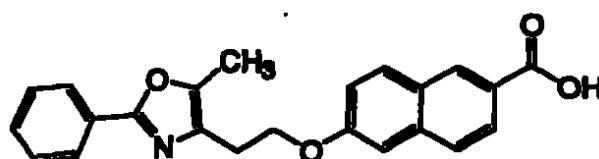
249

-232-

A solution of {4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester (0.30 g, 0.66 mmol) and triethylamine (0.10 mL, 0.72 mmol) in CH_2Cl_2 (5 mL) was treated with acetyl chloride (0.050 mL, 0.69 mmol). After 18 h, the reaction mixture was evaporated and chromatographed (5 to 20 % EtOAc in hexanes) to give the title compound in 85 % yield. MS m/z 499 ($\text{M}+\text{H}$)⁺.

Example 89

6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-naphthalene-2-carboxylic acid (231).

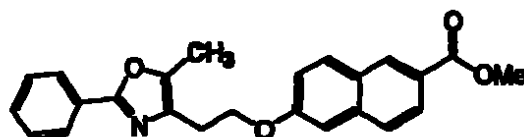


232

A solution of 6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-naphthalene-2-carboxylic acid methyl ester (231) in MeOH (5 mL) was treated with excess LiOH (1.0 M) and stirred at ambient temperature. After completion, the reaction was diluted with sat. NH_4Cl and extracted with EtOAc. The combined organic extracts were dried with brine followed by Na_2SO_4 and chromatographed (5 to 60 % EtOAc in hexanes) to provide 131 mg of the title compound. MS m/z 374 ($\text{M}+\text{H}$)⁺.

6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-naphthalene-2-carboxylic acid methyl ester (231) was prepared in the following manner.

(a) 6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-naphthalene-2-carboxylic acid methyl ester (231).



290

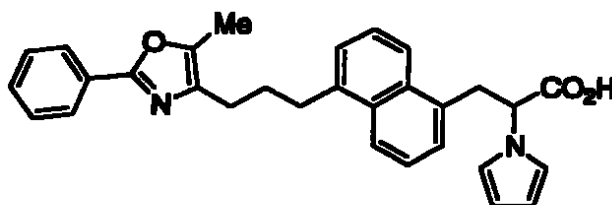
-233-

231

Triphenylphosphine (1.65 g, 6.29 mmol), 6-hydroxynaphthalene-2-carboxylic acid methyl ester (1.06 g, 5.24 mmol), and 2-(5-methyl-2-phenyloxazol-4-yl)-ethanol (1.28 g, 6.29 mmol) were combined in THF (25 mL),
5 purged with nitrogen, and cooled to 0 °C. DEAD (1.00 mL, 6.29 mmol) was added, and the mixture was allowed to warm to ambient temperature overnight. The reaction was diluted with EtOAc and washed with 5 % NaHCO₃, water, and brine, dried over Na₂SO₄, and chromatographed (0 to 60 % EtOAc in hexanes) to
10 provide 0.58 g of the title compound.

Example 90

3-{5-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-naphthalen-1-yl}-2-pyrrol-1-yl-propionic acid (237).



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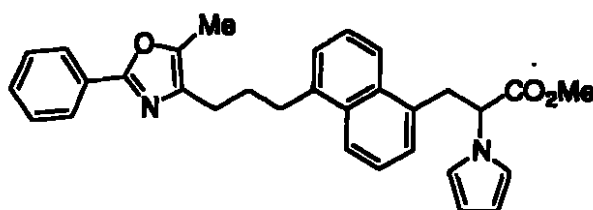
237

A solution of 3-{5-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-naphthalen-1-yl}-2-pyrrol-1-yl-propionic acid methyl ester (236, 0.15 g, 0.31 mmol) in methanol was treated with excess LiOH (1 M in water). After stirring at
20 ambient temperature overnight, the reaction mixture was diluted with water and washed with ether. The aqueous layer was acidified with 1 M HCl and extracted with EtOAc. The combined extracts were washed with brine, dried over Na₂SO₄, and evaporated to provide 84 mg (56 %) of the title compound.

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3-{5-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-naphthalen-1-yl}-2-pyrrol-1-yl-propionic acid methyl ester (236) was prepared in the following manner.

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236

- (a) 3-{5-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-naphthalen-1-yl}-2-pyrrol-1-yl-propionic acid methyl ester (236).

5

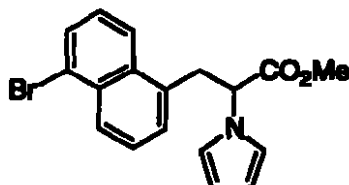
A solution of 4-allyl-5-methyl-2-phenyl-oxazole (0.38 g, 1.89 mmol) was purged with nitrogen, cooled to 0 °C, and treated with 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 7.6 mL). The reaction was allowed to slowly warm to ambient temperature overnight. The 9-BBN adduct solution was transferred to a purged mixture of 3-(5-bromo-naphthalen-1-yl)-2-pyrrol-1-yl-propionic acid methyl ester (235, 0.52 g, 1.45 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloro palladium(II) complex with dichloromethane (1:1) (0.10 g, 0.15 mmol), cesium carbonate (1.32 g, 4.06 mmol), triphenylarsine (44 mg, 0.15 mmol), water (0.31 mL, 17.4 mmol), and DMF (4 mL). The reaction stirred at room temperature 24 h before cooling to 0 °C and adding NaOAc (3.0 M, 6 mL) and H₂O₂ (30 %, 3 mL). After 2 h, the mixture was diluted with water and extracted with a 7:1 mixture of ether/EtOAc. The combined organic extracts were washed with water and brine, dried over anhydrous Na₂SO₄, evaporated, and flashed (5 to 50 % EtOAc in hexanes) to give 0.15 g (22 %) of the title compound.

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- (b) 3-(5-bromo-naphthalen-1-yl)-2-pyrrol-1-yl-propionic acid methyl ester (235).



235

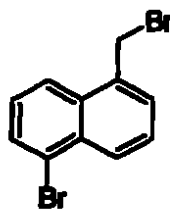
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-235-

A solution of 1-bromo-5-bromomethyl-naphthalene (234, 1.05 g, 3.50 mmol) and pyrrole-1-yl-acetic acid methyl ester (0.97 g, 7.00 mmol) in anhydrous THF (20 mL) was purged with nitrogen and treated with $\text{LiN}(\text{TMS})_2$ (1.0 M, 7.0 mL). After about 30 min at ambient temperature, the reaction was heated to 50 °C for 48 h. The reaction mixture was concentrated and chromatographed (5 to 50 % EtOAc in hexanes) to provide 0.80 g (64 %) of the title compound.

(c) 1-bromo-5-bromomethyl-naphthalene (234).



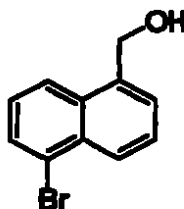
234

10

A solution of (5-bromo-naphthalen-1-yl)-methanol (233, 1.13 g, 4.77 mmol) in anhydrous CH_2Cl_2 (20 mL) was purged with nitrogen and cooled to 0 °C. Triphenylphosphine (1.33 g, 5.05 mmol) was added followed by NBS (0.94 g, 5.29 mmol). After 30 min at 0 °C, the mixture was concentrated and chromatographed twice (5 to 25 % EtOAc in hexanes) to give 1.05 g (73 %) of the title compound.

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(d) (5-bromo-naphthalen-1-yl)-methanol (233).



233

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A solution of 5-bromonaphthalene-1-carboxylic acid (2.50 g, 9.96 mmol, PD-59348, Lot P) in anhydrous THF (100 mL) was purged with nitrogen. Borane (1.0 M in THF, 20 mL) was added, and the reaction was refluxed for 6 h. The reaction was cooled to ambient temperature, treated with 10 mL MeOH, and

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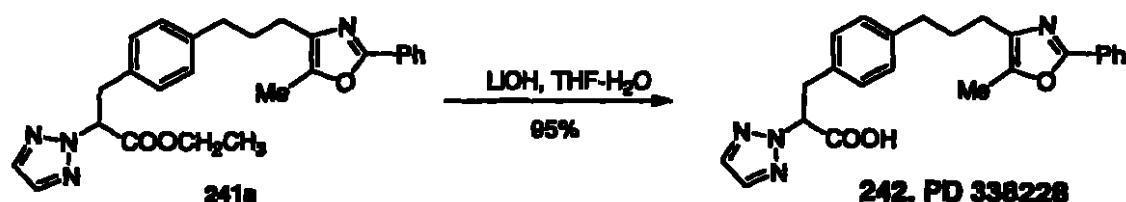
953

-236-

stirred at ambient temperature overnight. The mixture was concentrated, dissolved in ether, washed with 1 M NaOH, water, and brine, dried over anhydrous Na₂SO₄. The crude product was purified by crystallization from CH₂Cl₂/hexanes to provide 1.5 g (64 %) of the title compound.

5 Example 91

3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-1,2,3-triazol-1-yl-propionic acid (242).

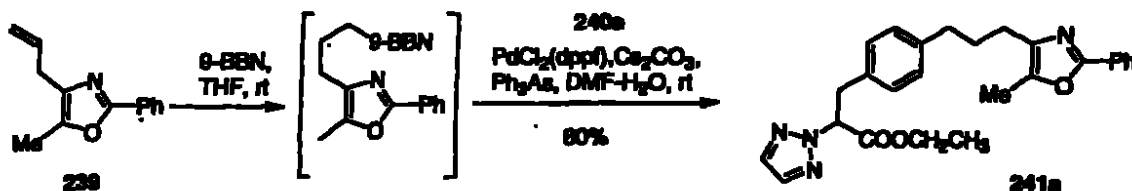


10 GENERAL METHOD 91. 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-
propyl]-phenyl]-2-1,2,3-triazol-2-yl-propionic acid ethyl ester (241a) (2.37 g,
5.331 mmol) was dissolved in THF (60 mL) and water was added (15 mL).
Lithium hydroxide monohydrate (0.335 g, 8.00 mmol) was incorporated and the
mixture was stirred at room temperature for 1 h. The organic solvent was removed
15 in the rotary evaporator at room temperature. The aqueous residue was diluted
with water and extracted with Et₂O (2 × 45 mL). A flow of air was passed through
the aqueous phase to remove residual ether. The aqueous phase was then acidified
with 10% HCl. The precipitated solid was separated by vacuum filtration and
washed with water. The solid was dried on air overnight and then at 45 °C for 14 h
20 to give the title compound as an off-white solid (2.11 g, 95%): mp (softens or
melts between 50-85 °C; forms another solid that melts at 153-153.5 °C); ¹H
NMR (CDCl₃, 400 MHz) δ 7.98-7.96 (m, 2 H), 7.62 (s, 2 H), 7.43-7.40 (m, 3 H),
7.03 (d, *J* = 8.1 Hz, 2 H), 6.98 (d, *J* = 8.1 Hz, 2 H), 5.52 (dd, *J* = 10.4 and 5.0 Hz,
1 H), 3.65-3.49 (m, 2 H), 2.58 (t, *J* = 7.6 Hz, 2 H), 2.48 (t, *J* = 7.6 Hz, 2 H), 2.27
25 (s, 3 H), 1.93 (m, *J* = 7.6 Hz, 2 H); CIMS *m/z* 417 (M+1). HPLC: purity: 100%;
column: symmetry C₁₈, 4.6 × 150 mm, 5 μm; mobile phase: A: water + 0.1% TFA,
B: acetonitrile + 0.1 TFA; retention time: 15.914 min; wavelength: 254 nm.

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3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,3-triazol-2-yl-propionic acid ethyl ester (241a) was prepared in the following manner.

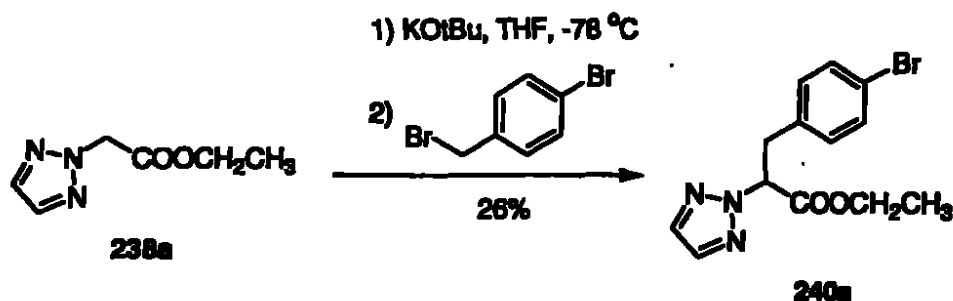
- 5 (a) 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,3-triazol-2-yl-propionic acid ethyl ester (241a).



GENERAL METHOD 92-a. A solution of 5-methyl-2-phenyl-4-prop-2-enyloxazole (compound 239) (1.716 g, 8.614 mmol) in dry THF (25 mL) was added to a 0.5 M solution of 9-BBN in THF (34.45 mL) at 0 °C under a nitrogen atmosphere. The ice bath was removed and the mixture was stirred at room temperature overnight. The 9-BBN adduct was then added to a flask containing bromide 238a (2.148 g, 6.626 mmol), PdCl₂(dppf) (0.485 g, 0.662 mmol), Cs₂CO₃ (3.88 g, 11.927 mmol), Ph₃As (0.203 g, 0.662 mmol), water (1.4 mL, 79.5 mmol) and DMF (15 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 2 days. At the end of this time, the mixture was cooled in an ice bath and 3 M NaOAc (16 mL) was added followed by 30% H₂O₂ (8 mL). Stirring was continued for 2 h, allowing the reaction to warm to room temperature slowly. Water (100 mL) was added followed by Et₂O and EtOAc. The phases were separated and the aqueous phase was extracted with Et₂O-EtOAc (60:10 mL × 4). The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent removed. Purification by column chromatography on silica gel eluting with EtOAc in hexanes (0 to 22%) afforded ester 241a as a thick oil (2.37 g, 80%): ¹H NMR (CDCl₃, 400 MHz) δ 7.98-7.95 (m, 2 H), 7.61 (s, 2 H), 7.44-7.38 (m, 3 H), 7.03 (d, *J* = 8.3 Hz, 2 H), 7.00 (d, *J* = 8.3 Hz, 2 H), 5.50 (dd, *J* = 10.2 and 5.6 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.71-3.57 (m, 2 H), 2.58 (t, *J* = 7.6 Hz, 2 H), 2.46 (t, *J* = 7.6 Hz, 2 H), 2.24 (s, 3 H), 1.93 (m, *J* = 7.6 Hz, 2 H), 1.19 (t, *J* = 7.1 Hz, 3 H); CIMS *m/z* 445 (M+1).

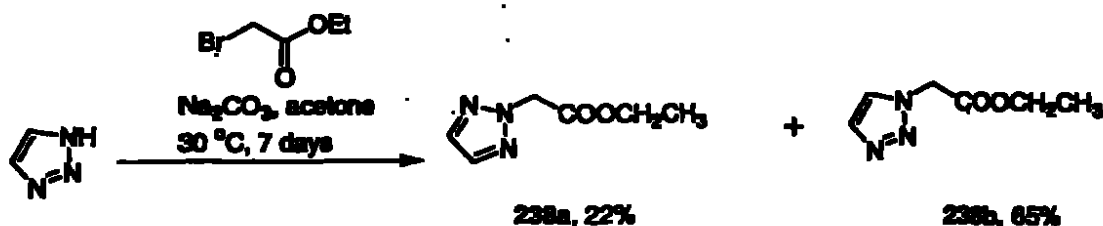
- (b) Bromide 240a (PD 0341554).

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General Method 91-b. Ester 238a (3.0 g, 19.336 mmol) was dissolved in dry THF (60 mL) and cooled to -78°C under a nitrogen atmosphere. A 1.0 M solution of potassium *tert*-butoxide in THF (20.3 mL, 20.3 mmol) was added. The mixture was stirred at -78°C for 45 min. A solution of 4-bromobenzyl bromide (5.56 g, 22.236 mmol) in THF (20 mL) was added. The reaction was allowed to reach room temperature slowly and then stirred at room temperature for 6 days. The mixture was quenched with water (60 mL) and diluted with Et_2O and EtOAc. The phases were separated and the aqueous phase was extracted with Et_2O -EtOAc (50:5 mL $\times$ 3). The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent removed. Purification by column chromatography on silica gel eluting with EtOAc in hexanes (0 to 16%) afforded the title compound as an oil (1.668 g, 26%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.62 (s, 2 H), 7.32 (d, $J = 8.5$ Hz, 2 H), 6.97 (d, $J = 8.5$ Hz, 2 H), 5.48 (dd, $J = 10.4$ and 5.4 Hz, 1 H), 4.19 (q, $J = 7.1$ Hz, 2 H), 3.70-3.55 (m, 2 H), 1.20 (t, $J = 7.1$ Hz, 3 H); CIMS m/z 324 (M) $^+$.

(c) 2-(2H-1,2,3-Triazol-2-yl)ethyl acetate (238a).



The title compound was prepared following the procedure described by Kume et. al. (Kume, M.; Kubota, T.; Kimura, Y.; Nakashimizu, H.; Motokawa, K.; Nakano, M. *J. Antibiotics* 1993, 46, 177-192.) Following this procedure,

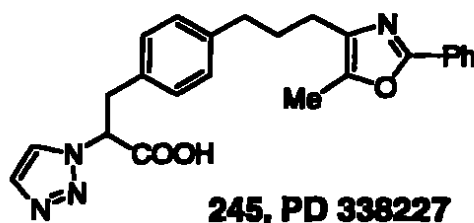
-239-

starting from 1*H*-1,2,3-triazole (18.17 g, 0.263 mol), ester 238a was obtained as a liquid (9.2 g, 22%) after column chromatography on silica gel eluting with EtOAc in hexanes (0 to 55%): ¹H NMR (CDCl₃, 400 MHz) δ 7.68 (s, 2 H), 5.23 (s, 2 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 1.27 (t, *J* = 7.1 Hz, 3 H); CIMS *m/z* 156 (*M*+1).

- 5 From the same purification, the *N*-1 alkylated product 238b was obtained as the major product (26.45 g, 65%): ¹H NMR (CDCl₃, 400 MHz) δ 7.75 (d, *J* = 1.0 Hz, 1 H), 7.71 (d, *J* = 1.0 Hz, 1 H), 5.19 (s, 2 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H); CIMS *m/z* 156 (*M*+1).

Example 92

- 10 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-1,2,3-triazol-1-yl-propionic acid (245).



- 15 Prepared from ester 244 (1.0 g, 2.249 mmol) following General Method 92. The title compound was obtained as white solid (0.854 g, 91%): mp 162-163.5 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.93 (m, 2 H), 7.66 (s, 1 H), 7.63 (s, 1 H), 7.41 (m, 3 H), 7.01 (d, *J* = 8.0 Hz, 2 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 5.62 (dd, *J* = 8.3 and 6.1 Hz, 1 H), 3.46-3.35 (m, 2 H), 2.56 (t, *J* = 7.3 Hz, 2 H), 2.48 (t, *J* = 7.3 Hz, 2 H), 2.28 (s, 3 H), 1.89 (m, 2 H); CIMS *m/z* 417 (*M*+1).

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3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-1,2,3-triazol-1-yl-propionic acid methyl ester (244) was prepared in the following manner.

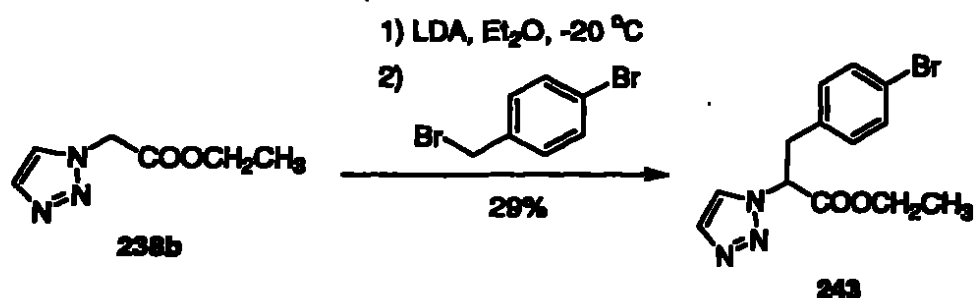
- 25 (a) 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-1,2,3-triazol-1-yl-propionic acid methyl ester (244).

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-240-

The title compound was prepared from bromide 243 (1.2 g, 3.702 mmol) using the General Method 92a. Ester 244b was obtained as a thick oil (1.00 g, 61%): ¹H NMR (CDCl₃, 400 MHz) δ 7.98 (m, 2 H), 7.66 (s, 1 H), 7.63 (s, 1 H), 7.44-7.38 (m, 3 H), 7.06 (d, J = 8.0 Hz, 2 H), 6.93 (d, J = 8.0 Hz, 2 H), 5.59 (dd, J = 8.3 and 6.6 Hz, 1 H), 4.19 (q, J = 7.3 Hz, 2 H), 3.49-3.38 (m, 2 H), 2.61 (t, J = 7.6 Hz, 2 H), 2.48 (t, J = 7.3 Hz, 2 H), 2.27 (s, 3 H), 1.96 (m, 2 H), 1.21 (t, J = 7.1 Hz, 3 H); CIMS *m/z* 445 (M+1).

(b) Bromide 243



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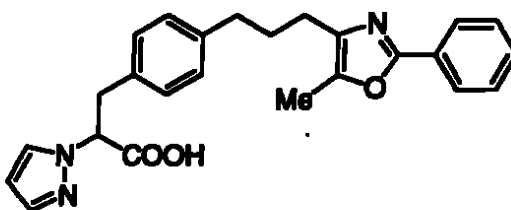
A solution of diisopropylamine (2.0 mL, 14.18 mmol) in Et₂O (30 mL) was cooled at -20 °C under a nitrogen atmosphere. A 1.6 M solution of BuLi in hexanes (9.7 mL, 15.47 mmol) was added. The mixture was stirred for 25 min. A solution of ester 238b (2.0 g, 12.89 mmol) in Et₂O (20 mL) was added. The mixture was stirred for 30 min. A solution of 4-bromobenzyl bromide (3.70 g, 14.82 mmol) in Et₂O (20 mL) was incorporated. The reaction mixture was kept at -20 °C for 2.5 h and then allowed to warm to room temperature slowly. Stirring was continued at room temperature for 24 h. At this time, the mixture was quenched with water and diluted with Et₂O. The phases were separated and the aqueous layer was extracted with Et₂O (3 × 40 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent removed. Purification by column chromatography over silica gel afforded bromide 243 as a pale yellow oil (1.21 g, 29%): ¹H NMR (CDCl₃, 400 MHz) δ 7.67 (d, J = 0.7 Hz, 1 H), 7.63 (d, J = 1.0 Hz, 1 H), 7.35 (d, J = 8.5 Hz, 2 H), 6.89 (d, J = 8.5 Hz, 2 H), 5.54 (dd, J = 8.7 and 6.5 Hz, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 3.51-3.39 (m, 2 H), 1.22 (t, J = 7.3 Hz, 3 H); CIMS *m/z* 324 (M)⁺.

958

-241-

Example 93

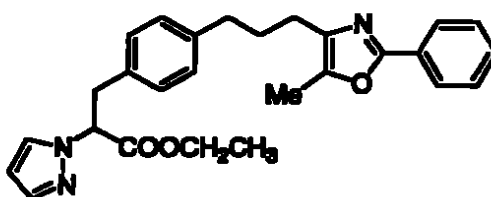
3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrazol-1-yl-propionic acid (249).

**249, PD 339165**

5 The title compound was prepared from 248 (0.735 g, 1.657 mmol) by the General Method 92. PD 0339165 was obtained as a yellowish solid (0.602 g, 87%); mp 75-77 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.96 (m, 2 H), 7.61 (d, J = 2.0 Hz, 1 H), 7.40 (m, 3 H), 7.09 (d, J = 2.0 Hz, 1 H), 7.02 (d, J = 8.0 Hz, 2 H), 6.80 (d, J = 8.0 Hz, 2 H), 6.19 (t, J = 2.2 Hz, 1 H), 5.02 (dd, J = 10.0 and 4.6 Hz, 1 H),
10 3.45-3.27 (m, 2 H), 2.59 (t, J = 7.6 Hz, 2 H), 2.47 (t, J = 7.6 Hz, 2 H), 2.27 (s, 3 H), 1.93 (m, 2 H); CIMS m/z 416 (M+1). Anal. calcd for C₂₅H₂₃N₃O₃·0.4 H₂O: C, 71.04; H, 6.15; N, 9.94. Found: C, 70.76; H, 6.08; N, 9.91.

15 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrazol-1-yl-propionic acid ethyl ester (248) was prepared in the following manner.

(a) 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrazol-1-yl-propionic acid ethyl ester (4c).

**248**

20

Prepared from bromide 247 (0.760 g, 2.351 mmol) by the General Method 95. Purification by column chromatography afforded 248 (0.735 g, 70%); ¹H NMR (CDCl₃, 400 MHz) δ 7.96 (m, 2 H), 7.52 (d, J = 1.5 Hz, 1 H), 7.44-7.38 (m,

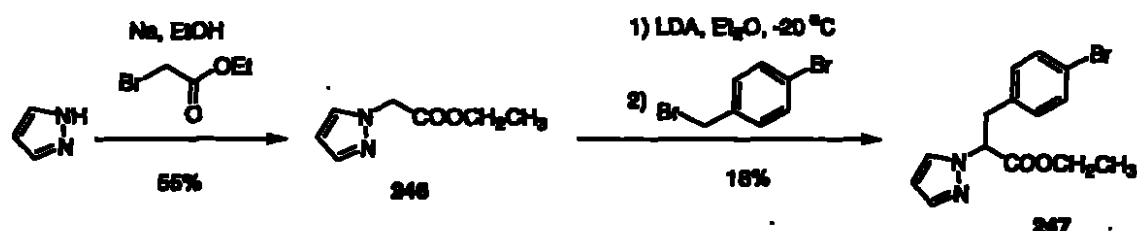
259

-242-

4 H), 7.05 (d, $J = 8.0$ Hz, 2 H), 6.94 (d, $J = 8.0$ Hz, 2 H), 6.22 (t, $J = 2.1$ Hz, 1 H), 5.11 (t, $J = 7.7$ Hz, 1 H), 4.16 (q, $J = 7.1$ Hz, 2 H), 2.60 (t, $J = 7.6$ Hz, 2 H), 2.47 (t, $J = 7.3$ Hz, 2 H), 2.26 (s, 3 H), 1.95 (m, 2 H), 1.18 (t, $J = 7.1$ Hz, 3 H); CIMS m/z 444 ($M+1$).

5

(b) Pyrazol-1-yl acetic acid ethyl ester (247).



Sodium (3.7 g, 161 mmol) was dissolved in ethanol (150 mL) with ice cooling. Pyrazole (10 g, 146 mmol) was added. Ethyl bromoacetate (32 mL, 292 mmol) was added dropwise. The ice bath was removed after the addition was finished and the mixture stirred at room temperature for 5 days. The solvent was removed and the residue diluted with cold 6 N HCl and extracted with Et₂O (2 × 50 mL). The aqueous layer was neutralized with solid sodium carbonate, then it was extracted with chloroform. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent removed. Purification by distillation afforded 247 as an oil (12.495 g, 55%): bp 65-80 °C at 2 mm Hg; ¹H NMR (CDCl₃, 400 MHz) δ 7.55 (d, $J = 1.7$ Hz, 1 H), 7.47 (d, $J = 2.2$ Hz, 1 H), 6.32 (t, $J = 2.0$ Hz, 1 H), 4.92 (s, 2 H), 4.22 (q, $J = 7.1$ Hz, 2 H), 1.27 (t, $J = 7.1$ Hz, 3 H); CIMS m/z 155 ($M+1$).

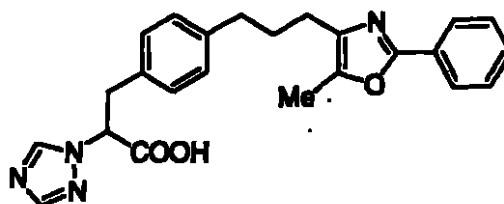
Bromide 246. The title compound was prepared from ester 246 (2.0 g, 12.97 mmol) by General Method 92-b. Bromide 247 was obtained as a thick oil (0.768 g, 18%): ¹H NMR (CDCl₃, 400 MHz) δ 7.53 (d, $J = 1.7$ Hz, 1 H), 7.36 (d, $J = 2.0$ Hz, 1 H), 7.33 (d, $J = 8.5$ Hz, 2 H), 6.88 (d, $J = 8.3$ Hz, 2 H), 5.07-5.03 (m, 1 H), 4.18 (q, $J = 7.0$ Hz, 2 H), 3.49-3.39 (m, 2 H), 1.20 (t, $J = 7.1$ Hz, 3 H); CIMS m/z 323 (M)⁺.

260

-243-

Example 94

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,4-triazol-1-yl-propionic acid (253).

**253, PD 336683**

5

Prepared from ester 252 (0.492 g, 1.106 mmol) by the General Method 92.

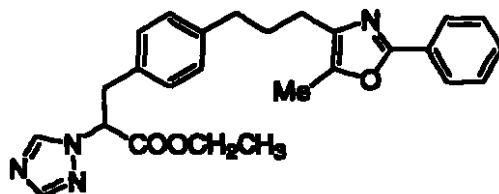
The title compound was obtained as a white solid (0.33 g, 72%): mp 169-171 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.16 (s, 1 H), 8.00 (m, 2 H), 7.98 (s, 1 H), 7.45-7.40 (m, 3 H), 7.01 (d, J = 8.0 Hz, 2 H), 6.87 (d, J = 8.0 Hz, 2 H), 5.24 (t, J = 7.1 Hz, 1 H), 3.42 (d, J = 7.1 Hz, 2 H), 2.57 (t, J = 7.6 Hz, 2 H), 2.52 (t, J = 7.6 Hz, 2 H), 2.28 (s, 3 H), 1.93 (m, 2 H); CIMS m/z 417 (M+1).

10

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,4-triazol-1-yl-propionic acid ethyl ester (252) was prepared in the following manner.

15

(a) 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,4-triazol-1-yl-propionic acid ethyl ester (252).

**252**

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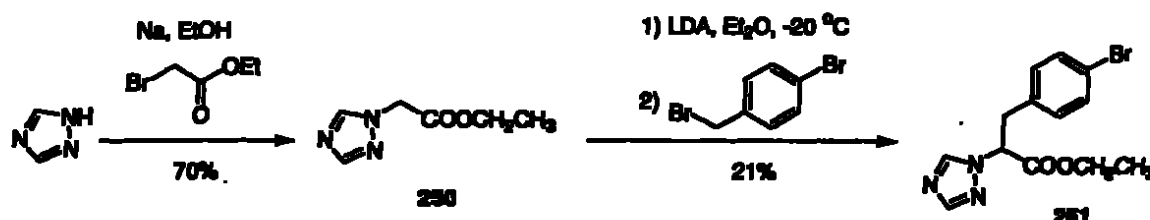
Prepared from bromide 251 (0.440 g, 1.357 mmol) by the General Method 95-a. The title compound was obtained as a thick oil (0.492 g, 82%): ¹H NMR (CDCl₃, 400 MHz) δ 8.08 (m, 2 H), 8.00 (s, 1 H), 7.94 (s, 1 H), 7.48-7.41 (m, 3 H), 7.06 (d, J = 8.0 Hz, 2 H), 6.88 (d, J = 8.0 Hz, 2 H), 5.17 (dd, J = 8.0 and 6.6 Hz, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 3.43 (d, J = 7.3 Hz, 2 H), 2.62 (t, J = 7.6 Hz, 2

261

-244-

H), 2.53 (d, $J = 7.3$ Hz, 2 H), 2.28 (s, 3 H), 1.23 (t, $J = 7.1$ Hz, 3 H); CIMS m/z 445 (M+1).

(b) Ethyl 2-1,2,4-Triazol-1-yl acetate (250) and Bromide (251).



Ester 250 was prepared following the procedure described by Ainsworth and Jones (Ainsworth, C.; Jones, R. G. *J. Am. Chem. Soc.* 1955, 77, 621-624). ¹H NMR (CDCl₃, 400 MHz) δ 8.19 (s, 1 H), 7.97 (s, 1 H), 4.96 (s, 2 H), 4.25 (q, $J = 7.1$ Hz, 2 H), 1.28 (t, $J = 7.1$ Hz, 3 H); CIMS m/z 156 (M+1).

Bromide 251. The title compound was prepared from ester 250 (1.0 g, 6.445 mmol) following the General Method III. Bromide 251 was obtained as a thick oil (0.447 g, 21%): ¹H NMR (CDCl₃, 400 MHz) δ 8.10 (s, 1 H), 7.98 (s, 1 H), 7.35 (d, $J = 8.3$ Hz, 2 H), 6.86 (d, $J = 8.5$ Hz, 2 H), 5.16 (dd, $J = 8.1$ and 6.7 Hz, 1 H), 4.22 (q, $J = 7.1$ Hz, 2 H), 3.46 (d, $J = 7.6$ Hz, 2 H), 1.23 (t, $J = 7.1$ Hz, 3 H); CIMS m/z 324 (M)⁺.

Example 95

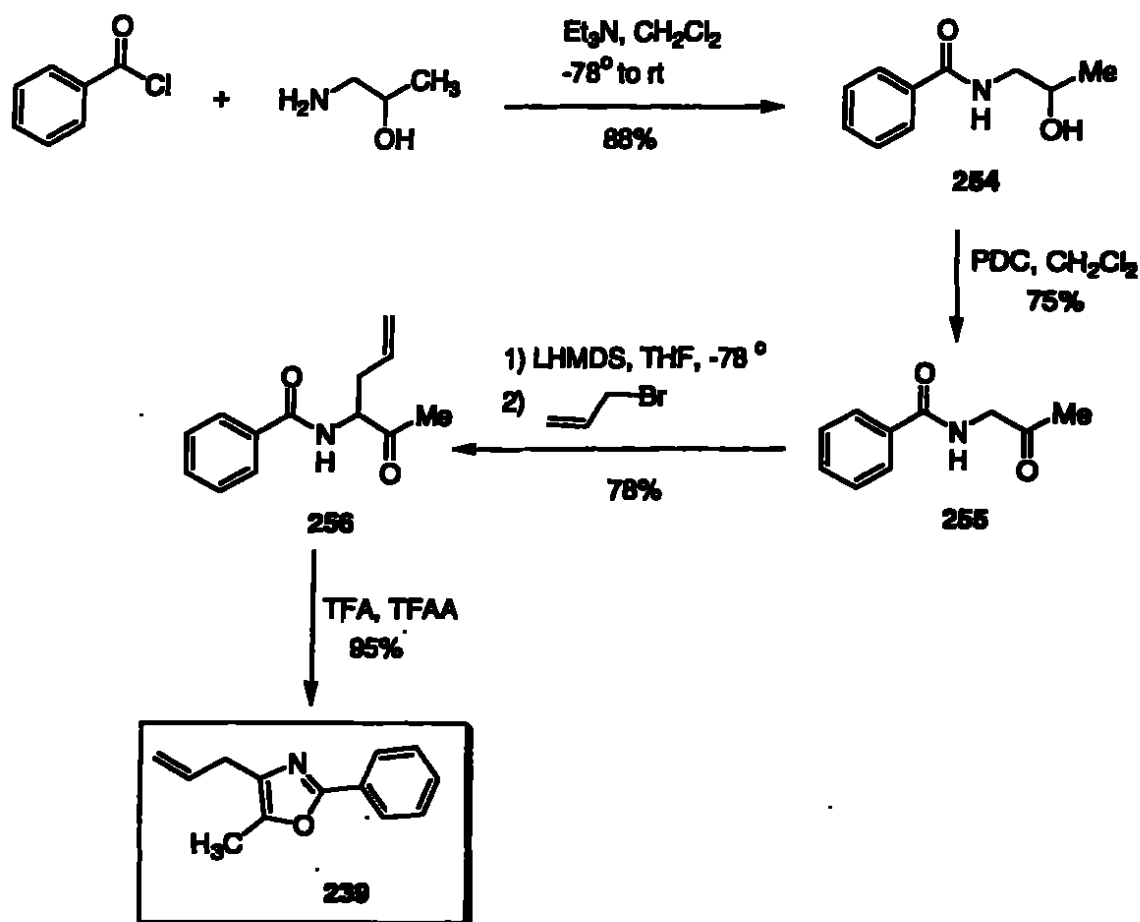
5-Methyl-2-phenyl-4-prop-2-enyloxazole (239).

Amide 256 (2.00 g, 9.205 mmol) was dissolved in TFA (16 mL) and TFAA (8 mL) was added. The mixture was heated at 35-40 °C for 16 h. The mixture was allowed to cool and the solvents removed under reduced pressure. The residue was diluted with saturated NaHCO₃ (50 mL) and solid NaHCO₃ was added to neutralize the mixture. It then was extracted with ethyl acetate (3 x 60 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and the solvent removed. Purification by flash chromatography on silica gel eluting with hexanes:ethyl acetate (15:1) gave oxazole 239 (1.75 g, 95%): ¹H

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NMR (CDCl₃, 400 MHz) δ 7.98 (d, J = 7.8 Hz, 2 H), 7.43-7.35 (m, 3 H), 6.03-5.93 (m, 1 H), 5.13 (dq, J = 16.9 and 1.7 Hz, 1 H), 5.09 (dq, J = 10.0 and 1.5 Hz, 1 H), 3.29 (d, J = 6.3 Hz, 2 H), 2.32 (s, 3 H); CIMS m/z 200 ($M + H$)⁺; IR 3070, 2924, 1638, 1450 cm⁻¹.



5.

Amide (256) was prepared in the following manner.

(a) *N*-(1-Acetylbut-3-enyl)benzamide (256).

10

Amide 255 (2.098 g, 11.839 mmol) was dissolved in THF (120 mL) and cooled to -78 °C under nitrogen. A 1.0 M solution of LHMDS in THF (11.9 mL, 11.9 mmol) was added and the mixture stirred for 40 min. A solution of allyl bromide (1.33 mL, 15.39 mmol) in THF (10 mL) was added. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was

15

diluted with brine and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were

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dried over MgSO_4 , filtered, and the solvent removed. Purification by flash chromatography on silica gel eluting with hexanes:ethyl acetate (2:1 to 1:1) gave amide 256 (2.02 g, 78%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.79 (d, $J = 7.1$ Hz, 2 H), 7.51-7.41 (m, 3 H), 6.95 (bd, $J = 5.4$ Hz, 1 H), 5.74-5.64 (m, 1 H), 5.17-5.12 (m, 2 H), 4.88 (dt, $J = 6.8$ and 5.4 Hz, 1 H), 2.85-2.78 (m, 1 H), 2.61-2.54 (m, 1 H), 2.28 (s, 3 H); CIMS m/z 218 ($M + H$) $^+$; IR 3263, 3081, 1719, 1632, 1556 cm^{-1} . Anal. calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.91; H, 7.03; N, 6.52.

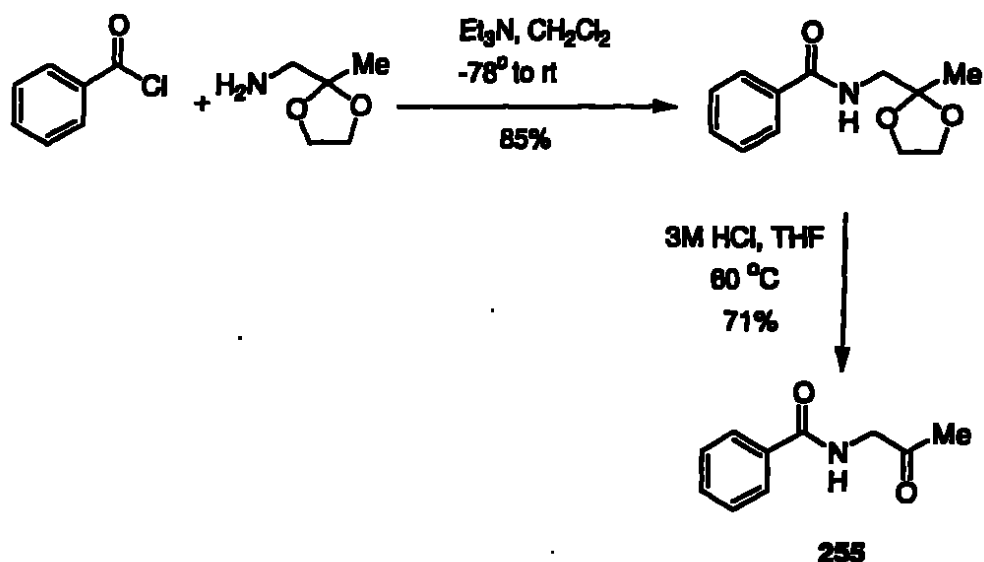
10 (b) Amide (255).

According to the method of Ellinger, L. P.; Goldberg, A. A. *J. Chem. Soc.* 1949, 263. Alcohol 254 (3.0 g, 16.7 mmol) was dissolved in CH_2Cl_2 (60 mL) and PDC (9.42 g, 25.0 mmol) was added. The mixture was stirred at room temperature for 24 and more PDC (9.42 g, 25.0 mmol) was added. Stirring was continued for 24 h. The mixture was diluted with ethyl acetate and filtered through a celite pad. The residue was then passed through a shoroom temperature silica gel column eluting with ethyl acetate. The solvent was removed and the residue was purified by flash chromatography on silica gel eluting with hexanes:ethyl acetate (1:1) containing MeOH (0 to 4%). This purification afforded amide 255 as a white solid (2.21 g, 75%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.76 (dd, $J = 7.0$ and 1.5 Hz, 2 H), 7.48-7.36 (m, 3 H), 6.96 (bs, 1 H), 4.30 (d, $J = 4.6$ Hz, 2 H), 2.21 (s, 3 H); CIMS m/z 178 ($M + H$) $^+$.

25 (b-1) An alternative route to benzamidoacetone 255 is shown below.
This route eliminates the PDC oxidation that is tedious to work up.
This method does not require chromatographic purification and affords amide 6 in 63% for the two steps.

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(c) *N*-(2-Hydroxypropyl)benzamide (254).

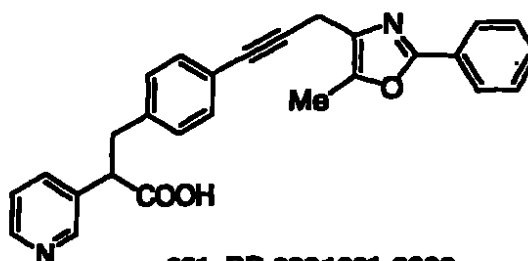
- 5 The title compound was prepared according to the method of Arai, K.; Tamura, S.; Masumizu, T.; Kawai, K.-I.; Nakajima, S.; Ueda, A. *Can. J. Chem.* 1990;68:903-907. A solution of DL-1-amino-2-propanol (3.4 mL, 43.2 mmol) and triethylamine (16.4 mL, 117.9 mmol) in CH_2Cl_2 (60 mL) under nitrogen was cooled at -78°C . Benzoyl chloride (4.6 mL, 39.3 mmol) was added dropwise. The mixture was allowed to warm slowly and stirred at room temperature overnight. It was then diluted with CH_2Cl_2 (100 mL) and washed with cold 5% HCl and brine. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over MgSO_4 , filtered, and the solvent removed. The residue was dried under vacuum to give amide 254 as a pale yellow solid (6.21 g, 88%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.75 (d, $J = 6.8$ Hz, 2 H), 7.49-7.39 (m, 3 H), 6.57 (bs, 1 H), 4.00 (m, 1 H), 3.67-3.61 (m, 1 H), 3.31-3.24 (m, 1 H), 1.22 (d, $J = 6.3$ Hz, 3 H).
- 10
- 15

Example 96

- 20 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-2-pyridin-3-yl-propionic acid (261).

265

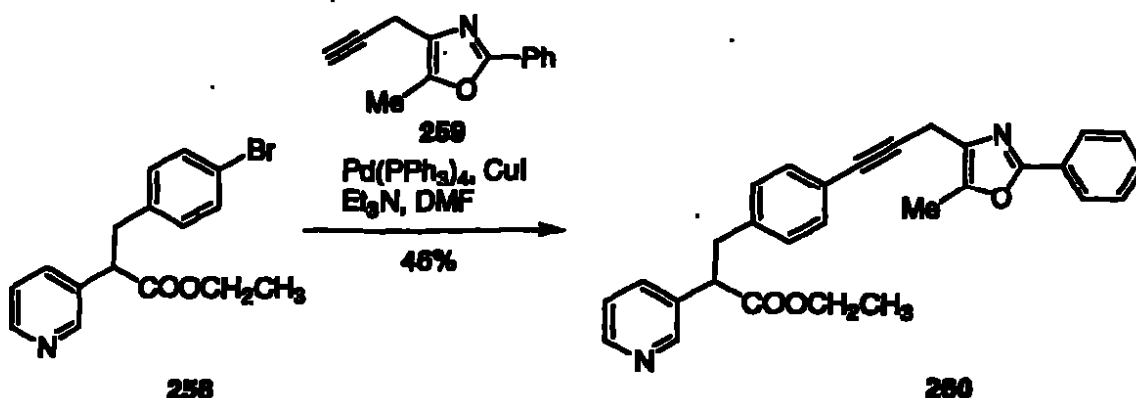
-248-



General Procedure 96. 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-2-pyridin-3-yl-propionic acid methyl ester 4a (0.284 g, 0.630 mmol) was dissolved in THF (15 mL) and water was added (5 mL). Lithium hydroxide monohydrate (0.040 g, 0.945 mmol) was incorporated and the mixture was stirred at room temperature for 1 h. The organic solvent was removed in the rotary evaporator at room temperature. The aqueous residue was diluted with water and extracted with Et₂O (2 × 45 mL). The aqueous phase was then acidified with 10% HCl. The product was extracted with CH₂Cl₂-CHCl₃. The extracts were dried over magnesium sulfate, filtered and the solvent removed. Purification by column chromatography on silica gel eluting with methanol in chloroform (0 to 10%) afforded the title compound as a solid (0.100 g, 37%): mp 115-117 °C; CIMS *m/z* 423.1 (M+1).

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-2-pyridin-3-yl-propionic acid methyl ester (260) was prepared in the following manner.

(a) 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-2-pyridin-3-yl-propionic acid methyl ester (260).

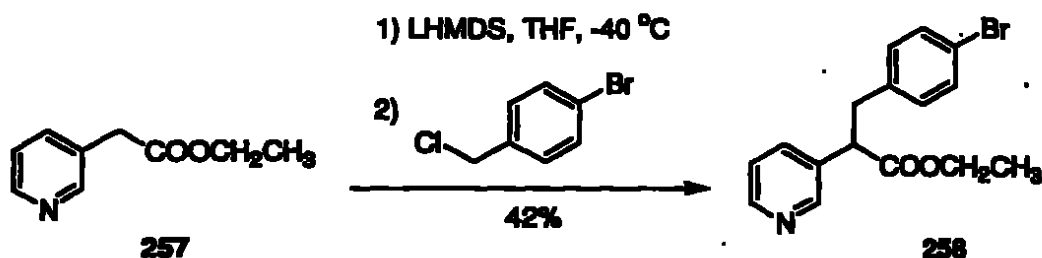


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General Procedure 96-a. Bromide 258.354 g, 4.051 mmol) and alkyne 259.04 g, 5.266 mmol) were dissolved in dry DMF (14 mL). Triethylamine (1.7 mL, 12.153 mmol) was added and nitrogen was passed through the reaction mixture for 0.5 h. Pd(PPh₃)₄ (0.328 g, 0.284 mmol) was added followed by CuI (0.154 g, 0.810 mmol). The mixture was heated at 80 °C for 24 h under nitrogen. The mixture was allowed to cool and diluted with water (100 mL) and Et₂O (70 mL). The phases were separated and the aqueous phase was extracted with Et₂O (4 × 60 mL). The combined organic extracts were washed with water and brine. Activated carbon was added and the mixture was boiled for 15-20 min. After cooling to room temperature, the mixture was dried over MgSO₄, filtered and the solvent removed. Purification by flash chromatography on silica gel eluting with ethyl acetate in hexanes (0 to 30%) gave pure 260 as a thick oil (0.838 g, 46%); CIMS *m/z* 451 (M + H)⁺.

(b) 3-(4-Bromo-phenyl)-2-pyridin-3-yl-propionic acid ethyl ester (258).



General Procedure 96-b Ester 257.63 g, 9.861 mmol) was dissolved in dry THF (20 mL) and cooled to -78°C under a nitrogen atmosphere. A 1.0 M solution of LHMDS in THF (10.8 mL, 10.8 mmol) was added. The mixture was stirred at -78 to -40 °C for 1.25 h. A solution of 4-chlorobenzyl bromide (2.43 g, 11.833 mmol) in THF (5 mL) was added. The reaction was allowed to reach room temperature overnight. The mixture was quenched with water (40 mL) and diluted with EtOAc (30 mL). The phases were separated and the aqueous phase was extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent removed. Purification by

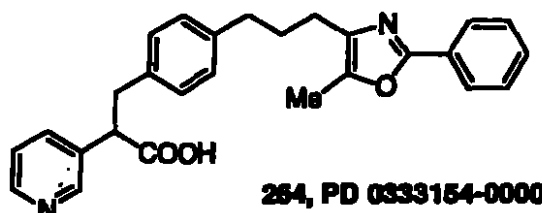
267

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column chromatography on silica gel eluting with EtOAc in hexanes (0 to 45%) afforded bromide 258 an oil (1.37 g, 42%); CIMS m/z 334.0 (M)⁺.

Example 97

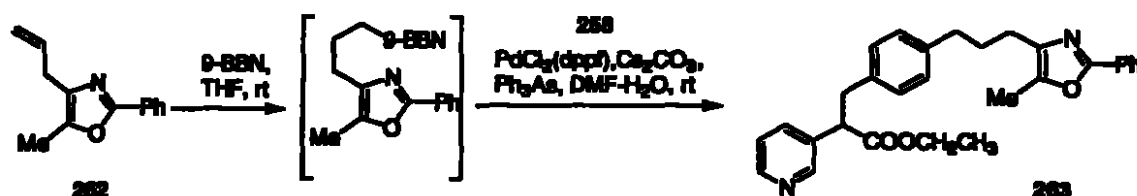
3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyridin-3-yl-propionic acid (264).



This compound was prepared from 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyridin-3-yl-propionic acid ethyl ester 263 following General Procedure 100. The title compound was obtained as a solid in 58% yield: mp 138-141 °C; CIMS m/z 427.2 (M+1). Anal. calcd for C₂₇H₂₆N₂O₃·1.0 H₂O: C, 72.95; H, 6.35; N, 6.30. Found: C, 72.64; H, 6.32; N, 5.97.

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyridin-3-yl-propionic acid ethyl ester (263) was prepared in the following manner.

(a) 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyridin-3-yl-propionic acid ethyl ester (263).



General Procedure 97-a. A solution of 5-methyl-2-phenyl-4-prop-2-enyloxazole (262) (0.20 g, 1.003 mmol) in dry THF (5 mL) was added to a 0.5 M solution of 9-BBN in THF (4 mL, 2.0 mmol) at 0 °C under a nitrogen atmosphere. The ice bath was removed and the mixture was stirred at room temperature overnight. The 9-BBN adduct was then added to a flask containing bromide 258

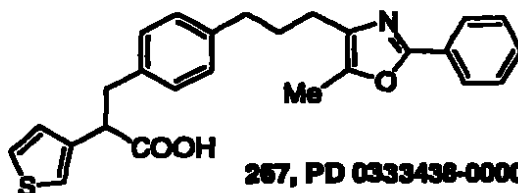
268

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(0.351 g, 1.053 mmol), PdCl₂(dppf) (0.073 g, 0.1 mmol), Cs₂CO₃ (0.588 g, 1.805 mmol), Ph₃As (0.030 g, 0.1 mmol), water (0.22 mL, 12 mmol) and DMF (5 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight. At the end of this time, the mixture was cooled in an ice bath and 3 M NaOAc (6 mL) was added followed by 30% H₂O₂ (3 mL). Stirring was continued for 2 h, allowing the reaction to warm to room temperature slowly. Water (50 mL) was added followed by Et₂O and EtOAc. The phases were separated and the aqueous phase was extracted with Et₂O-EtOAc (30:5 mL × 4). The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent removed. Purification by column chromatography on silica gel eluting with EtOAc in hexanes (0 to 25%) afforded ester 263 as a thick oil (0.272, 60%): CIMS *m/z* 455.2 (*M*+1).

Example 98

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyridin-3-yl-propionic acid (267).



This compound was prepared from 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-thiophen-3-yl-propionic acid ethyl ester (266).. The purification was carried out by chromatography on silica gel eluting with ethyl acetate in hexanes (0 to 45%). The title compound was obtained as a solid in 58% yield: mp 112-114 °C; CIMS *m/z* 432.1 (*M*+1). Anal. calcd for C₂₆H₂₃NO₃S: C, 72.36; H, 5.84; N, 3.25. Found: C, 72.18; H, 5.97; N, 3.04.

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-thiophen-3-yl-propionic acid ethyl ester (266) was prepared in the following manner.

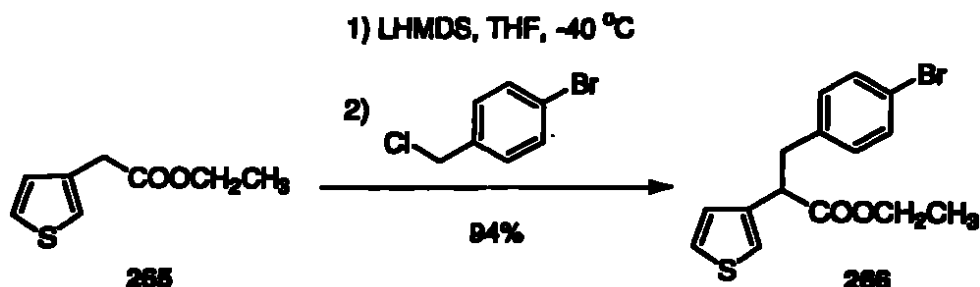
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- (a) 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-thiophen-3-yl-propionic acid ethyl ester (267).

This compound was prepared following General Procedure 98-a using bromide 266 for the Suzuki coupling. Ester 267 was obtained as thick oil in 78 yield: CIMS m/z 460.2 ($M+1$).

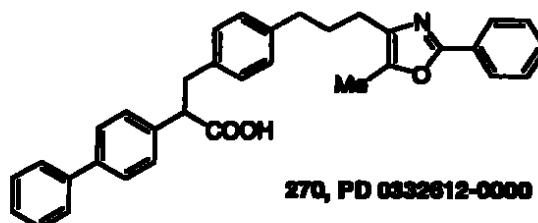
- (b) 3-(4-Bromo-phenyl)-2-thiophen-3-yl-propionic acid ethyl ester (266).



This compound 266 was prepared from ester 265 following General Procedure 98-b and obtained as thick oil in 94% yield: CIMS m/z 339.0 (M)⁺.

Example 99

2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid (270).



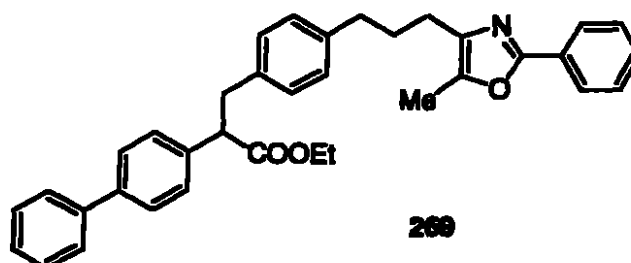
This compound was prepared from 2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid ethyl ester (269) by hydrolysis. The purification was carried out by chromatography on silica gel eluting with ethyl acetate in hexanes (0 to 30%). The title compound was obtained as a solid in 96% yield: mp 158-160 °C; CIMS m/z 502.3 ($M+1$). Anal. calcd for $C_{34}H_{31}NO_3$: C, 81.41; H, 6.23; N, 2.79. Found: C, 81.05; H, 6.42; N, 2.63.

270

-253-

2-Biphenyl-4-yl-3-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid ethyl ester (269) was prepared in the following manner.

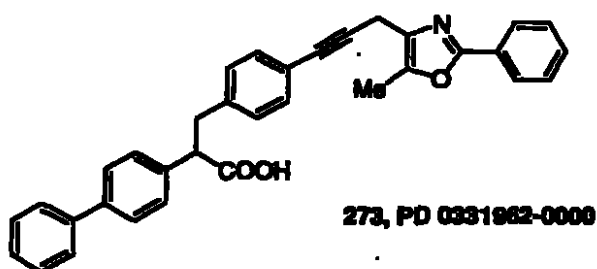
- 5 (a) 2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid ethyl ester (269).



- 10 2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid ethyl ester (268, See Example 104) (0.325 g, 0.618 mmol) was dissolved in THF (50 mL) and hydrogenated over Raney Nickel (1.0 g) overnight. The mixture was filtered off and the solvent removed. Purification by chromatography on silica gel eluting with ethyl acetate in hexanes gave 6c as clear oil (0.254 g, 77%): CIMS m/z 530.2 ($M+1$).

15 **Example 100**

2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid (273).



- 20 This compound was prepared from ester 272. The reaction mixture was heated at 80 °C for 7 h. The purification was carried out by chromatography on silica gel eluting with methanol in chloroform (0 to 6%). The title compound was

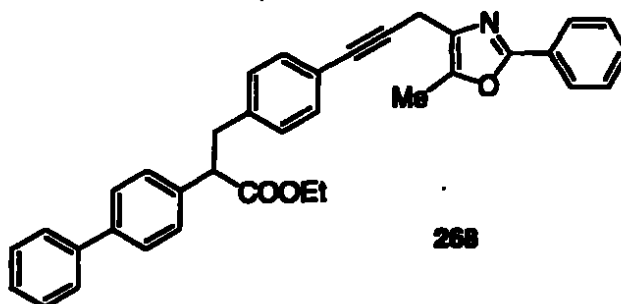
221

-254-

obtained as an orange solid in 54% yield: mp 163-165 °C; CIMS m/z 498.2 (M+1).

5 2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid ethyl ester (268) was prepared in the following manner.

(a) 2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid ethyl ester (268)

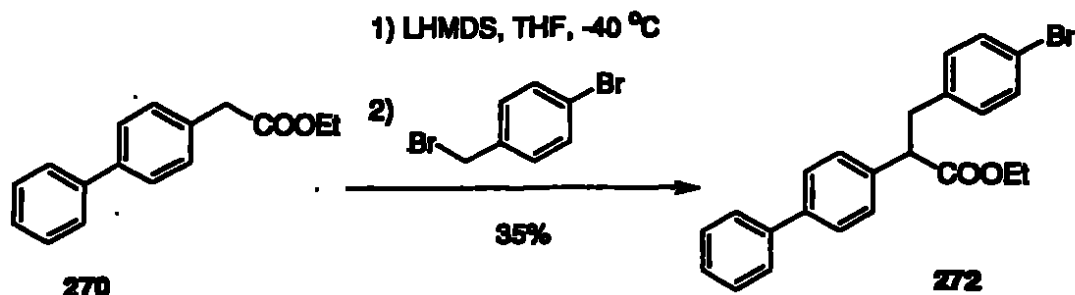


10

This compound was obtained from bromide 271 by following the General Method II. Ester 268 was obtained as a thick orange oil in 37% yield: CIMS m/z 526 (M+1).

15

(b) 2-Biphenyl-3-(4-Bromo-phenyl)-propionic acid ethyl ester (271).



This compound was prepared from 27. It was obtained as a white solid in 35% yield: CIMS m/z 409.0 (M)⁺.

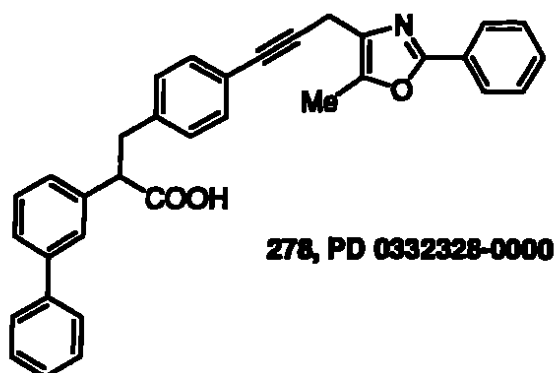
20

Example 101

2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid (278).

222

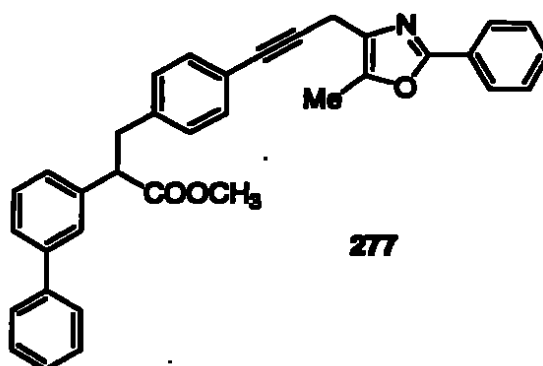
-255-



This compound was prepared from ester 277. The purification was carried out by chromatography on silica gel eluting with ethyl acetate in hexanes (0 to 45%). The title compound was obtained as a solid in 96% yield: mp 105-107 °C; CIMS m/z 498.2 ($M+1$). Anal. calcd for $C_{34}H_{27}NO_3 \cdot 1.3 H_2O$: C, 78.38; H, 5.73; N, 2.69. Found: C, 78.22; H, 5.57; N, 2.59.

2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid methyl ester (277) was prepared in the following manner.

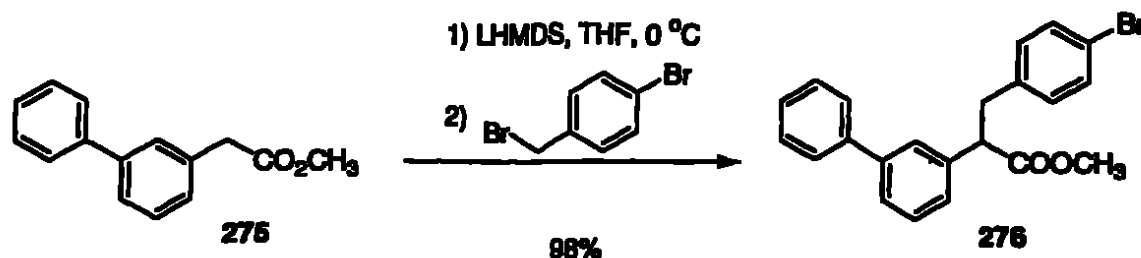
(a) 2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid methyl ester (277).



This compound was obtained from bromide 276 following General Procedure 100-a. Ester 277 was obtained as a thick orange oil in 12% yield: CIMS m/z 512.2 ($M+1$).

(b) 2-Biphenyl-3-yl-3-(4-Bromo-phenyl)-propionic acid methyl ester (276).

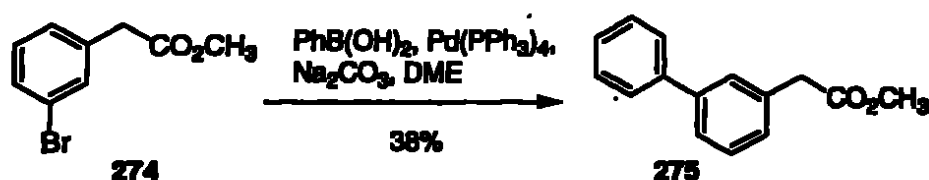
-256-



This compound was prepared from ester 275. It was obtained as a thick, colorless oil in 98% yield: CIMS m/z 395.1 (M)⁺.

5

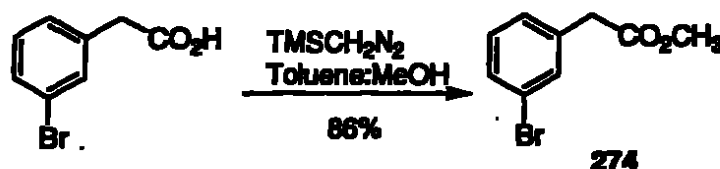
(c) 2-biphenyl-3-yl-acetic acid methyl ester (275).



Bromide 274 (1.872 g, 8.172 mmol) and phenylboronic acid (1.49 g, 12.258 mmol) were dissolved in DME. Sodium carbonate (1.73 g, 16.344 mmol) was added. Nitrogen was bubble into the reaction mixture for 25 min. Pd(PPh₃)₄ (0.471 g, 0.408 mmol) was added and the reaction mixture was heated at 90 °C for 40 h. Mixture cooled at rt, diluted with ethyl acetate (30 mL) and water (30 mL) was added. Phases separated. Aqueous phase extracted with ethyl acetate (3 × 35 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed. The residue was purified by column chromatography on silica gel eluting with ethyl acetate in hexanes (0 to 5 %). Ester 275 was obtained as a thick oil (0.706 g, 38%): CIMS m/z 227.0 (M+1).

20

(d) 2-(3-Bromo-phenyl)-acetic acid methyl ester (274).



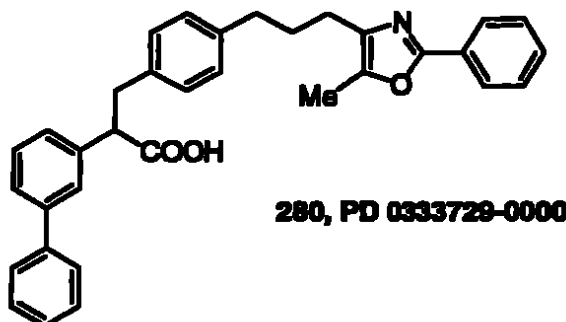
924

-257-

2-(3-Bromo-phenyl)-acetic acid (5.00 g, 23.25 mmol) was dissolved in toluene/MeOH (10:5 mL). The solution was cooled in an ice bath and 2.0 M solution of trimethylsilyldiazomethane in hexanes (14 mL, 28 mmol) was added dropwise. The mixture was stirred at room temperature overnight. The mixture was quenched with acetic acid and stirred for 0.5 h. Solvents removed and the residue purified by column chromatography on silica gel eluting with ethyl acetate in hexanes (0 to 5 %). Ester 274 was obtained as a clear oil (4.59 g, 86%): CIMS m/z 228.9 (M)⁺.

Example 102

2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid (280).



This compound was prepared from ester 279 following General Procedure 100. Purification was carried out by chromatography on silica gel eluting with ethyl acetate in hexanes (0 to 30%). The title compound was obtained as a solid in 69% yield: mp 75-80 °C; CIMS m/z 502.3 (M+1). Anal. calcd for C₃₄H₃₁NO₃·0.1 H₂O: C, 81.12; H, 6.25; N, 2.78. Found: C, 80.80; H, 6.33; N, 2.69.

2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester (279) was prepared in the following manner.

(a) 2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester (279).

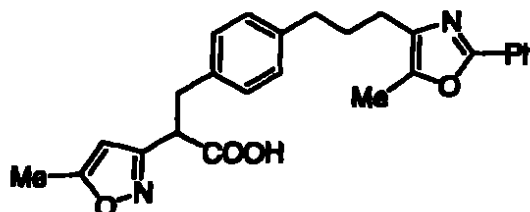
725

-258-

This compound was prepared following Example 104 using bromide 272 for the Suzuki coupling. Ester 279 was obtained as a thick oil in 37% yield: CIMS m/z 516.3 (M+1).

Example 103

5 2-(5-Methyl-isoxazol-3-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid (284).



284, PD 0336453-0000

10 This compound was prepared from ester 3-(4-Bromo-phenyl)-2-(5-Methyl-isoxazol-3-yl)-propionic acid ethyl ester (283) by LiOH-mediated hydrolysis. The purification was carried out by chromatography on silica gel eluting with ethyl acetate in hexanes (0 to 30%). The title compound was obtained as a solid in 69% yield: mp 75-80 °C; CIMS m/z 502.3 (M+1). Anal. calcd for $C_{34}H_{31}NO_3 \cdot 0.1 H_2O$: C, 81.12; H, 6.25; N, 2.78. Found: C, 80.80; H, 6.33; N, 2.69.

15

2-(5-Methyl-isoxazol-3-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid ethyl ester (283) (PD 0335776-0000) was prepared in the following manner.

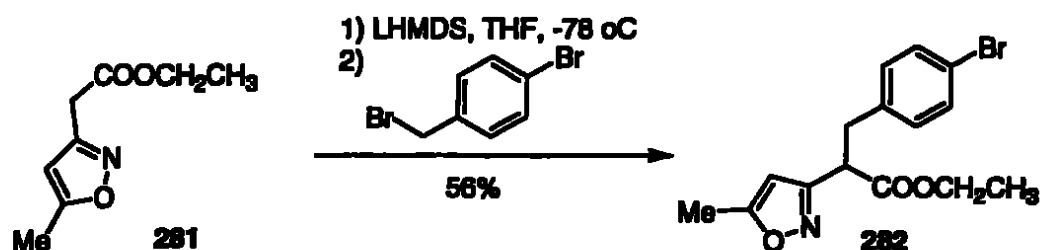
20 (a) 2-(5-Methyl-isoxazol-3-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid ethyl ester (283).

25 This compound was prepared following General Procedure 100-a using bromide 282 for the Suzuki coupling. Ester 283 was obtained as thick oil in 84% yield: CIMS m/z 459.3 (M+1).

276

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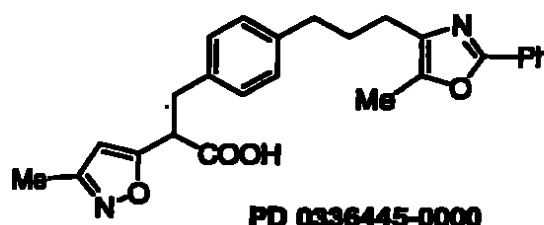
(b) 3-(4-Bromo-phenyl)-2-(5-Methyl-isoxazol-3-yl)-propionic acid ethyl ester (282).



5 This compound was prepared from ester 281 following General Procedure 97-b and was obtained as a thick oil in 56% yield: CIMS m/z 338.0 (M)⁺.

Example 104

2-(3-Methyl-isoxazol-5-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid (288).



10

This compound was prepared from 2-(3-Methyl-isoxazol-5-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester (287) following General Procedure 96. The purification was carried out by chromatography on silica gel eluting with methanol in chloroform (0 to 5%). The title compound was obtained as an off-white solid in 85% yield: mp 133-135 °C; CIMS m/z 431.2 (M+1). Anal. calcd for C₂₆H₂₆N₂O₄: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.32; H, 6.28; N, 6.41.

15

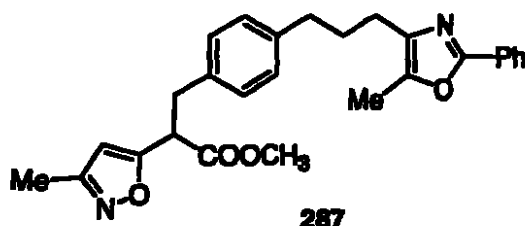
20

2-(3-Methyl-isoxazol-5-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester (287) was prepared in the following manner.

272

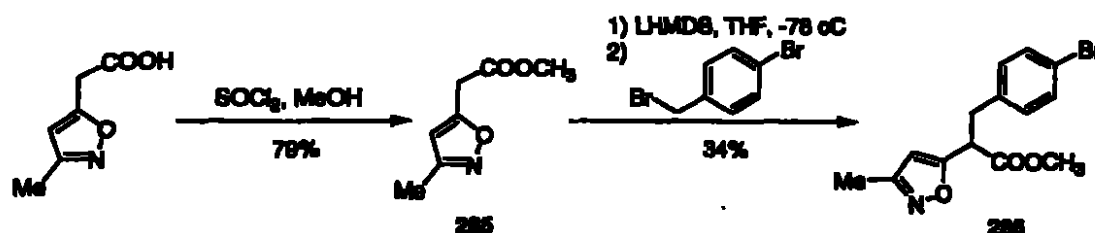
-260-

- (a) 2-(3-Methyl-isoxazol-5-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester (287).



5 This compound was prepared following General Procedure 96-a using bromide 286 for the Suzuki coupling. 2-(3-Methyl-isoxazol-5-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester (287) was obtained as thick oil in 60% yield: CIMS m/z 459.3 (M+1).

- 10 (b) 3-(4-Bromo-phenyl)-2-(3-Methyl-isoxazol-5-yl)-propionic acid ethyl ester (286).



15 This compound was prepared from ester 285 following General Procedure 96-b and was obtained as a thick oil in 34% yield: CIMS m/z 324.0 (M)⁺.

- (c) 3-Methyl-isoxazol-5-yl-acetic acid methyl ester (285).

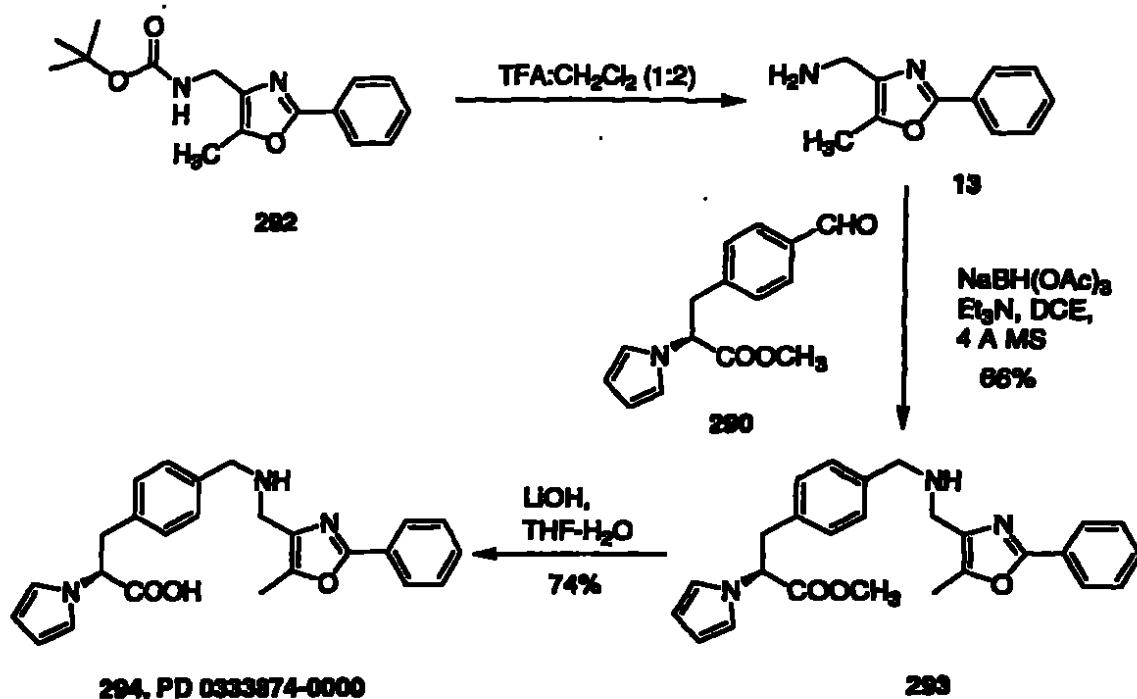
20 3-Methyl-isoxazol-5-yl-acetic acid (3.0 g, 21.257 mmol) was dissolved in MeOH (50 mL) and cooled in an ice bath. Thionyl chloride (2.3 mL, 31.9 mmol) was added and the ice bath removed. The mixture was heated at 40 °C for 24 h. The solvent was removed and the residue purified by distillation. The title compound was obtained as a clear oil (2.62 g, 79%); bp 81-82 °C (at 0.7 mmHg); CIMS m/z 154.1 (M+1).

298

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Example 105

(*S*)-3-(4-(((5-Methyl-2-phenyl-oxazol-4-ylmethyl)-amino)-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid (294).



5

This compound was prepared from ester 293 following General Procedure 100. The purification was carried out by chromatography on silica gel eluting with methanol in chloroform (0 to 5%). The title compound was obtained as an off-white solid in 74% yield: mp 163-165 °C; CIMS *m/z* 416.2 (M+1). Anal. calcd for C₂₃H₂₅N₃O₃·0.42 CHCl₃: C, 65.57; H, 5.50; N, 9.02. Found: C, 65.26; H, 5.81; N, 8.86.

10

(*S*)-3-(4-(((5-Methyl-2-phenyl-oxazol-4-ylmethyl)-amino)-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (293) was prepared in the following manner.

15

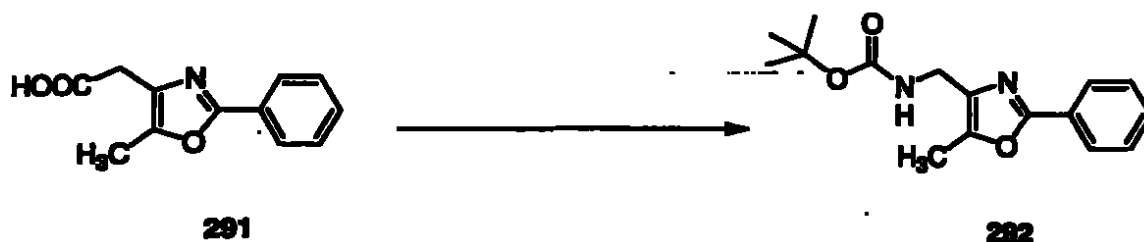
- (a) (*S*)-3-(4-(((5-Methyl-2-phenyl-oxazol-4-ylmethyl)-amino)-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (293).

279

-262-

Carbamate 292 (0.326 g, 1.130 mmol) was dissolved in dichloromethane (6 mL) and cooled in an ice bath. TFA (3 mL) was added and the mixture was stirred for 10 min and the ice bath was removed. The reaction mixture was stirred at room temperature for 3 h. The solvents were removed and the residue dried under high vacuum. The residue was then dissolved in 1,2-dichloroethane (15 mL) and Et₃N (0.39 mL, 2.825 mmol) added. After 5 min, aldehyde 290 (0.215 g, 0.837 mmol) was added, followed by NaBH(OAc)₃ (0.283 g, 1.339 mmol) after 10 min. The mixture was stirred at room temperature for 18 h. Additional NaBH(OAc)₃ (0.300 g) was added and stirring continued for 5 h. The mixture was diluted with dichloromethane and filtered through a celite pad. Saturated NaHCO₃ was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 25 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed. The solvents were removed and the residue was purified by column chromatography on silica gel eluting with methanol in chloroform (0 to 5 %). Ester 293 was obtained as a thick oil (0.236 g, 66%); CIMS *m/z* 430.2 (M+1).

(b) Preparation of (5-Methyl-2-phenyl-oxazol-4-ylmethyl)-carbamic acid tert-butyl ester (292).

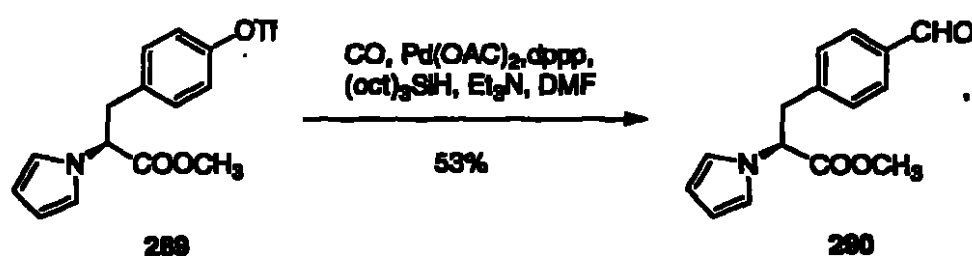


Acid 291 (3.0 g, 13.8 mmol) was dissolved in dichloromethane (70 mL) under nitrogen. The mixture was cooled in an ice bath and then oxalyl chloride (1.7 mL, 19.32 mmol) was added, followed by DMF (0.053 mL, 0.69 mmol). The ice bath was removed after 20 min and the reaction mixture stirred at room temperature for 5 h. The solvent was removed. The residue was dissolved in acetone and cooled at 0 °C. A solution of sodium azide (1.19 g, 18.354 mmol) in water (4.2 mL) was added. The mixture was stirred at 0 °C for 1 h, then it was

-263-

diluted with water and extracted with toluene (4 x 35 mL). The combined extracts
 were dried over magnesium sulfate, filtered and the solvent removed. The residue
 was dissolved in toluene (80 mL) and tert-BuOH (2.64 mL, 27.6 mmol) was
 added. The solution was heated at reflux for 18 h. The solvents were removed and
 the residue was purified by column chromatography on silica gel eluting with
 ethyl acetate in hexanes (0 to 25 %). Carbamate 292 was obtained as a solid (2.33
 g, 58%); CIMS m/z 289.1 (M+1).

(c) (S)-2-Pyrrol-1-yl-3-(4-formyl-phenyl)-propionic acid methyl ester
 (290).



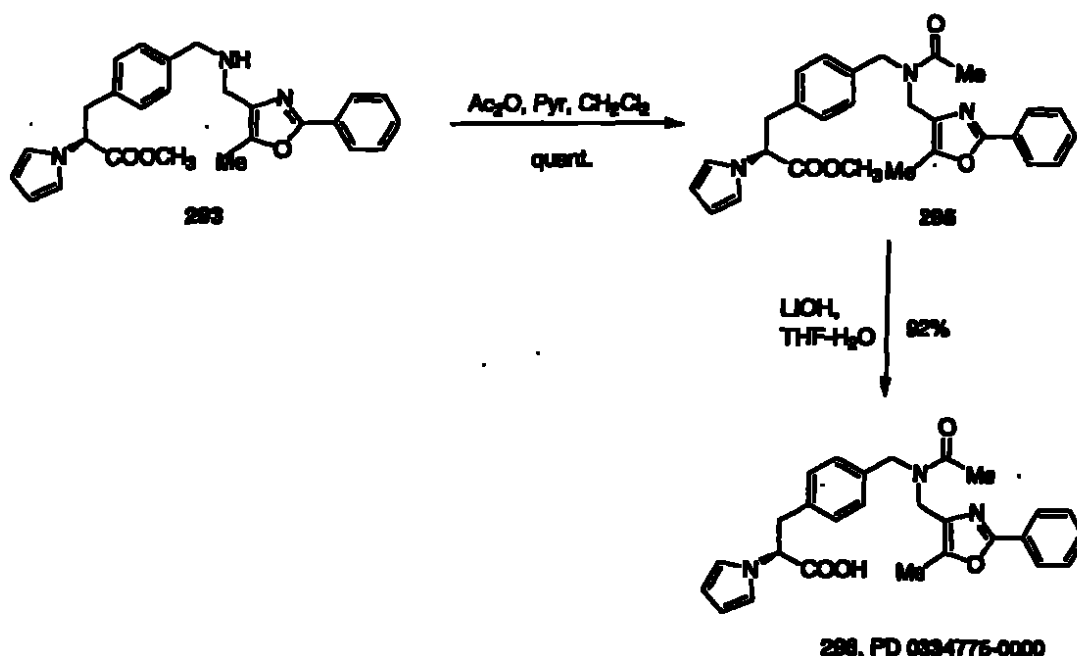
A mixture of triflate 289 (3.0 g, 7.950 mmol), Pd(OAc)₂ (0.065 g, 0.289
 mmol), dppp (0.122 g, 0.295 mmol), Et₃N (0.92 mL, 6.60 mmol), (octyl)₃SiH
 (2.38 mL, 5.298 mmol) in DMF (45 mL) was stirred and heated at 70 °C under
 500 psi of CO for 14 h. The solvent was removed and the residue was diluted with
 Et₂O (50 mL) and washed with water (70 mL). The aqueous phase was extracted
 with Et₂O (4 x 50 mL). The combined extracts were dried over magnesium
 sulfate, filtered and the solvent removed. The residue was purified by column
 chromatography on silica gel eluting with ethyl acetate in hexanes (0 to 25 %).
 The title compound 290 was obtained as an orange solid (1.11 g, 54%); CIMS m/z
 258.1 (M+1).

Example 106

(S)-3-(4-([Acetyl-(5-methyl-2-phenyl-oxazol-4-yl)methyl]-amino)-
 methyl)-phenyl)-2-pyrrol-1-yl-propionic acid (296).

981

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Ester 295 (0.268 g, 0.570 mmol) was dissolved in THF (15 mL) and water was added (5 mL). Lithium hydroxide monohydrate (0.036 g, 0.885 mmol) was incorporated and the mixture was stirred at room temperature for 2.5 h. The organic solvent was removed in the rotary evaporator at room temperature. The aqueous residue was diluted with water and cooled in an ice bath. It was then acidified with 10% HCl. The solid that was obtained was separated by filtration, washed with water, and dried under high vacuum at 50 °C for 12 h to give the title compound as a yellowish-pale brown solid (0.241 g, 92%): mp 97-100 °C; CIMS m/z 458.2 ($M+1$). Anal. calcd for $C_{27}H_{27}N_3O_4 \cdot 0.5 H_2O$: C, 69.51; H, 6.05; N, 9.01. Found: C, 69.32; H, 6.02; N, 8.73.

Preparation of (S)-3-(4-([Acetyl-(5-methyl-2-phenyl-oxazol-4-yl)methyl)-amino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (295) was prepared in the following manner.

- (a) (S)-3-(4-([Acetyl-(5-methyl-2-phenyl-oxazol-4-yl)methyl)-amino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (15).

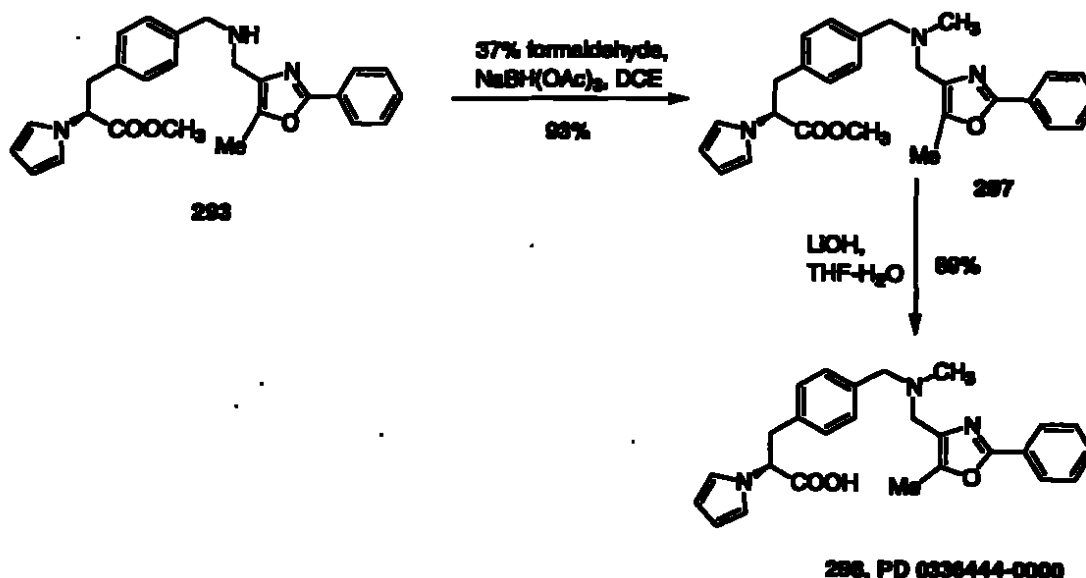
262

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(*S*)-3-(4-([(5-Methyl-2-phenyl-oxazol-4-ylmethyl)-amino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (293) (0.245 g, 0.570 mmol) was dissolved in dichloromethane (10 mL) and cooled in an ice bath. Pyridine (0.115 mL, 1.425 mmol) was added followed by Ac₂O (0.107 mL, 1.14 mmol).
5 The ice bath was removed after 30 min and the mixture stirred at room temperature for 20 h. dichloromethane (50 mL) was added and the solution was washed with 10% HCl, sat. NaHCO₃, sat. NaCl. The organic phase was dried over magnesium sulfate, filtered and the solvent removed. The solvents were removed and the residue was dried under high vacuum overnight to give a pale yellow oil
10 (0.295 g): CIMS *m/z* 472 (M+1).

Example 107

(*S*)-3-(4-([Methyl-(5-methyl-2-phenyl-oxazol-4-ylmethyl)-amino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid (298).



15

This compound was prepared from ester (*S*)-3-(4-([Methyl-(5-methyl-2-phenyl-oxazol-4-ylmethyl)-amino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (297) following General Procedure 96. The purification was carried out by chromatography on silica gel eluting with methanol in chloroform (0 to
20 10%). The title compound was obtained as a solid in 89% yield: mp 133-135 °C;

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CIMS m/z 430.3 (M+1). Anal. calcd for $C_{26}H_{27}N_3O_3 \cdot 1.71 H_2O$: C, 67.84; H, 6.66; N, 9.13. Found: C, 67.85; H, 6.39; N, 8.73.

5 (S)-3-(4-([Methyl-(5-methyl-2-phenyl-oxazol-4-ylmethyl)-amino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (297) was prepared in the following manner.

(a) (S)-3-(4-([Methyl-(5-methyl-2-phenyl-oxazol-4-ylmethyl)-amino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (16).

10

(S)-3-(4-([(5-Methyl-2-phenyl-oxazol-4-ylmethyl)-amino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (293) (0.432 g, 1.006 mmol) was dissolved in 1,2-dichloroethane (10 mL) and 37% formaldehyde solution (0.090 mL, 1.106 mmol) was added, followed by $NaBH(OAc)_3$ (0.300 g, 1.408 mmol). The mixture was stirred at room temperature for 24 h under nitrogen. Sat. $NaHCO_3$ (30 mL) was added and the mixture was stirred for 20 min. At this time, it was diluted with dichloromethane and the phases were separated. The aqueous phase was extracted with dichloromethane (3×30 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed. The solvents were removed and the residue was purified by column chromatography on silica gel eluting with methanol in chloroform (0 to 3%). Ester 16 was obtained as a thick pale yellow oil (0.417 g, 93%): CIMS m/z 444.2 (M+1).

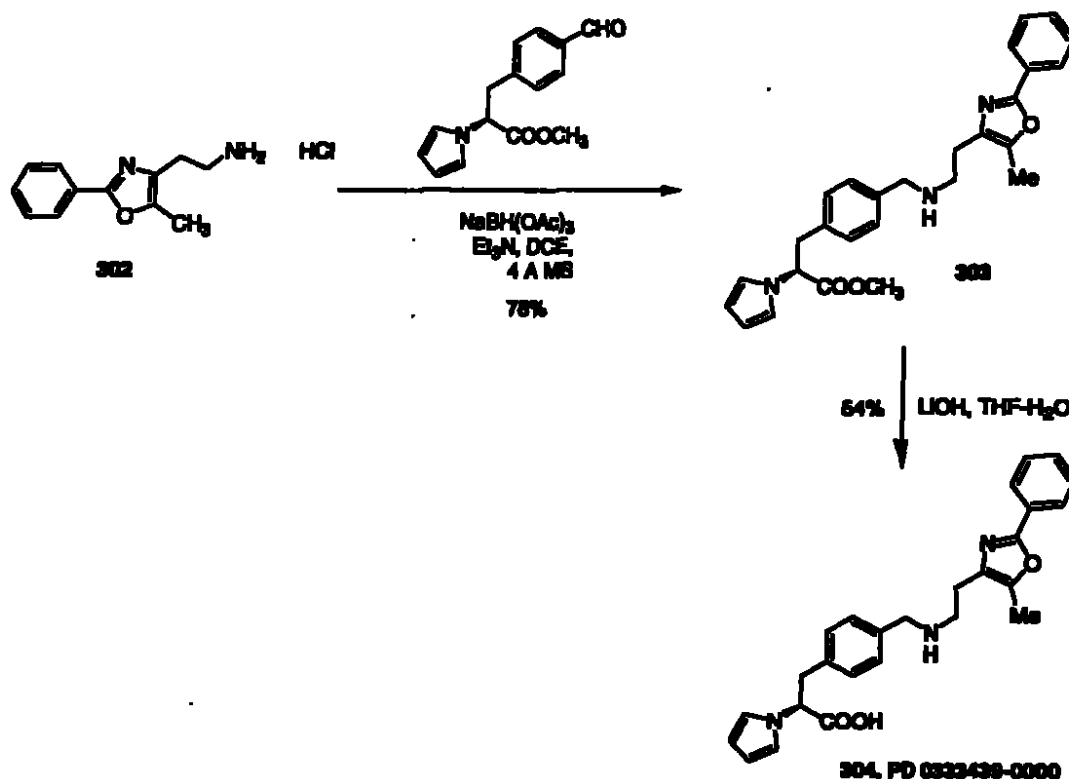
15

20

Example 108

25 (S)-3-(4-([2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid (304).

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This compound was prepared from (*S*)-3-(4-{[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-methyl}-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (303) following General Procedure 97. The purification was carried out by chromatography on silica gel eluting with methanol in chloroform (0 to 12%). The title compound was obtained as a white solid in 54% yield: mp 208-210 °C; CIMS *m/z* 430.2 (*M*+1). Anal. calcd for C₂₆H₂₇N₃O₃·0.6 H₂O: C, 70.92; H, 6.46; N, 9.54. Found: C, 70.60; H, 6.34; N, 9.48.

(*S*)-3-(4-{[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-methyl}-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (303) was prepared in the following manner.

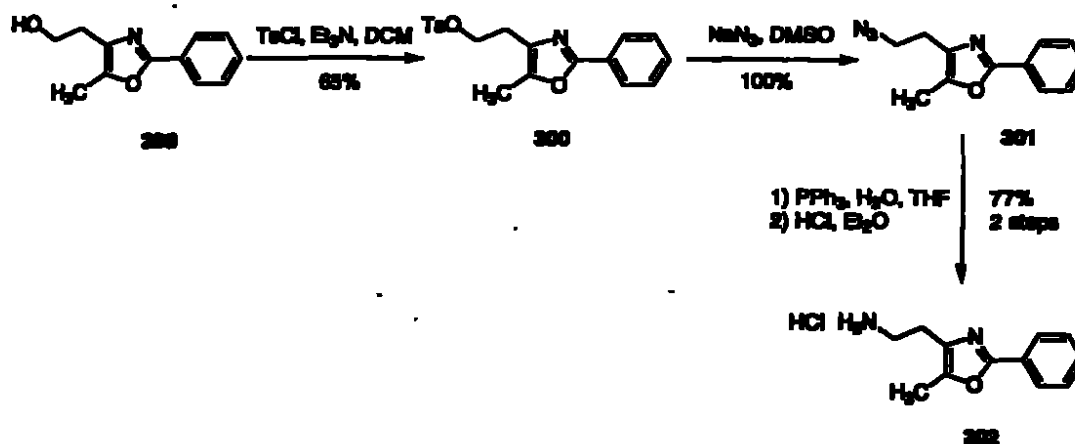
(a) (*S*)-3-(4-{[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-methyl}-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (303).

Amine 302 (0.392 g, 1.642 mmol) was suspended in 1,2-dichloroethane (15mL). Et₃N (0.252 mL, 1.806 mmol) added and the mixture stirred for 10 min.

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A solution of aldehyde 290 (0.352 g, 1.368 mmol) in 1,2-dichloroethane (15 mL) was incorporated. After 10 min, $\text{NaBH}(\text{OAc})_3$ (0.405 g, 1.915 mmol) was added. The mixture was stirred at room temperature for 18 h. Additional $\text{NaBH}(\text{OAc})_3$ (0.290 g) and 4Å MS (0.4 g) were added and stirring continued for 12 h. More $\text{NaBH}(\text{OAc})_3$ (0.150 g) was added and stirring continued for 3 days. The mixture was diluted with dichloromethane and filtered through a celite pad. Saturated NaHCO_3 was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3×25 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed. The solvents were removed and the residue was purified by column chromatography on silica gel eluting with methanol in chloroform (0 to 5 %). Ester 21 was obtained as a yellow oil (0.461 g, 76%); CIMS m/z 444.2 ($M+1$).

(b) 2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamine hydrochloride (302).



Alcohol 299 (3.87 g, 19.04 mmol) was dissolved in dichloromethane (60 mL) and cooled to 0 °C. TsCl (4.35 g, 22.85 mmol) was added followed by Et_3N (5.3 mL, 38.08 mmol). The mixture was allowed to warm to room temperature overnight. Then, it was diluted with dichloromethane (100 mL) and the solution washed with cold 5% HCl (2×50 mL), sat. NaHCO_3 (50 mL), dried over magnesium sulfate, filtered and the solvent removed. The solvents were removed and the residue was purified by column chromatography on silica gel eluting with

946

-269-

ethyl acetate in hexanes (0 to 30%). Tosylate 300 was obtained as a yellowish solid (4.41 g, 65%): CIMS m/z 358.1 (M+1).

5 Tosylate 300 (4.41 g, 12.34 mmol) was dissolved in DMSO and NaN_3 (1.04 g, 16.04 mmol) was added. The mixture was stirred at room temperature for 3 days. The solution was diluted with water (150 mL) and extracted with Et_2O (5 $\times$ 100 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed. Azide 301 was obtained as an orange oil (2.86 g): CIMS m/z 229.1 (M+1).

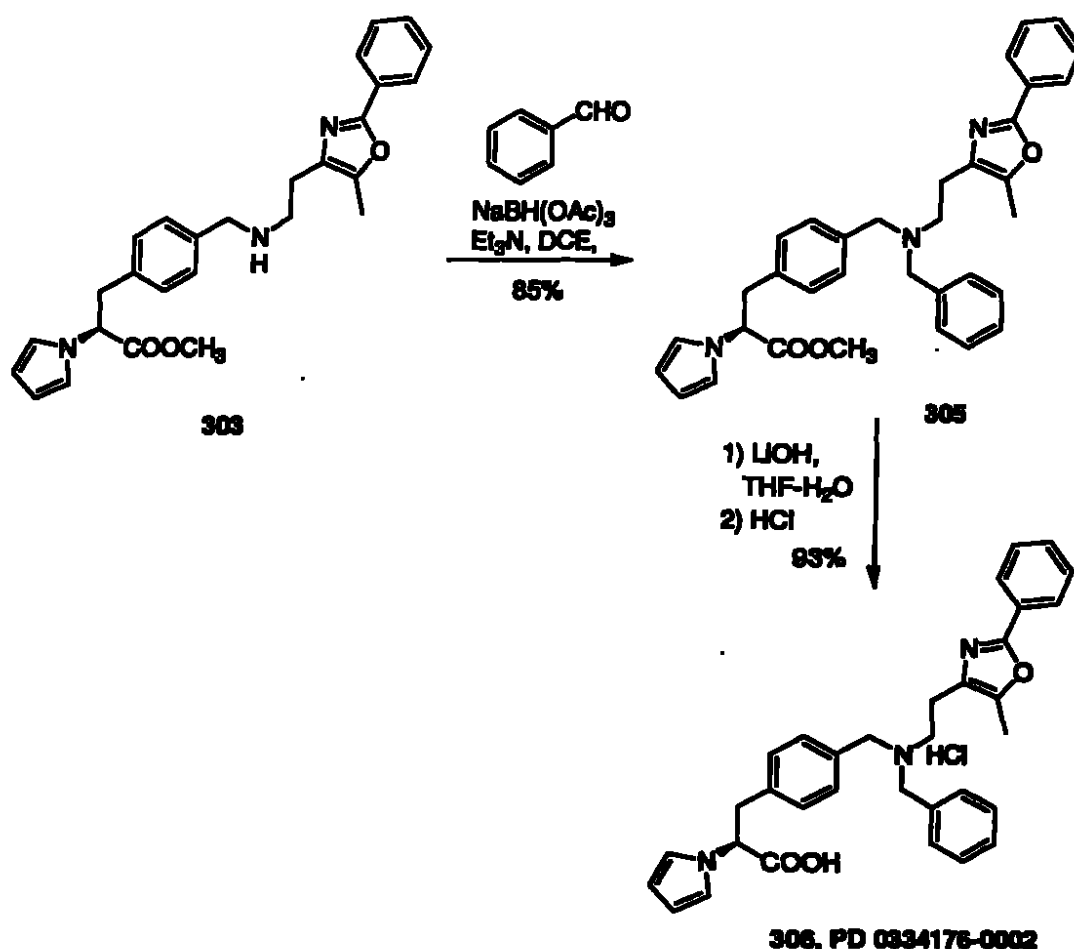
10 Azide 301 (2.86 g, 12.53 mmol) was dissolved in THF (50 mL) and PPh_3 (6.57 g, 25.06 mmol) was added followed by water (2.25 mL, 125.3 mmol). The mixture was stirred at room temperature for 20 h. The solvents were removed, the residue dissolved in Et_2O and the solution extracted with 10% HCl (3 $\times$ 20 mL). The combined aqueous extracts were washed with Et_2O . The pH of the solution was adjusted to 14 with sodium hydroxide pellets. The mixture was extracted with
15 Et_2O (3 $\times$ 30 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed to leave a small volume. A 1.0 N solution of HCl in Et_2O was added dropwise. The solid that precipitated was separated by
20 filtration, washed with Et_2O and dried overnight to give amine 302 as the hydrochloride salt. Amine 302 was obtained as an off-white solid (2.316 g, 77%): CIMS m/z 203.1 (M+1).

Example 109

(S)-3-[4-({Benzyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino}-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid (306).

98X

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This compound was prepared from (S)-3-[4-((benzyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino)-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (22), following General Procedure 96. A solid was obtained after acidification with 10% HCl. The solid was separated by filtration, washed with water and dried under high vacuum to give an off-white solid (93%): mp 110-113 °C; CIMS *m/z* 520.3 (M+1). Anal. calcd for C₃₃H₃₃N₃O₃·HCl: C, 71.27; H, 6.16; N, 7.56. Found: C, 71.22; H, 6.26; N, 7.42.

(S)-3-[4-((benzyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino)-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (305) was prepared in the following manner.

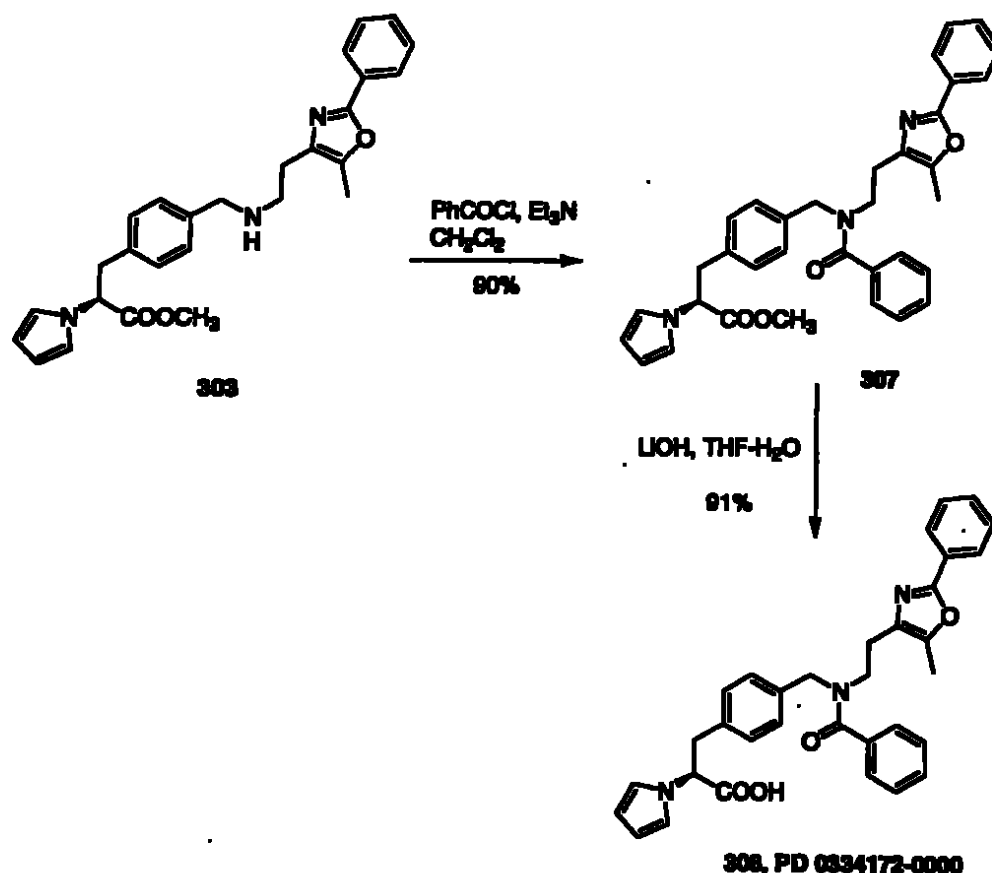
This compound was prepared from (S)-3-[4-([2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl

-271-

ester (303) and benzaldehyde following Example 112, step a, and was obtained as an oil in 85% yield: CIMS m/z 534.3 (M+1).

Example 110

5 (S)-3-[4-({Benzoyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino}-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid (308).



10 This compound was prepared from (S)-3-[4-({Benzoyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino}-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (307). The title compound was obtained as a white solid in 91%): mp 105-110 °C; CIMS m/z 534.2 (M+1). Anal. calcd for C₃₃H₃₁N₃O₄·0.2 H₂O: C, 73.78; H, 5.89; N, 7.82. Found: C, 73.46; H, 5.76; N, 7.70.

15 (S)-3-[4-({Benzoyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino}-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (307) was prepared in the following manner.

289

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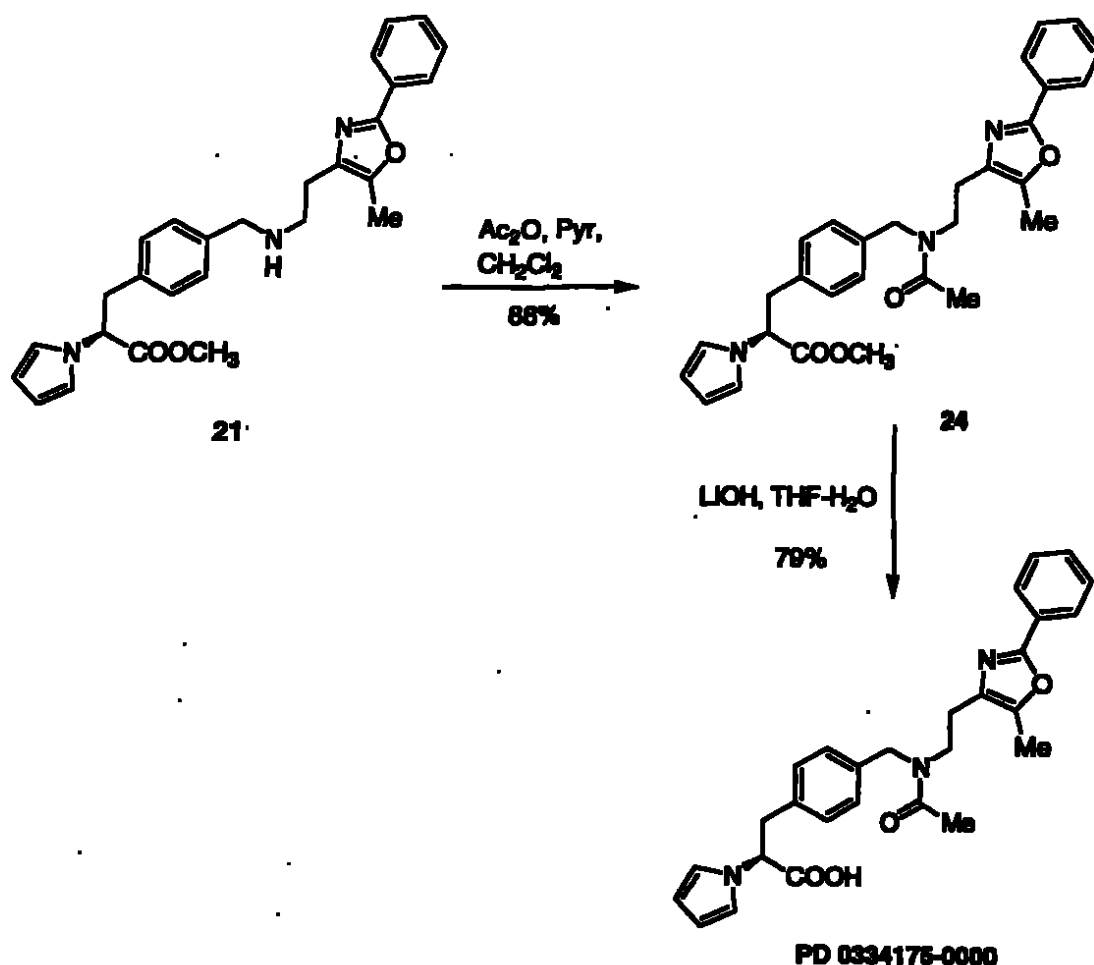
(a) (S)-3-[4-({Benzoyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino]-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (307).

5 (S)-3-(4-([2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (303) (0.286 g, 0.645 mmol) was dissolved in dichloromethane (10 mL) and cooled in an ice bath. Et₃N (0.180 mL, 1.29 mmol) was added followed by PhCOCl (0.082 mL, 0.709 mmol). The ice bath was removed after 30 min and the mixture stirred at room temperature for
10 20 h. dichloromethane (50 mL) was added and the solution was washed with 10% HCl, sat. NaHCO₃, sat. NaCl. The organic phase was dried over magnesium sulfate, filtered and the solvent removed. The solvents were removed and the residue was purified by column chromatography on silica gel eluting with ethyl acetate in hexanes (0 to 45%). The title compound was obtained as a clear oil
15 (0.319 g, 90%): CIMS *m/z* 548.2 (M+1).

Example 111

(S)- 3-[4-({Acetyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino]-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid (311).

-273-



5 This compound was prepared from (S)- 3-[4-({Acetyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino)-methyl]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (310) following General Procedure 97. The purification was carried out by chromatography on silica gel eluting with methanol in chloroform (0 to 10%). The title compound was obtained as a white solid in 79% yield: mp 82-87°C; CIMS *m/z* 472.2 (*M*+1). Anal. calcd for C₂₈H₂₉N₃O₄·0.4 H₂O: C, 70.25; H, 6.27; N, 8.78. Found: C, 69.92; H, 6.16; N, 8.47.

10

(S)- 3-[4-({Acetyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino)-methyl]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (310) was prepared in the following manner.

291

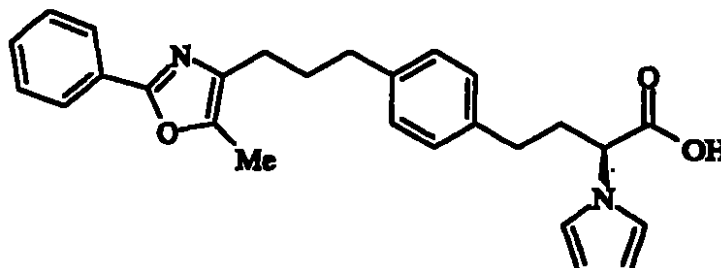
-274-

- (a) (S)- 3-[4-({Acetyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino}-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (310).

5 (S)-3-(4-([2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (303) (0.388 g, 0.875 mmol) was dissolved in dichloromethane (10 mL) and cooled in an ice bath. Pyridine (0.177 mL, 2.187 mmol) was added followed by Ac₂O (0.165 mL, 1.75 mmol). The ice bath was removed after 30 min and the mixture stirred at room
10 temperature for 20 h. dichloromethane (50 mL) was added and the solution was washed with 10% HCl, sat. NaHCO₃, sat. NaCl. The organic phase was dried over magnesium sulfate, filtered and the solvent removed. The residue was purified by column chromatography on silica gel eluting with ethyl acetates in hexanes (0 to 40%). The title compound was obtained as a pale yellow oil (0.376 g, 88%):
15 CIMS *m/z* 486.3 (M+1).

Example 112

4-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-butyric acid (312).



20

312

4-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-butyric acid methyl ester was hydrolyzed as in general procedure A to give carboxylic acid 312 in 90% yield. (δ) NMR (CHCl₃) 7.86 (2H, m); 7.33 (3H, m); 7.03 (2H, d, J=8.1Hz); 6.97 (2H, d, J=8.8Hz), 6.68 (2H, m); 6.14 (2H, m); 4.46

292

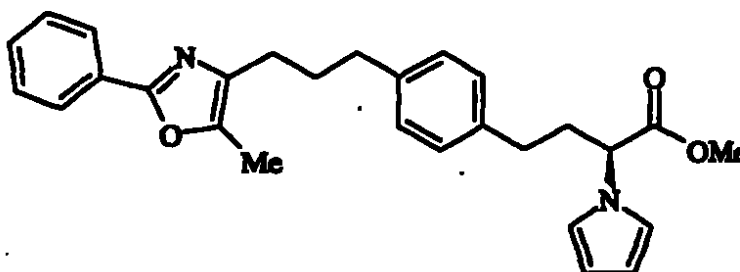
-275-

(1H, m); 2.56 (3H, m); 2.44 (5H, m); 2.22 (3H, s); 1.88 (2H, m). CIMS m/z 429.3 (M)⁺.

4-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-pyrrol-1-yl-butyrac acid methyl ester was prepared in the following manner.

5

- (a) 4-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-pyrrol-1-yl-butyrac acid methyl ester (311).



311

10

The title compound was prepared as in the procedure outlined for the preparation of esters 120 a-d in 38% yield. 2-Pyrrol-1-yl-4-(4-trifluoromethanesulfonyl-phenyl)-butyrac acid methyl ester was used as the triflate component. (δ) NMR (CHCl₃) 8.00 (2H, m); 7.47 (3H, m); 7.10 (2H, d, J=7.6Hz); 7.62 (2H, d, J=7.6Hz); 6.74 (2H, s); 6.21 (2H, s); 4.50 (1H, m); 3.69 (3H, s); 2.58 (6H, m); 2.37 (2H); 2.31 (3H, s); 1.99 (2H, m). CIMS m/z 44.3 (M)⁺.

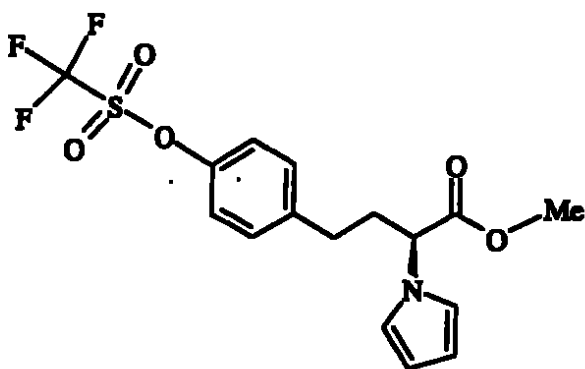
15

Example 116

2-Pyrrol-1-yl-4-(4-trifluoromethanesulfonyl-phenyl)-butyrac acid methyl ester (314).

993

-276-

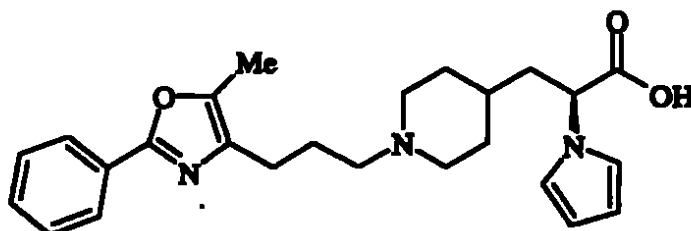


314

The title compound was prepared as described in the synthesis of (*S*)-2-Pyrrol-1-yl-3-[(4-trifluoromethanesulfonyloxy)phenyl]-propionic acid methyl ester (119) from homo-tyrosine (CAS 141899-12-9) via esterification and pyrrole condensation as described in the preparation of pyrrolotyrosine methyl ester (1).
 5 (δ) NMR (CHCl₃) 7.18 (4H, s); 6.71 (2H, s); 6.21 (2H, s); 4.51 (1H, m); 3.70 (3H, s); 2.45 (4H, s). CIMS *m/z* 391.9 (M)⁺.

Example 117

10 3-[1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl]-2-pyrrol-1-yl-propionic acid (318).



318

The title compound was prepared from 3-[1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl]-2-pyrrol-1-yl-propionic acid methyl ester (317) via general procedure A in 43% yield. NMR (δ;CHCl₃); 7.9 (2H, m); 7.40 (3H, m); 6.65 (2H, s); 6.13 (2H, s); 6.01 (1H, m); 4.61 (1H, m); 3.50 (2H, m);

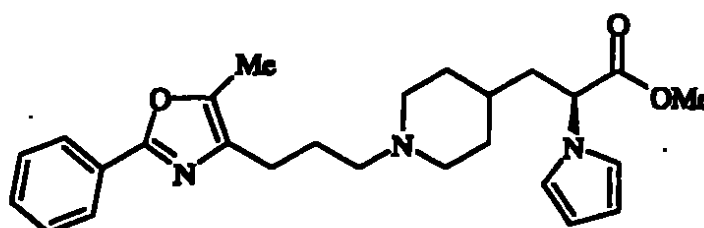
294 *294*

-277-

2.91 (2H, m); 2.59 (2H, m); 2.29 (3H, m); 2.27 (3H, s); 2.05 (3H, m); 1.85 (1H, m); 1.55 (1H, m). CIMS m/z 422.3 (M)⁺.

3-{1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-2-pyrrol-1-yl-propionic acid methyl ester (317) was prepared in the following manner.

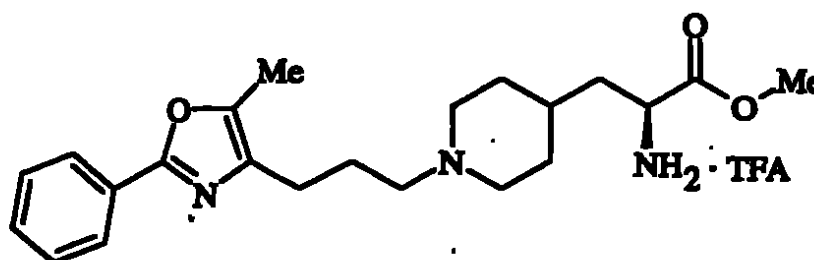
- 5 (a) 3-{1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-2-pyrrol-1-yl-propionic acid methyl ester (317).



317

10 The title compound was prepared from the TFA salt of the amino ester (316) by the pyrrole formation reaction as in Example 1 in 28% yield. NMR (δ ;CHCl₃); 7.95 (2H, m); 7.45 (3H, m); 6.70 (2H, s); 6.16 (2H, s); 4.66 (1H, m); 3.71 (3H, s); 2.52 (2H, m); 2.31 (3H, s); 2.03 (3H, m); 1.59 (3H, m); 1.21 (6H, m). CIMS m/z 436.3 (M)⁺.

- 15 (b) 2-Amino-3-{1-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-propionic acid methyl ester trifluoroacetic acid salt (316).



316

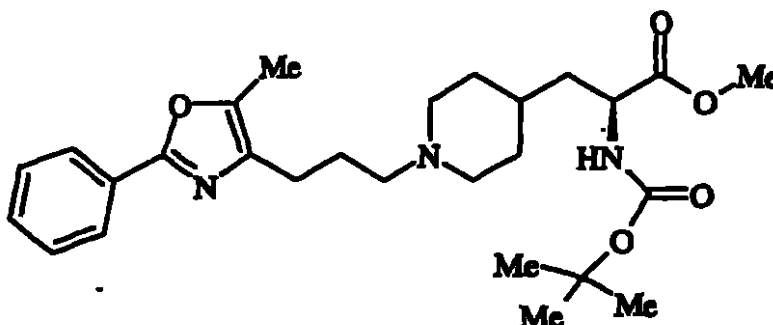
20 Prepared by treating 2-tert-Butoxycarbonylamino-3-{1-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-propionic acid methyl ester (315)

795

-278-

with 5 equiv of trifluoroacetic acid in dichloromethane for 24 hours at 23°C. Removal of solvent gave the trifluoroacetic acid salt which was used without further purification.

- 5 (c) 2-tert-Butoxycarbonylamino-3-[1-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl]-propionic acid methyl ester



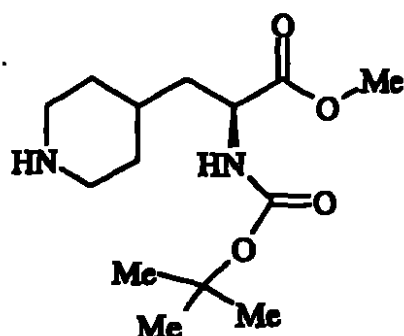
315

- 10 The title compound was prepared by combining 4-(3-Bromo-propyl)-5-methyl-2-phenyl-oxazole (1.21 g, 4.6 mmol), 2-tert-Butoxycarbonylamino-3-piperidin-4-yl-propionic acid methyl ester (315, 1 g, 3.67 mmol) and Ca_2Co_3 (1.79 g, 5.5 mmol) in acetonitrile (30 mL) at 23°C under N_2 atm. The mixture was stirred vigorously for 2 days after which the reaction was filtered, and solvent removed *in vacuo*. The residue was chromatographed (SiO_2) with 30% EtOAc/Hexanes and gave 525 mg (30% yield) as a pale yellow oil. NMR (δ ; CHCl_3); 7.86 (2H, m); 7.43 (3H, m); 4.35 (1H, m); 3.72 (3H, s); 2.51 (3H, m); 2.40 (4H, m); 2.32 (3H, s); 1.51 (5H, m); 1.40 (9H, s). CIMS m/z 486.4 (M^+).
- 15

- (d) 2-tert-Butoxycarbonylamino-3-piperidin-4-yl-propionic acid methyl ester (315, CAS 256925-70-9).

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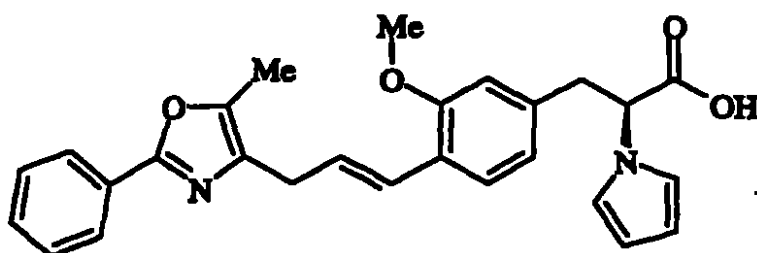


315

The title compound was prepared as in the esterification of pyrrolotyrosine (1). Used without further purification.

5 Example 118

3-[3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl]-2-pyrrol-1-yl-propionic acid (321).



321

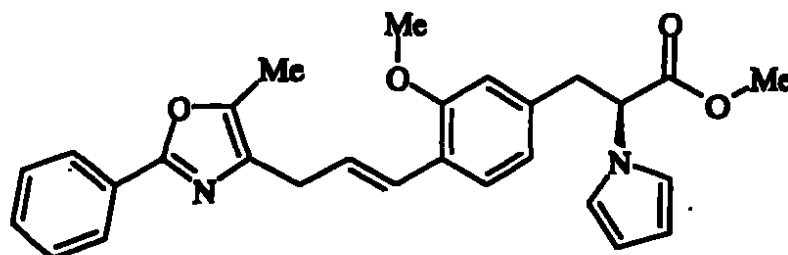
- 10 Prepared from 3-[3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (320) utilizing general hydrolysis procedure A in 57% yield as a beige foam. NMR (δ ; CHCl_3); 8.02 (2H, m); 7.41 (4H, m); 7.29 (1H, d, $J=7.8\text{Hz}$); 6.73 (1H, d, $J=16\text{Hz}$); 6.64 (2H, m); 6.60 (1H, d, $J=7.8\text{Hz}$); 6.32 (1H, m); 6.19 (1H, s); 6.14 (2H, s); 4.60 (1H, m); 3.63 (3H, s); 3.45 (2H, d, $J=6.8\text{Hz}$); 3.25 (2H, m); 2.03 (3H, s). CIMS m/z 441.3 (M)⁺.
- 15

297

-280-

3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (320) was prepared in the following manner.

- (a) 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (320).



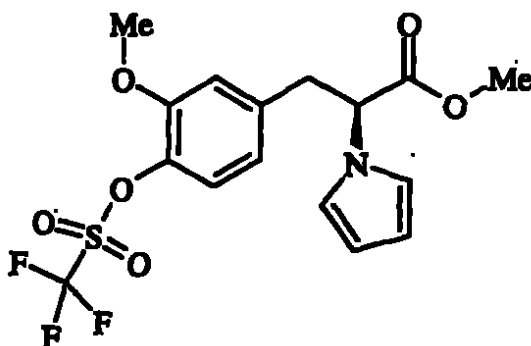
321

The title compound was prepared as in the Pd coupling procedure used to prepare esters (120) a-d from 3-(3-Methoxy-4-trifluoromethanesulfonyloxy-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester and organo borane (117) in 7 yield as a beige foam. NMR (δ ; CHCl_3); 8.00 (2H, d, $J=8.0\text{Hz}$); 7.44 (3H, m); 7.23 (1H, d, $J=7.1\text{Hz}$); 6.74 (1H, d, $J=16\text{Hz}$); 6.69 (2H, m); 6.61 (1H, d, $J=7.8\text{Hz}$); 6.30 (1H, m); 6.25 (1H, s); 6.14 (2H, m); 4.70 (1H, m); 3.75 (1H, m); 3.71 (3H, s); 3.66 (3H, s); 3.45 (2H, d, $J=6.6\text{Hz}$); 3.25 (2H, m); 2.40 (3H, s). CIMS m/z 457.3 (M)⁺.

- (b) 3-(3-Methoxy-4-trifluoromethanesulfonyloxy-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (319).

296

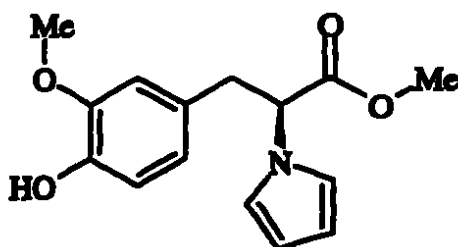
-281-



319

5 The title compound was prepared using the general procedure for the synthesis of triflate (119). Obtained the product as a light brown oil in 57% yield from 3-(4-Hydroxy-3-methoxy-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester. Microanalysis CHN Theoretical; C=47.18, H=3.96, N=3.44; Observed; C=47.19, H=3.64; N=3.42.

(c) 3-(4-Hydroxy-3-methoxy-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester. (CAS256925-70-9)



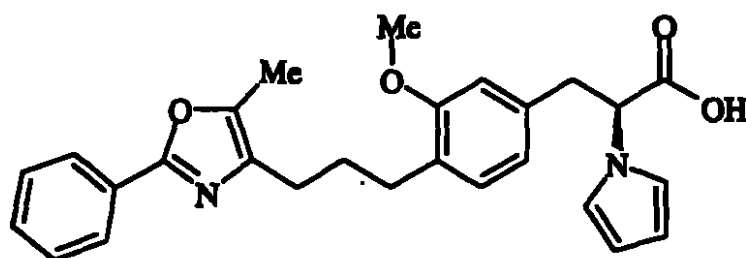
10

The title compound was obtained from 2-Amino-3-(4-hydroxy-3-methoxy-phenyl)-propionic acid methyl ester as in the formation of pyrrolotyrosine (1) in 69% yield as a yellow oil. CIMS m/z 276.1 (M)⁺.

Example 119

gdp

-282-

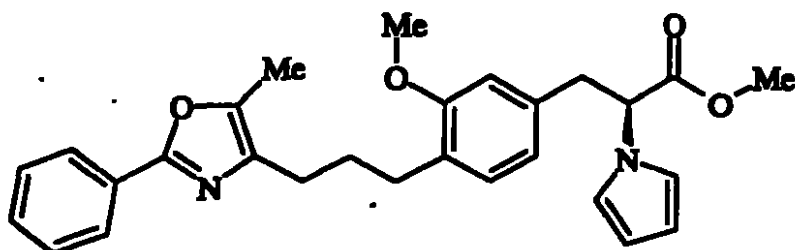


323

The title compound was obtained in 92% yield from the corresponding methyl ester by general procedure A. Microanalysis CHN theoretical; 72.95, H=6.35, N=6.30; Observed C=72.94, H=6.42, N=6.00. M.P. 120-121°C.

3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (322) was obtained in the following manner.

(a) 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (322).

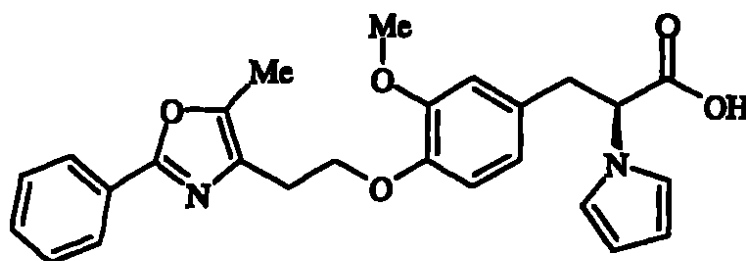


322

The title compound was obtained via general hydrogenation procedure used to prepare esters 130 a-c. Microanalysis CHN theoretical C=73.34, H=6.59; N=6.11; Observed; C=73.29, H=6.53; N=6.03.

Example 120

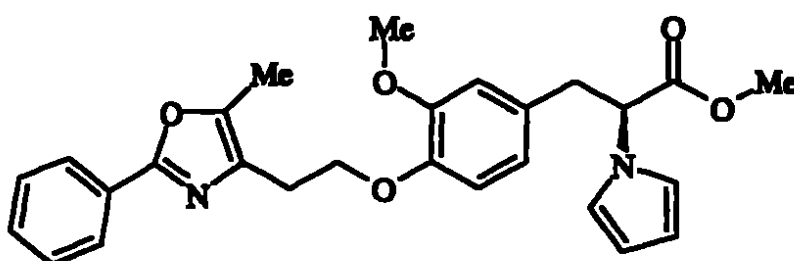
3-{3-Methoxy-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid (325).



325

5 The title compound was obtained from 3-{3-Methoxy-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (324) via general hydrolysis procedure A in 86% yield. Microanalysis CHN theoretical C=69.94, H=5.87, N=6.27; Observed C=70.25, H=5.75, N=6.04; M.P.=142-143°C.

10 3-{3-Methoxy-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (324) was obtained in the following manner.

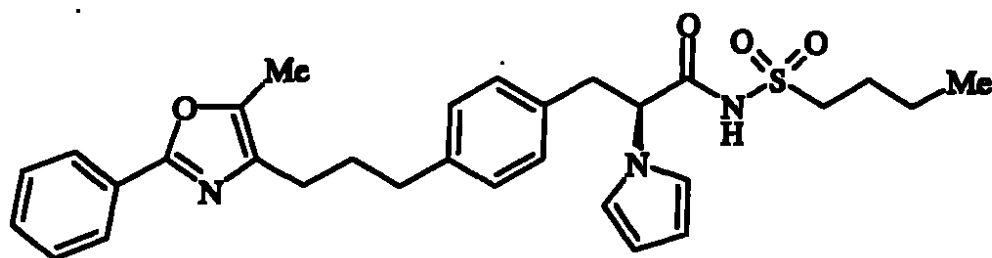


324

15 The title compound was obtained from 3-(4-Hydroxy-3-methoxy-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester via general coupling procedure B in 35%. Microanalysis CHN theoretical C=70.42, H=6.13, N=6.08; Observed C=70.42, H=6.03, N=6.04.

Example 121

Butane-1-sulfonic acid (3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-amide (326).



5

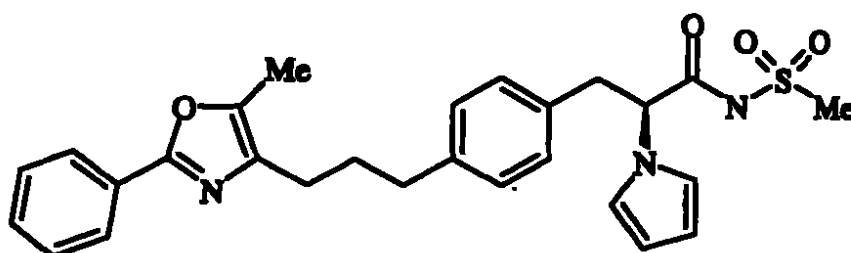
326

The title compound was obtained from the corresponding acid in 50% yield via the same procedure used to obtain acyl sulfonamide (17). NMR (δ ;CHCl₃); 7.96 (2H, m); 7.43 (3H, m); 7.04 (2H, d, $J=8$ Hz); 6.88 (2H, d, $J=8.0$ Hz); 6.61 (2H, m); 6.22 (2H, m); 4.71 (1H, m); 3.35 (1H, m); 3.30 (2H, m); 3.20 (1H, m); 2.60 (2H, m); 2.45 (2H, m); 2.25 (3H, s); 1.95 (2H, m); 1.69 (2H, m); 1.45 (2H, m); 0.95 (3H, m). CIMS m/z 534.3 (M)⁺.

10

Example 122

N-(3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-methanesulfonamide (327).



15

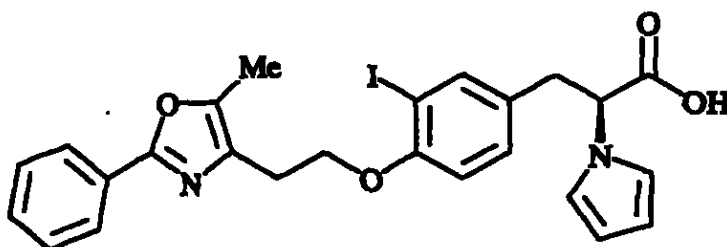
327

202

The title compound was obtained as a brown oil from the corresponding acid in 40% yield via the same procedure used to obtain acyl sulfonamide (327). NMR (δ ; CHCl₃); 7.96 (2H, m); 7.40 (3H, m); 7.03 (2H, d, $J=8.1$ Hz); 6.89 (2H, d, $J=8.1$ Hz); 6.65 (1H, s); 6.14 (2H, s); 4.69 (2H, m); 3.49 (1H, m); 3.17 (1H, m); 3.08 (2H, m); 2.58 (2H, t, $J=7.3, 8.0$ Hz); 2.45 (2H, t, $J=7.3, 7.6$ Hz); 2.24 (3H, s); 1.85 (2H, m). CIMS m/z 492.3 (M)⁺.

Example 123

3-{3-Iodo-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid (330).



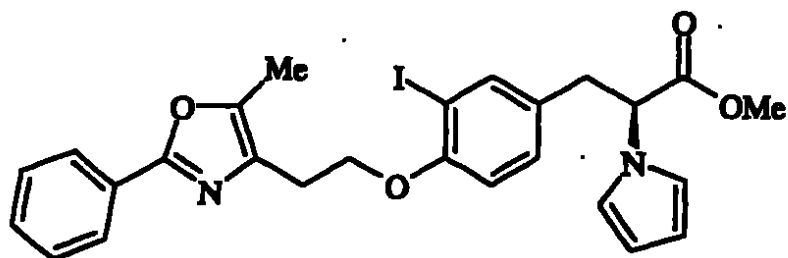
330

The title compound was obtained from hydrolysis of the corresponding 3-{3-Iodo-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (329) via general procedure A. White crystals. 68% yield. Microanalysis CHN Theoretical C=72.95, H=6.35, N=6.30; Observed C=72.71, H=6.44, N=6.29. M.P.=202-203°C.

3-{3-Iodo-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (329) was prepared in the following manner.

203

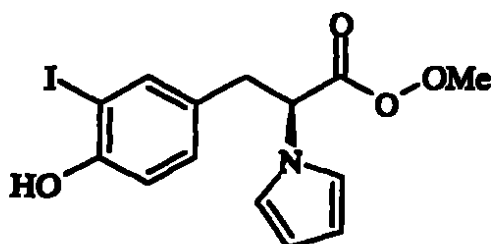
-286-



329

The title compound was obtained via general coupling method B from 3-(4-Hydroxy-3-iodo-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester in 63% yield. CIMS m/z 557.1 (M)⁺.

(b) 3-(4-Hydroxy-3-iodo-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester (328).



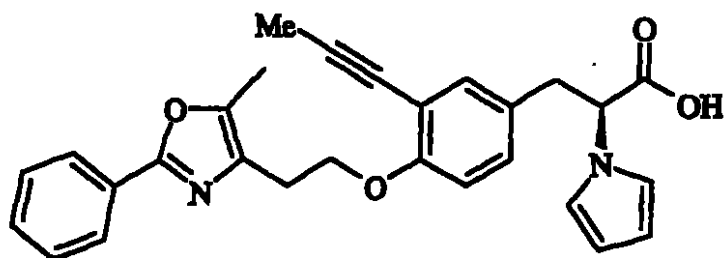
328

The title compound was obtained in 84% over two steps as in the synthesis of pyrrolotyrosine methyl ester (1). CIMS m/z 372.0 (M)⁺.

Example 124

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-phenyl}-2-pyrrol-1-yl-propionic acid (332).

-287-

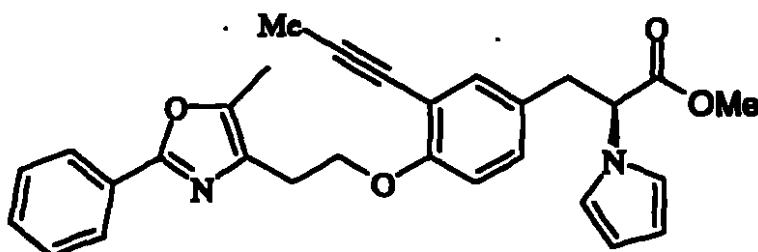


332

The title compound was obtained from 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester. (331, PD0333000-0000) via general hydrolysis procedure A in 66% yield as white crystals from Ethyl acetate M.P.=155-156°C. Microanalysis CHN theoretical: 73.99, H=5.77, N=6.16; Observed C=74.04, H=5.72, H=5.85.

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (331) was prepared in the following manner.

(a) 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (331).



331

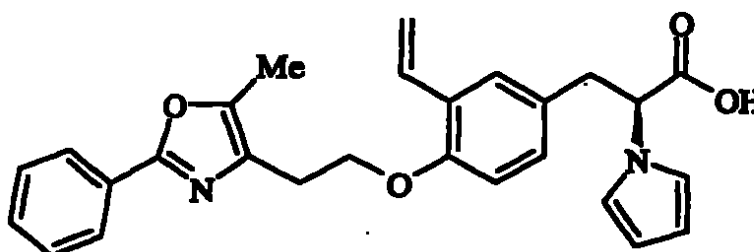
The title compound (1.0 g, 1.8 mol) was dissolved in toluene under N₂ atmosphere at 23°C. To this solution was added tributyl-prop-1-ynyl-stannane (1.10 mL, 3.6 mmol) and Pd(Cl₂(PPh₃)₂) (38 mg, 0.054 mmol) and the flask was heated to reflux for 18 hours. The reaction was washed with aqueous KF (1x

205

50 mL), water (2x 50 mL), and brine (1x 50 mL). The organic layer was dried over Na_2SO_4 and solvent removed *in vacuo*. The residue was chromatographed with 10-30% EtOAc/Hex to give 400 mg (47% yield) of product as a beige gum. CIMS m/z 469.2 (M).

5 **Example 125**

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-vinyl-phenyl]-2-pyrrol-1-yl-propionic acid (334).



334

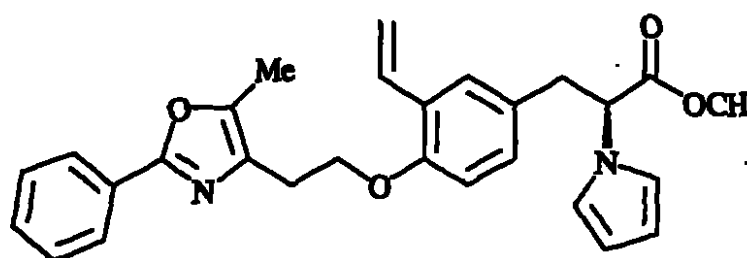
10 The title compound was obtained from 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-vinyl-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (333) 54% yield utilizing hydrolysis procedure A. NMR (δ ; CHCl_3); 7.96 (2H, m); 7.41 (3H, m); 6.99 (1H, s); 6.90 (2H, m); 6.71 (3H, m); 6.15 (2H, s); 5.58 (1H, d, $J=17\text{Hz}$); 5.17 (1H, d, $J=11\text{Hz}$); 4.72 (1H, m); 4.20 (2H, m); 3.36 (1H, m); 3.20 (1H, m); 2.99 (2H, m); 2.35 (3H, s). CIMS m/z 443.1 (M)⁺.

15

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-vinyl-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (333) was obtained in the following manner.

(a) 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-vinyl-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester (333).

20



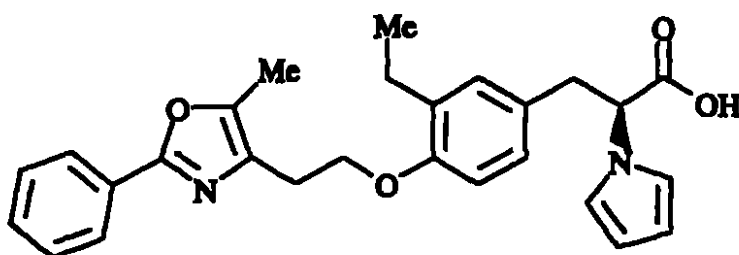
333

The title compound was obtained in 61% utilizing vinyl tributyl stannane and a procedure similar to that used in the synthesis of Example 125.

5 MICROANALYSIS CHN theoretical C=73.66, H=6.18, N=6.14. Observed C=73.55, H=5.92, N=5.60 with 0.1 eq. EtOAc as impurity.

Example 126

3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid (336).



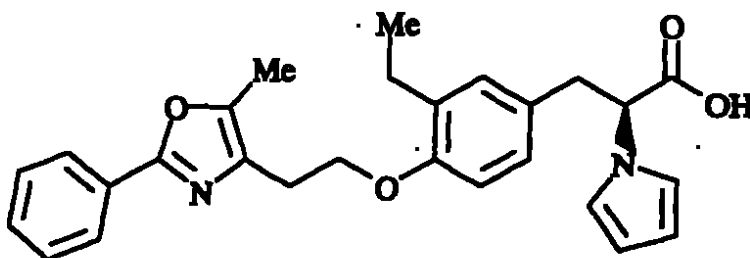
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336

The title compound was obtained from 3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (335) in 68% yield utilizing general hydrolysis procedure A. Microanalysis CHN
15 theoretical C=72.95, H=6.35, N=6.30; Observed 72.71, H=6.44, N=6.29.
M.P.=164-165.

3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (335) was prepared in the following manner.

- (a) 3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester (335)

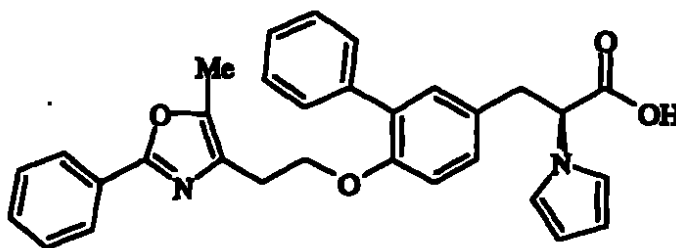


335

- 5 The title compound was obtained from the corresponding vinyl-phenyl derivative via hydrogenation procedure used in the preparation of esters 130a-c in 70% yield as white powder. Microanalysis CHN theoretical C=73.34, H=6.59, N=6.11; Observed 72.96, H=6.60, N=6.10.

Example 127

- 10 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-biphenyl-3-yl}-2-pyrrol-1-yl-propionic acid (338).



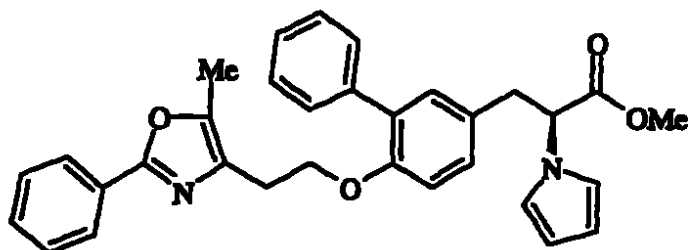
338

- 15 The title compound was obtained from 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-biphenyl-3-yl}-2-pyrrol-1-yl-propionic acid methyl ester (337) via general hydrolysis procedure A in 56% yield as white crystals. M.P. 163-164°C. Microanalysis CHN theoretical C=75.59, H=5.73, N=5.69; Observed 75.39, H=5.83, N=5.43.

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3-[6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-biphenyl-3-yl]-2-pyrrol-1-yl-propionic acid methyl ester (338) was prepared in the following manner.



337

5 The title compound was obtained in 96% yield from phenyl-boronic acid via a Pd catalyzed procedure similar to that used to obtain the vinyl-phenyl group. CIMS m/z 507.2 (M)⁺.

Example 128

10 The following illustrates representative pharmaceutical dosage forms, containing a compound of Formula I (Compound 4f), for therapeutic or prophylactic use in humans.

(i)	Tablet	mg/tablet
	Invention Compound	25.0
	Lactose	50.0
	Corn Starch (for mix)	10.0
	Corn Starch (paste)	10.0
	Magnesium Stearate (1%)	3.0
		300.0

15 The biphenylsulfonamide, lactose, and corn starch (for mix) are blended to uniformity. The corn starch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four

200

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times a day for treatment of pathogenic bacterial infections.

(ii) Tablet	mg/capsule
Invention Compound	10.0
Colloidal Silicon Dioxide	1.5
Lactose	465.5
Pregelatinized Starch	120.0
Magnesium Stearate (1%)	3.0
	600.0

(iii) Preparation for Oral Solution	Amount
'Compound 4f'	400 mg
Sorbitol Solution (70 % N.F.)	40 mL
Sodium Benzoate	20 mg
Saccharin	5 mg
Cherry Flavor	20 mg
Distilled Water q.s.	100 mL

5 The sorbitol solution is added to 40 mL of distilled water, and the biphenylsulfonamide is dissolved therein. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water. Each milliliter of syrup contains 4 mg of invention compound.

10 (iv) Parenteral Solution

 In a solution of 700 mL of propylene glycol and 200 mL of water for injection is suspended 20 g of 2-Amino-4-cyclopropyl-7-fluoro-5-methyl-6-[3-(1-methylamino-ethyl)-pyrrolidin-1-yl]-pyrido[1,2-c]pyrimidine-1,3-dione (Compound 4f). After suspension is complete, the pH is adjusted to 6.5 with 1 N hydrochloric acid, and the volume is made up to 1000 mL with water for injection. 15 The Formulation is sterilized, filled into 5.0 mL ampoules each containing 2.0 mL, and sealed under nitrogen.

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(v)	Injection 1 (1 mg/mL)	Amount
	Invention Compound	1.0
	Dibasic Sodium Phosphate	12.0
	Monobasic Sodium Phosphate	0.7
	Sodium Chloride	4.5
	N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
	Water for injection	q.s. ad 1 mL
(vi)	Injection 2 (10 mg/mL)	Amount
	Invention Compound	10.0
	Dibasic Sodium Phosphate	1.1
	Monobasic Sodium Phosphate	0.3
	Polyethylene glyco 400	200.0
	N hydrochloric acid solution (pH adjustment to 7.0-7.5)	q.s.
	Water for injection	q.s. ad 1 mL
(vii)	Injection 2 (10 mg/mL)	Amount
	Invention Compound	20.0
	Oleic Acid	10.0
	Trichloromonofluoromethane	5,000.0
	Dichlorodifluoromethane	10,000.0
	Dichlorotetrafluoroethane	5,000.0.

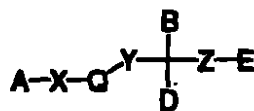
- 5 All patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

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CLAIMS

What is claimed is:

1. A compound of formula (I)



I

or a pharmaceutically acceptable salt thereof, wherein:

Aryl and substituted aryl,
heteroaryl and substituted heteroaryl,
fused heteroaryl and substituted fused heteroaryl,
(C₃-C₇)cycloalkyl and substituted cycloalkyl, or
heterocycloalkyl and substituted heterocycloalkyl;

X is a tether 2 to 5 atoms in length selected from



Q is aryl or substituted aryl;

heteroaryl or substituted heteroaryl;
fused heteroaryl, or substituted fused heteroaryl; provided that
when q is a five-membered heteroaryl, the point of attachment
from X to Q is not at the heteroatom of the heteroaryl;

Y and Z are independently absent or are (CR₁R₂)_n and (CR₃R₄)_m, wherein
R₁-R₄ are each independently H, halo, (C₁-C₆)alkyl, hydroxy, (C₁-
C₆)alkoxy, and m and n are each independently 1, 2, or 3;

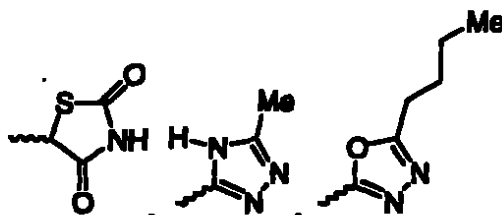
B is H, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or (C₁-C₆)alkoxy;

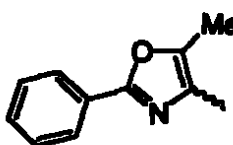
D is H, H, —NH-aryl and —NH-substituted aryl,

(C₁-C₆)alkanoyl and substituted alkanoyl,
benzoyl and substituted benzoyl,
aryl and substituted aryl,
heteroaryl and substituted heteroaryl,

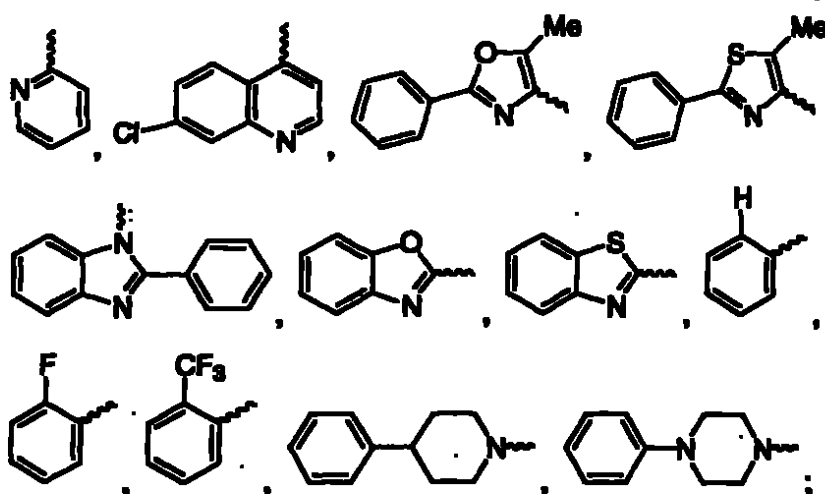
(C₃-C₇)cycloalkyl and substituted cycloalkyl, or
heterocycloalkyl and substituted heterocycloalkyl;

E is COR₅, wherein R₅ is (C₁-C₆)alkyl, OH, (C₁-C₆)alkoxy, NR₆R₇,
wherein R₆ and R₇ are each independently H or (C₁-C₆)alkyl, or
one of R₆ and R₇ is H or (C₁-C₆)alkyl and the other is SO₂R₈,
wherein R₈ is H or (C₁-C₆)alkyl, or E is substituted heteroaryl or

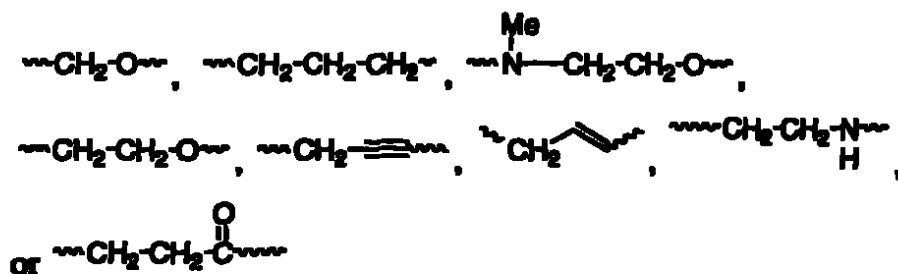


provided that when A is , X is $\sim\text{CH}_2\text{CH}_2\text{O}\sim$ Q is phenyl, Y and Z are CH₂, B is H, and E is CO₂H, D is not pyrrolyl.

2. The compound of claim 1, wherein
A is



X is a tether 2 to 5 atoms in length selected from



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Q is aryl or substituted aryl;

heteroaryl or substituted heteroaryl;

fused heteroaryl, or substituted fused heteroaryl; provided that

when q is a five-membered heteroaryl, the point of attachment

from X to Q is not at the heteroatom of the heteroaryl;

Y is CH₂;

Z is absent;

B is H, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or (C₁-C₆)alkoxy;

D is H, H, —NH-aryl and —NH-substituted aryl,

(C₁-C₆)alkanoyl and substituted alkanoyl,

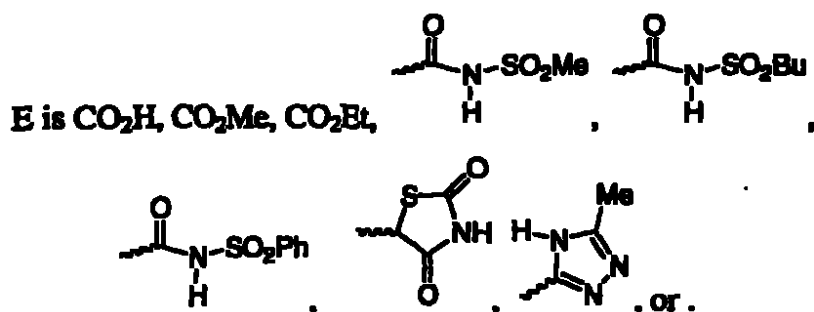
benzoyl and substituted benzoyl,

aryl and substituted aryl,

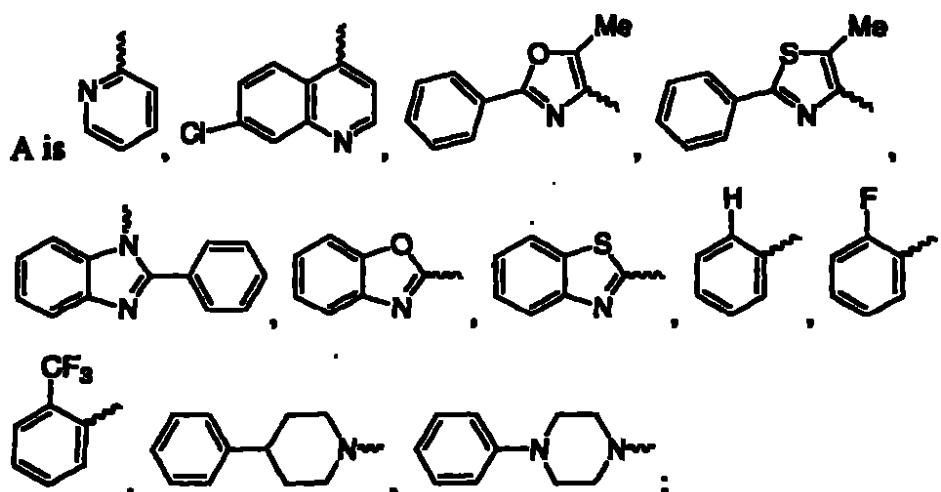
heteroaryl and substituted heteroaryl,

(C₃-C₇)cycloalkyl and substituted cycloalkyl, or

heterocycloalkyl and substituted heterocycloalkyl; and



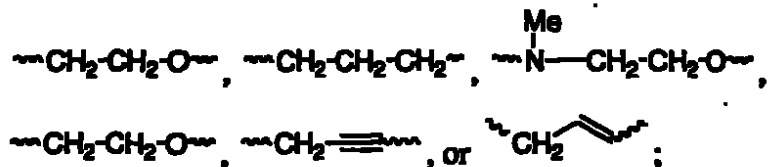
3. The compound of claim 1, wherein



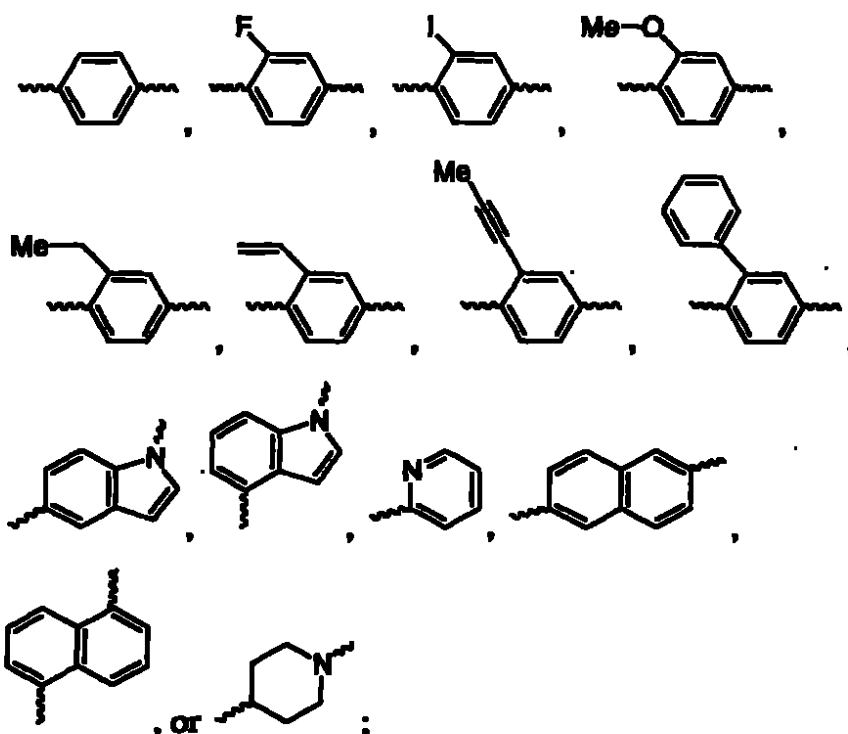
314

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X is a tether 2 to 5 atoms in length selected from



Q is



Y is CH₂;

Z is absent

B is H, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or (C₁-C₆)alkoxy;

D is H, H, —NH-aryl and —NH-substituted aryl,

(C₁-C₆)alkanoyl and substituted alkanoyl,

benzoyl and substituted benzoyl,

aryl and substituted aryl,

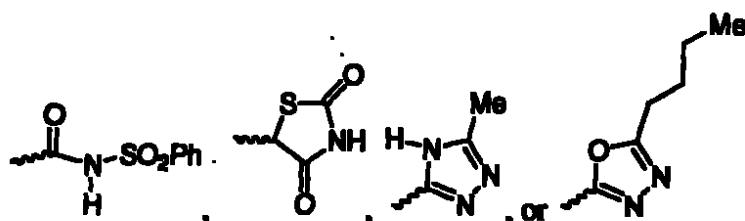
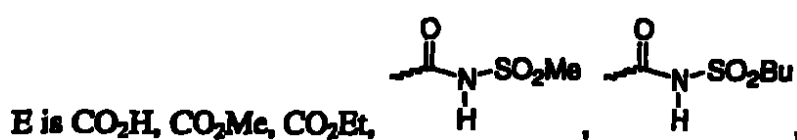
heteroaryl and substituted heteroaryl,

(C₃-C₇)cycloalkyl and substituted cycloalkyl, or

heterocycloalkyl and substituted heterocycloalkyl; and

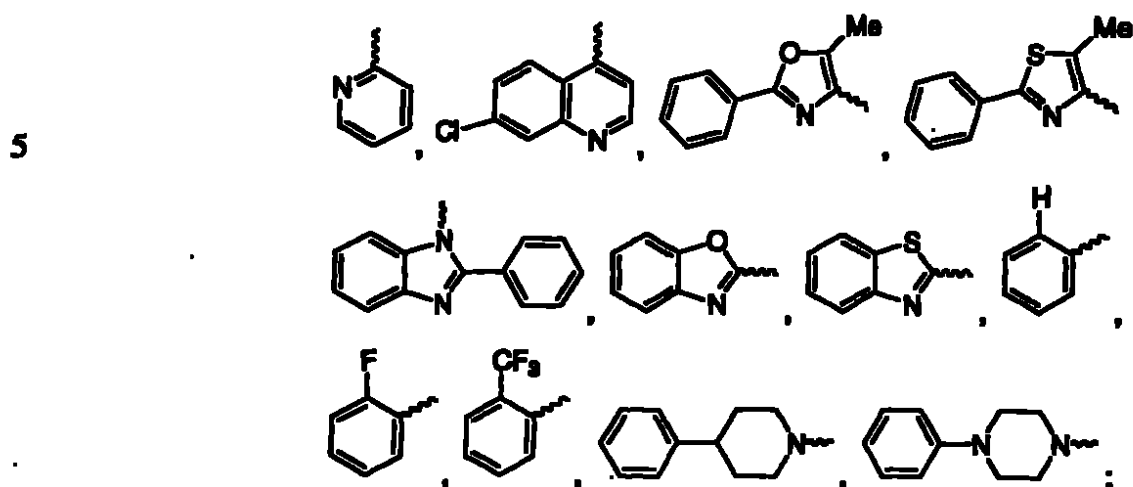
315

-298-

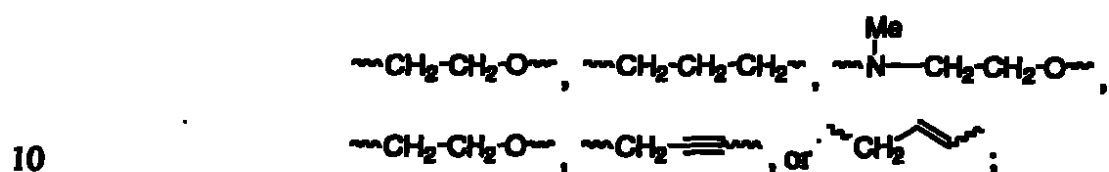


4. The compound of claim 1, wherein

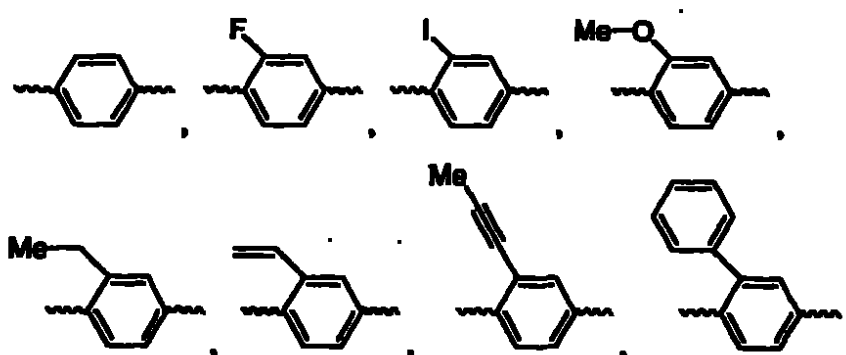
A is



X is a tether 2 to 5 atoms in length selected from

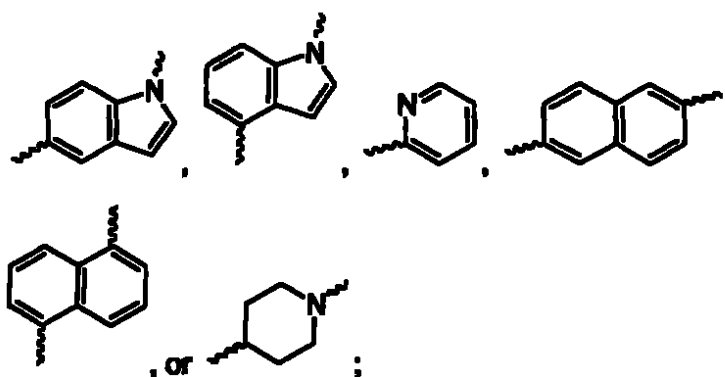


Q is



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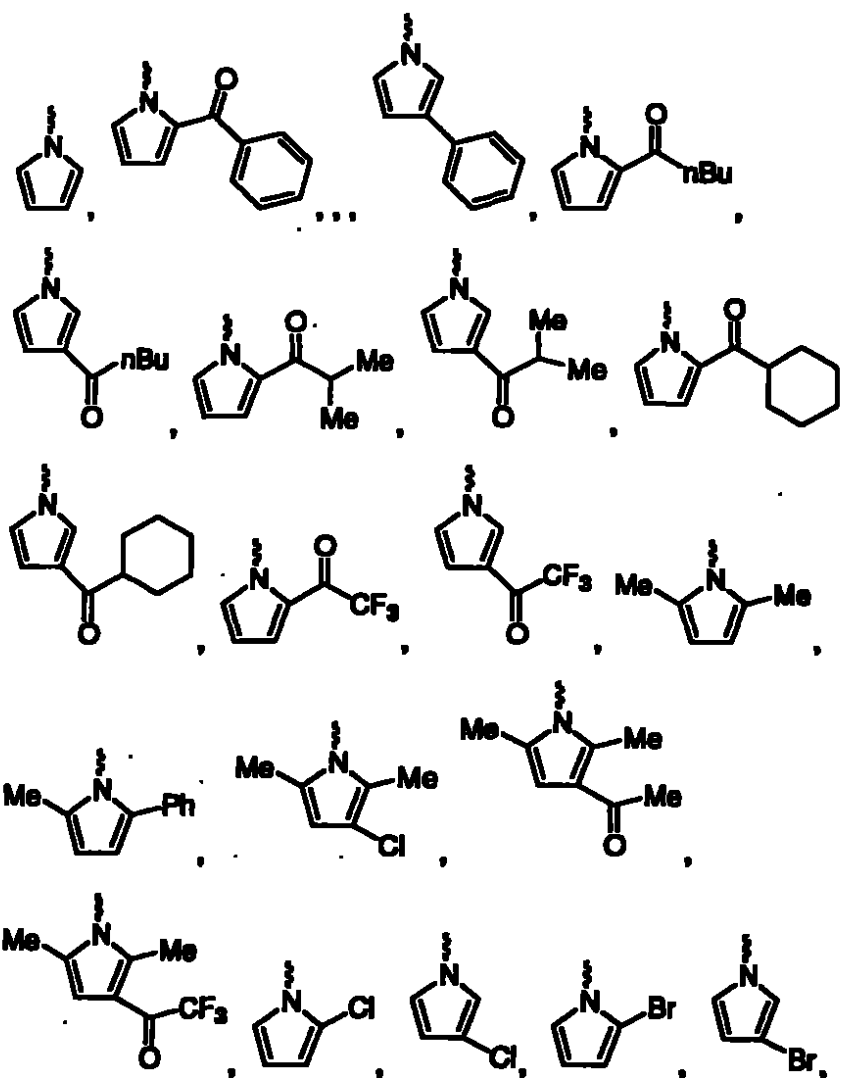
Y is CH₂;

Z is absent;

5

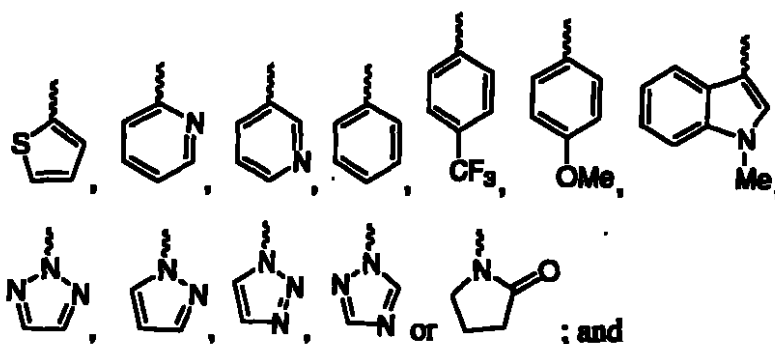
B is H, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or (C₁-C₆)alkoxy;

D is H, Me,

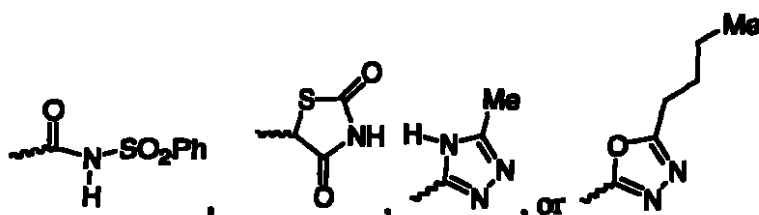


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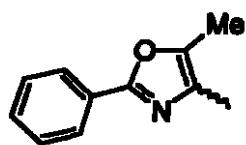
317



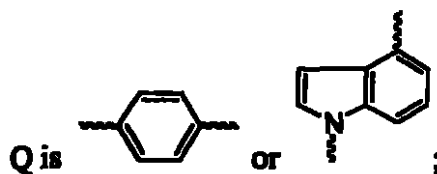
E is CO_2H , CO_2Me , CO_2Et , $\text{NH-CO-SO}_2\text{Me}$, $\text{NH-CO-SO}_2\text{Bu}$, $\text{NH-CO-SO}_2\text{Ph}$, or $\text{NH-CO-SO}_2\text{Ph}$.



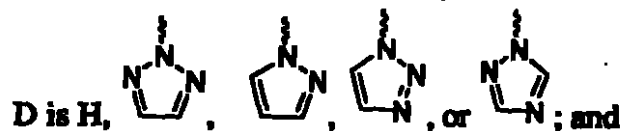
5. The compound of claim 1, wherein
A is



X is $\text{CH}_2\text{CH}_2\text{O}$ or $\text{CH}_2\text{CH}_2\text{CH}_2$;



- Y is CH_2 ;
Z is absent;
B is H;



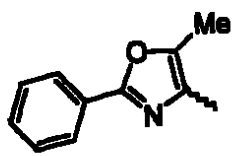
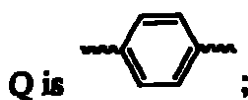
E is CO_2H .

6. The compound of claim 1, wherein

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A is

X is $\sim\text{CH}_2\text{CH}_2\text{O}\sim$ or $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$;

5

Y is CH_2 ;

Z is absent;

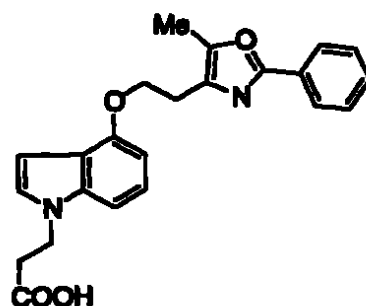
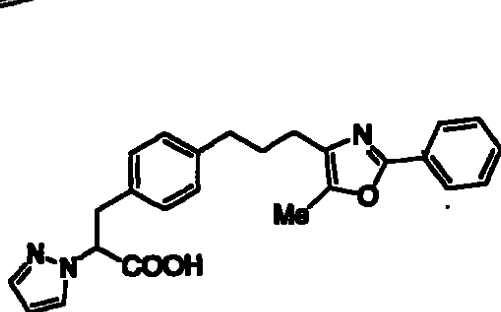
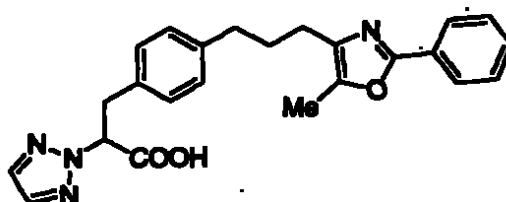
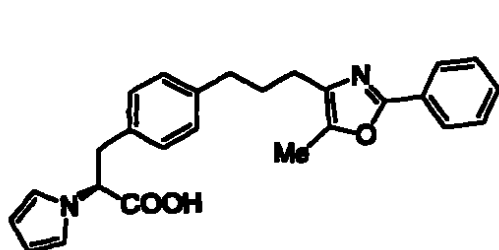
B is H;

D is H, , , , or ; and

E is CO_2H .

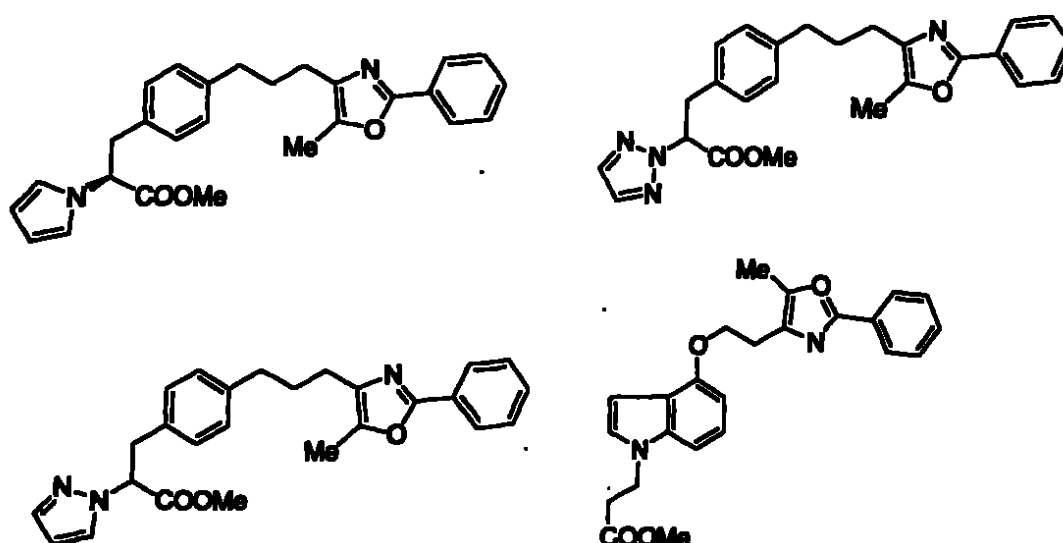
10

7. The compound which is:



8. The compound which is:

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9. The compound which is:

(R)-2-(2-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

5 (R)-2-Ethyl-5-(2-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

(R)-2-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

10 (R)-2-Methyl-3-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid;

(R)-3-Methyl-5-(2-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;

(R)-2-(3-Bromo-pyrrol-1-yl)-2-methyl-3-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-propionic acid;

15 (S)-3,3,3-Trifluoro-2-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl)-2-pyrrol-1-yl-propionic acid;

(R)-3,3,3-Trifluoro-2-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl)-2-pyrrol-1-yl-propionic acid;

20 (R)-2-ethyl-3-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid;

(S)-2-ethyl-3-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyrrol-1-yl-propionic acid;

(R)-2-propyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-propyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

5 (S)-3,3,3-Trifluoroethyl-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

(R)-3,3,3-Trifluoroethyl-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

10 (R)-2-Fluoromethyl-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-Fluoromethyl-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

(S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-fluoromethyl-2-pyrrol-1-yl-propionic acid;

15 (R)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-fluoromethyl-2-pyrrol-1-yl-propionic acid;

(S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

20 (R)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

(S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

(R)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

25 (S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

(R)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

30 (S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(R)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;

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(S)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;

(R)-2-(3-Bromo-pyrrol-1-yl)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-propionic acid;

5 (S)-2-(3-Bromo-pyrrol-1-yl)-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-propionic acid;

(S)-3,3,3-Trifluoro-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

10 (R)-3,3,3-Trifluoro-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(R)-2-ethyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-ethyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

15 (R)-2-propyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-propyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

20 (S)-3,3,3-Trifluoroethyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(R)-3,3,3-Trifluoroethyl-3-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-Pyrrol-1-yl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-propionic acid;

25 (R)-2-Pyrrol-1-yl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-propionic acid;

(R)-2-(2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl])-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

30 (S)-2-(2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl])-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

(R)-2-Ethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl])-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

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- (S)-2-Ethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;
- (R)-2-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;
- 5 (S)-2-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;
- (R)-2-Methyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;
- (S)-2-Methyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;
- 10 (R)-3-Methyl-5-(3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;
- (S)-3-Methyl-5-(3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;
- 15 (R)-2-(3-Bromo-pyrrol-1-yl)-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-propionic acid;
- (R)-2-(3-Bromo-pyrrol-1-yl)-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-propionic acid;
- (S)-3,3,3-Trifluoro-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;
- 20 (R)-3,3,3-Trifluoro-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;
- (R)-2-ethyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;
- 25 (S)-2-ethyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;
- (R)-2-propyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;
- (S)-2-propyl-3-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-phenyl]-2-pyrrol-1-yl-propionic acid;
- 30 (S)-3,3,3-Trifluoroethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;

(R)-3,3,3-Trifluoroethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;

(R) 2-Fluoromethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;

5 (S) 2-Fluoromethyl-2-[4-(4'-trifluoromethyl-biphenyl-4-ylmethoxy)-benzyl]-2-pyrrol-1-yl-propionic acid;

(S)-2-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

10 (R)-2-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

(S)-2-Ethyl-2-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

(R)-2-Ethyl-2-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

15 (R)-2-2-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

(S)-2-2-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

20 (R)-2-Methyl-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid;

(S)-2-Methyl-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-2-pyrrol-1-yl-propionic acid;

(R)-3-Methyl-5-(3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;

25 (S)-3-Methyl-5-(3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole;

(R)-2-(3-Bromo-pyrrol-1-yl)-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-propionic acid;

30 (S)-2-(3-Bromo-pyrrol-1-yl)-3-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl]-propionic acid;

(S)-3,3,3-Trifluoro-2-[4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl]-2-pyrrol-1-yl-propionic acid;

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(R)-3,3,3-Trifluoro-2-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

(R)-2-ethyl-3-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

5 (S)-2-ethyl-3-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(R)-2-propyl-3-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

10 (S)-2-propyl-3-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-3,3,3-Trifluoroethyl-2-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

(R)-3,3,3-Trifluoroethyl-2-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

15 (R)-2-Fluoromethyl-2-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid; or

(S)-2-Fluoromethyl-2-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid.

10. The compound which is:

20 (S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-(2-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

25 (S)-2-(3-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid;

(S)-3-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid;

30 N-(S)-(3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionyl)-Benzenesulfonamide

N-(S)-(3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionyl)-Methanesulfonamide

(S)-2-(3-Isobutyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

5 (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

(S)-3-{4-[2-(Benzoxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-cyclohexanecarbonyl-pyrrol-1-yl)-propionic acid;

10 (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-(2-fluorobenzyloxy)-phenyl]-propionic acid;

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid;

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyridin-4-yl-propionic acid;

15 2-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-2H-tetrazole

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-2-yl-propionic acid;

20 N-(2,2-Dimethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionyl)-methanesulfonamide

N-(2-Fluoro-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionyl)-methanesulfonamide

2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid;

25 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-phenyl-propionic acid;

30 (S)-2-(2-Acetyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

3-{4-[2-(Benzothiazol-2-ylsulfanyl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-Pyrrol-1-yl-3-(4-[2-(2-trifluoromethyl-phenyl)-ethoxy]-phenyl)-propionic acid;

(S)-3-{4-[2-(4-Phenyl-piperazin-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

5 (S)-3-{4-[2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

(S)-2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

10 (S)-3-(4-{2-[(7-Chloro-quinolin-4-yl)-methyl-amino]-ethoxy}-phenyl)-2-pyrrol-1-yl-propionic acid;

(S)-2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(4-methyl-2-phenyl-oxazol-5-yl)-ethoxy]-phenyl}-propionic acid;

(S)-2-[2,5-Dimethyl-3-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

15 3-{4-[2-(2-Phenyl-benzimidazol-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

2-(3-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

20 2-(2-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

2-(2-Chloro-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

(S)-2-(2-Butyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

25 (S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-{4-(2-fluoro-benzyloxy)-phenyl}-propionic acid;

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-methyl-5-phenyl-pyrrol-1-yl)-propionic acid;

30 (S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl}-2-pyrrol-1-yl-propionic acid;

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3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-thiophen-2-yl-propionic acid;

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyridin-3-yl-propionic acid;

5 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-propionic acid;

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-(3-triflorophenyl)-propionic acid;

10 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-propionic acid; (R)

2-(4-Methoxy-phenyl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid;

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-phenyl]-2-pyrrol-1-yl-propionic acid;

15 2-Methyl-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-propionic acid;

2,2-Dimethyl-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid;

20 2-Fluoro-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-propionic acid;

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-(2-oxo-pyrrolidin-1-yl)-propionic acid;

2-Ethyl-5-(2-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl])-1-phenyl-ethyl)-1,3,4-oxadiazole

25 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl]-2-pyrrol-1-yl-propionic acid;

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyridin-3-yl-propionic acid;

30 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-propionic acid;

3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-(3-triflorophenyl)-propionic acid;

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(R)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid;

(S)-2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

5 3-{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-propionic acid;

10 (S)-2-(2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;

(S)-2-Ethyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

(S)-2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;

15 (S)-3-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole

2-(3-Bromo-pyrrol-1-yl)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

20 3,3,3-Trifluoro-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid;

2-(4-Benzyloxy-indol-1-yl)-propionic acid;

3-(1-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-benzyl}-1H-pyrrol-2-yl)-propionic acid;

25 (1-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl]-1H-indol-5-yloxy)-phenyl-acetic acid;

2-(1-Methyl-1H-indol-3-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid;

3-(4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propoxy]-indol-1-yl)-propionic acid;

30 2-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl)-propionic acid;

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- 3-(4-[2-(2-Trifluoromethyl-phenyl)-ethoxy]-indol-1-yl)-propionic acid;
- (4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propoxy]-indol-1-yl)-acetic acid;
- 5 4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl)-acetic acid;
- 4-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl]-butyric acid;
- 3-(3-Fluoro-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-(S)-pyrrol-1-yl-propionic acid;
- 10 3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-pyridin-4-yl-propionic acid;
- 2-Methyl-5-(2-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-1-phenyl-ethyl)-2H-tetrazole;
- 15 1-Methyl-5-(2-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-1-phenyl-ethyl)-1H-tetrazole;
- 2-Methyl-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-thiophen-2-yl-propionic acid;
- 2-Methyl-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-thiophen-3-yl-propionic acid;
- 20 N-(2,2-Dimethyl-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionyl)-methanesulfonamide;
- N-(2-Fluoro-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-2-phenyl-propionyl)-methanesulfonamide;
- 25 3-[3-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-isoxazol-5-yl]-2-pyrrol-1-yl-propionic acid;
- 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-[4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-propionic acid;
- 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propionic acid;
- 30 3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-phenyl-propionic acid;

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- 3-{4-[3-(5-Methyl-2-phenyloxazol-4-yl)-propyl]-phenyl}-2-phenylpropionic acid;
- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-pyrrol-1-yl-propionic acid;
- 5 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-phenylpropionic acid;
- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-phenylpropionic acid;
- 10 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-thiophen-2-yl-propionic acid;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-acrylic acid;
- {4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid;
- 15 {4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid; methyl ester
- Methyl-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid;
- 6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-naphthalene-2-carboxylic acid;
- 20 3-{5-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-naphthalen-1-yl}-2-pyrrol-1-yl-propionic acid;
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,3-triazol-1-yl-propionic acid; ethyl ester
- 25 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,3-triazol-1-yl-propionic acid;
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrazol-1-yl-propionic acid;
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,4-triazol-1-yl-propionic acid;
- 30 5-Methyl-2-phenyl-4-prop-2-enyloxazole

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- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-2-pyridin-3-yl-propionic acid;
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyridin-3-yl-propionic acid;
- 5 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyridin-3-yl-propionic acid;
- 2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid;
- 2-Biphenyl-4-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid;
- 10 2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-propionic acid;
- 2-Biphenyl-3-yl-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid;
- 15 2-(5-Methyl-isoxazol-3-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid;
- 2-(3-Methyl-isoxazol-5-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid;
- (S)-3-(4-{[(5-Methyl-2-phenyl-oxazol-4-yl)methyl]-amino}-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid;
- 20 (S)-3-(4-{[Acetyl-(5-methyl-2-phenyl-oxazol-4-yl)methyl]-amino}-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid;
- (S)-3-(4-{[Methyl-(5-methyl-2-phenyl-oxazol-4-yl)methyl]-amino}-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid;
- 25 (S)-3-(4-{[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid;
- (S)-3-[4-{[Benzyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino]-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid;
- (S)-3-[4-{[Benzoyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino]-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid;
- 30 (S)-3-[4-{[Acetyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino]-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid;

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4-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-butyric acid;

3-{1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-2-pyrrol-1-yl-propionic acid;

5 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid;

10 3-{3-Methoxy-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

Butane-1-sulfonic acid; (3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-amide;

N-(3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-methanesulfonamide;

15 3-{3-Iodo-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-phenyl}-2-pyrrol-1-yl-propionic acid;

20 3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-biphenyl-3-yl}-2-pyrrol-1-yl-propionic acid;

4-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-butyric acid;

25 2-Pyrrol-1-yl-4-(4-trifluoromethanesulfonyl-phenyl)-butyric acid; methyl ester;

3-{1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-2-pyrrol-1-yl-propionic acid;

30 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionic acid;

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3-{3-Methoxy-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

Butane-1-sulfonic acid; (3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-amide;

5 N-(3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-methanesulfonamide;

3-{3-Iodo-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid;

10 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-phenyl}-2-pyrrol-1-yl-propionic acid;

3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid; or

3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-biphenyl-3-yl}-2-pyrrol-1-yl-propionic acid.

15 11. The compound which is:

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-2-(2-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

20 (S)-2-(3-Benzoyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

(S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester;

25 (S)-3-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-phenyl-pyrrol-1-yl)-propionic acid methyl ester;

N-(S)-(3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionyl)-benzenesulfonamide;

N-(S)-(3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionyl)-Methanesulfonamide;

30 (S)-2-(3-Isobutyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

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- (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;
- (S)-3-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenyl}-2-(3-cyclohexanecarbonyl-pyrrol-1-yl)-propionic acid methyl ester;
- 5 (S)-2-(3-Cyclohexanecarbonyl-pyrrol-1-yl)-3-[4-(2-fluorobenzyloxy)-phenyl]-propionic acid methyl ester;
- (S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-[2-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-propionic acid methyl ester;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-
- 10 pyridin-4-yl-propionic acid methyl ester;
- 2-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-2H-tetrazole
- 2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-2-yl-propionic acid methyl ester;
- 15 N-(2,2-Dimethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionyl)-methanesulfonamide
- N-(2-Fluoro-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionyl)-methanesulfonamide
- 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester;
- 20 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-phenyl-propionic acid methyl ester;
- 25 (S)-2-(2-Acetyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;
- 3-{4-[2-(Benzothiazol-2-ylsulfanyl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- (S)-2-Pyrrol-1-yl-3-{4-[2-(2-trifluoromethyl-phenyl)-ethoxy]-phenyl}-propionic acid methyl ester;
- 30 (S)-3-{4-[2-(4-Phenyl-piperazin-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

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(S)-3-{4-[2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-2-(3-Chloro-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

5 (S)-3-(4-{2-[(7-Chloro-quinolin-4-yl)-methyl-amino]-ethoxy}-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-2-(3-Acetyl-2,5-dimethyl-pyrrol-1-yl)-3-{4-[2-(4-methyl-2-phenyl-oxazol-5-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

10 (S)-2-[2,5-Dimethyl-3-(2,2,2-trifluoro-acetyl)-pyrrol-1-yl]-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

3-{4-[2-(2-Phenyl-benzimidazol-1-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

15 2-(3-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

2-(2-Bromo-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

2-(2-Chloro-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

20 (S)-2-(2-Butyryl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

(S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-{4-(2-fluoro-benzyloxy)-phenyl}-propionic acid methyl ester;

25 (S)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-methyl-5-phenyl-pyrrol-1-yl)-propionic acid methyl ester;

(S)-2-(2,5-Dimethyl-pyrrol-1-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;

3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

30 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-2-yl-propionic acid methyl ester;

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- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyridin-3-yl-propionic acid methyl ester;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid methyl ester;
- 5 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-triflorophenyl)-propionic acid methyl ester;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid methyl ester; ®
- 2-(4-Methoxy-phenyl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;
- 10 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid methyl ester;
- 15 2,2-Dimethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;
- 2-Fluoro-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid methyl ester;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-oxo-pyrrolidin-1-yl)-propionic acid methyl ester;
- 20 2-Ethyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1,3,4-oxadiazole
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionyl]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 25 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyridin-3-yl-propionic acid methyl ester;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid methyl ester;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-triflorophenyl)-propionic acid methyl ester;
- 30 (R)-3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionic acid methyl ester;

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- S)-2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester, methyl ester
- 3-{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester;
- 5 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester;
- (S)-2-(2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-5-propyl-1,3,4-oxadiazole;
- (S)-2-Ethyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;
- 10 (S)-2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-pyrrol-1-yl-ethyl)-1,3,4-oxadiazole;
- (S)-3-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-(S)-pyrrol-1-yl-ethyl)-4H-1,2,4-triazole
- 15 2-(3-Bromo-pyrrol-1-yl)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;
- 3,3,3-Trifluoro-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 2-(4-Benzyloxy-indol-1-yl)-propionic acid methyl ester;
- 20 3-(1-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-benzyl}-1H-pyrrol-2-yl)-propionic acid methyl ester;
- (1-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl]-1H-indol-5-yloxy)-phenyl-acetic acid methyl ester;
- 2-(1-Methyl-1H-indol-3-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;
- 25 3-(4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propoxy]-indol-1-yl)-propionic acid methyl ester;
- 2-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl)-propionic acid methyl ester;
- 30 3-(4-[2-(2-Trifluoromethyl-phenyl)-ethoxy]-indol-1-yl)-propionic acid methyl ester;

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- (4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propoxy]-indol-1-yl)-acetic acid methyl ester;
- 4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl)-acetic acid methyl ester;
- 5 4-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indol-1-yl}-butyric acid methyl ester;
- 3-(3-Fluoro-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-(S)-pyrrol-1-yl-propionic acid methyl ester;
- 3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl)-2-pyridin-4-yl-propionic acid methyl ester;
- 10 2-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-2H-tetrazole;
- 1-Methyl-5-(2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-1-phenyl-ethyl)-1H-tetrazole;
- 15 2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-2-yl-propionic acid methyl ester;
- 2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-thiophen-3-yl-propionic acid methyl ester;
- N-(2,2-Dimethyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionyl)-methanesulfonamide;
- 20 N-(2-Fluoro-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-propionyl)-methanesulfonamide;
- 3-{3-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-isoxazol-5-yl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 25 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-propionic acid methyl ester;
- 2-(5-Methyl-2-phenyl-oxazol-4-yl)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester;
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-phenyl-propionic acid methyl ester;
- 30 3-{4-[3-(5-Methyl-2-phenyloxazol-4-yl)-propyl]-phenyl}-2-phenylpropionic acid methyl ester;

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- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-phenylpropionic acid methyl ester;
- 5 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-phenylpropionic acid methyl ester;
- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-2-thiophen-2-yl-propionic acid methyl ester;
- 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenyl-acrylic acid methyl ester;
- 10 {4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester;
- {4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester; methyl ester;
- 15 Methyl-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzylamino}-phenylacetic acid methyl ester;
- 6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-naphthalene-2-carboxylic acid methyl ester;
- 3-{5-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-naphthalen-1-yl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 20 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,3-triazol-1-yl-propionic acid methyl ester; ethyl ester
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,3-triazol-1-yl-propionic acid methyl ester;
- 25 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrazol-1-yl-propionic acid methyl ester;
- 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,4-triazol-1-yl-propionic acid methyl ester;
- 5-Methyl-2-phenyl-4-prop-2-enyloxazole;
- 30 3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl}-2-pyridin-3-yl-propionic acid methyl ester;

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3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-pyridin-3-yl-propionic acid methyl ester;

3-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-pyridin-3-yl-propionic acid methyl ester;

5 2-Biphenyl-4-yl-3-[4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-propionic acid methyl ester;

2-Biphenyl-4-yl-3-[4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl]-propionic acid methyl ester;

10 2-Biphenyl-3-yl-3-[4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-prop-1-ynyl]-phenyl]-propionic acid methyl ester;

2-Biphenyl-3-yl-3-[4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-propionic acid methyl ester;

2-(5-Methyl-isoxazol-3-yl)-3-[4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-propionic acid methyl ester;

15 2-(3-Methyl-isoxazol-5-yl)-3-[4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-propionic acid methyl ester;

(S)-3-(4-([(5-Methyl-2-phenyl-oxazol-4-yl)methyl]-amino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester;

20 (S)-3-(4-([Acetyl-(5-methyl-2-phenyl-oxazol-4-yl)methyl]-amino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-3-(4-([Methyl-(5-methyl-2-phenyl-oxazol-4-yl)methyl]-amino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-3-(4-([2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-methyl)-phenyl)-2-pyrrol-1-yl-propionic acid methyl ester;

25 (S)-3-[4-({Benzyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino}-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester;

(S)-3-[4-({Benzoyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino}-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester;

30 (S)-3-[4-({Acetyl-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl]-amino}-methyl)-phenyl]-2-pyrrol-1-yl-propionic acid methyl ester;

4-[4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl]-2-pyrrol-1-yl-butyric acid methyl ester;

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- 3-{1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-
2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-
phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 5 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-
phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{3-Methoxy-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-
phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 10 Butane-1-sulfonic acid methyl ester; (3-{4-[3-(5-methyl-2-phenyl-
oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-amide;
- N-(3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-
pyrrol-1-yl-propionyl)-methanesulfonamide;
- 3-{3-Iodo-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-
2-pyrrol-1-yl-propionic acid methyl ester;
- 15 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-
phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-
2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-biphenyl-3-yl}-
2-pyrrol-1-yl-propionic acid methyl ester;
- 20 4-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-
pyrrol-1-yl-butyric acid methyl ester;
- 2-Pyrrol-1-yl-4-(4-trifluoromethanesulfonyl-phenyl)-butyric acid
methyl ester; methyl ester;
- 25 3-{1-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-piperidin-4-yl}-
2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propenyl]-
phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 3-{3-Methoxy-4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-
phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;
- 30 3-{3-Methoxy-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-
phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

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Butane-1-sulfonic acid methyl ester, (3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-amide;

N-(3-{4-[3-(5-Methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-pyrrol-1-yl-propionyl)-methanesulfonamide;

5 3-{3-Iodo-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3-prop-1-ynyl-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester;

10 3-{3-Ethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-pyrrol-1-yl-propionic acid methyl ester; or

3-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-biphenyl-3-yl}-2-pyrrol-1-yl-propionic acid methyl ester.

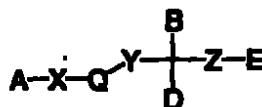
12. A pharmaceutical composition comprising a compound of Claim 1 admixed with a carrier, diluent, or excipient.

15 13. A method of treating, preventing or controlling non-insulin dependent diabetes mellitus, obesity, hyperglycemia, hyperlipidemia, hypercholesteremia, atherosclerosis, hypertriglyceridemia, hyperinsulinemia, or insulin resistance syndrome in a mammal comprising administering to the mammal in need thereof an effective amount of a
20 compound of Claim 1.

14. A method of modulating PPAR activity, lowering blood glucose, or modulating fat cell differentiation, in a mammal, comprising administering to a mammal an effective amount of a PPAR modulator of formula I, II, or III

25

15. A process for preparing a compound of formula I



I

wherein:

A is aryl and substituted aryl,
 heteroaryl and substituted heteroaryl,
 fused heteroaryl and substituted fused heteroaryl,
 (C₃-C₇)cycloalkyl and substituted cycloalkyl, or
 heterocycloalkyl and substituted heterocycloalkyl;

X is a tether 2 to 5 atoms in length selected from

$\sim\text{CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$,
 $\sim\text{CH}_2\text{-}\equiv\sim$, or $\sim\text{CH}_2\text{-}\text{CH}=\text{CH}\sim$, wherein " $\sim$ " indicates a point
 of attachment;

Q is aryl or substituted aryl;
 heteroaryl or substituted heteroaryl;
 fused heteroaryl, or substituted fused heteroaryl; provided that
 when q is a five-membered heteroaryl, the point of attachment
 from X to Q is not at the heteroatom of the heteroaryl;

Y and Z are independently absent or are (CR₁R₂)_n and (CR₃R₄)_m, wherein
 R₁-R₄ are each independently H, halo, (C₁-C₆)alkyl, hydroxy, (C₁-
 C₆)alkoxy, and m and n are each independently 1, 2, or 3;

B is H, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or (C₁-C₆)alkoxy;

D is H, H, —NH-aryl and —NH-substituted aryl,

(C₁-C₆)alkanoyl and substituted alkanoyl,

benzoyl and substituted benzoyl,

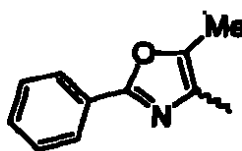
aryl and substituted aryl,

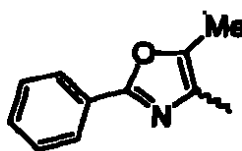
heteroaryl and substituted heteroaryl,

(C₃-C₇)cycloalkyl and substituted cycloalkyl, or

heterocycloalkyl and substituted heterocycloalkyl;

E is CO₂H;



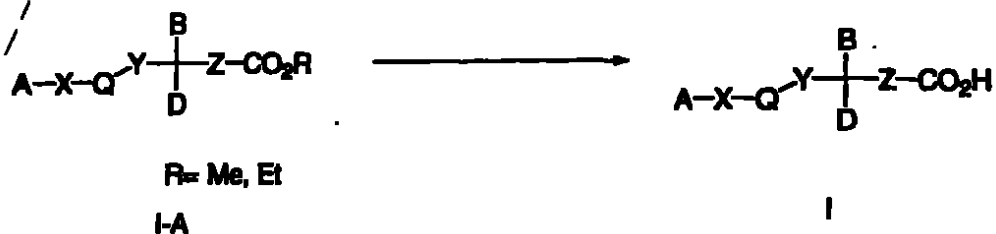
provided that when A is , X is $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$ Q is

phenyl, Y and Z are CH₂, B is H, and E is CO₂H, D is not pyrrolyl;

comprising:

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- (a) hydrolyzing the ester moiety in the compound of formula I-A to an acid moiety under basic conditions.



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AGENTES ANTIDIABÉTICOS**CAMPO DE LA INVENCION**

La presente invención se refiere a compuestos que son útiles como agentes antidiabéticos.

5 ANTECEDENTES DE LA INVENCION

La diabetes de tipo II, o la diabetes no dependiente de insulina (NIDDM), es un problema sanitario significativo cuya incidencia está en aumento. Entre 1990 y 1998, la prevalencia de NIDDM en los Estados Unidos aumentó un 33
10 por ciento, hasta aproximadamente 13 millones de personas. Se supone que 5 millones de personas más tienen una NIDDM no diagnosticada, mientras que otros 14 millones de personas presentan una reducción de la tolerancia a la glucosa. Los costes médicos directos asociados con la
15 diabetes fueron de 44.000 millones de dólares en 1997, debido principalmente a las complicaciones diabéticas relacionadas con hiperglucemias, incluyendo angiopatía diabética, aterosclerosis, nefropatía diabética, neuropatía diabética y complicaciones oculares diabéticas tales como
20 retinopatía, formación de cataratas y glaucoma.

La NIDDM es uno de varios estados de enfermedad asociados con el fenómeno de resistencia a la insulina. La resistencia a la insulina se define como la reducción de la sensibilidad a las acciones de la insulina en el cuerpo en
25 su conjunto o en tejidos individuales, tales como en el

tejido muscular esquelético, en el tejido miocárdico, en el tejido graso o en el tejido hepático. La resistencia a la insulina se produce en muchos individuos con o sin diabetes mellitus. El síndrome de resistencia a insulina (en lo
5 sucesivo IRS) se refiere al grupo de manifestaciones que incluyen resistencia a insulina; hiperinsulinemia; diabetes mellitus no dependiente de insulina (NIDDM); hipertensión arterial; obesidad central (visceral); y dislipidemia.

El objetivo principal de la terapia para el IRS y, por
10 lo tanto, de la terapia para la diabetes es reducir los niveles de glucosa en sangre para prevenir las complicaciones agudas de la enfermedad y las complicaciones a largo plazo. Para algunas personas, la modificación de la dieta y el aumento del ejercicio puede ser una opción
15 terapéutica satisfactoria para conseguir el objetivo del control de la glucosa. Cuando no es satisfactoria una modificación de la dieta y un aumento del ejercicio, se inicia una terapia con fármacos usando agentes antidiabéticos orales.

20 Hasta la fecha, se han desarrollado varios agentes antidiabéticos orales. Por ejemplo, para estimular la insulina generalmente se usan sulfonilureas. La biguanida metformina generalmente se usa para mejorar la sensibilidad a la insulina y reducir la producción de glucosa hepática.
25 La acarbosa se usa para limitar la hiperglucemia

postprandial, y las tiazolidina 2,4 dionas se usan para aumentar la acción de la insulina.

Las nuevas terapias de fármaco para el tratamiento de la NIDDM se han centrado, en parte, en el descubrimiento de 5 nuevos agonistas del Receptor de Activación del Proliferador de Peroxisomas (PPAR). Los PPAR son miembros de la superfamilia de receptores nucleares de factores de transcripción que incluyen receptores de esteroides, tiroideos y de vitamina D. Los PPAR juegan un papel para 10 controlar la expresión de proteínas que regulan el metabolismo de los lípidos. Hay tres subtipos de PPAR: PPAR α , PPAR δ y PPAR γ .

Cada receptor PPAR muestra un modelo diferente de expresión en tejidos, y diferencias en la activación por 15 compuestos estructuralmente diferentes. El PPAR γ , por ejemplo, se expresa más abundantemente en el tejido adiposo y en menores niveles en el músculo esquelético, corazón, hígado, intestino, riñón, endotelio vascular y células de músculo liso, así como en macrófagos. Existen dos isoformas 20 de PPAR γ , identificadas como γ_1 y γ_2 , respectivamente. El PPAR γ media la señalización de los adipocitos, el almacenamiento de lípidos y el metabolismo de las grasas. La evidencia acumulada hasta la fecha confirma la conclusión de que el PPAR γ es la diana molecular principal, 25 y quizás la única, que media la acción de sensibilización a

la insulina de una clase de agentes antidiabéticos, las tiazolidina 2,4 dionas.

En un contexto monoterapéutico o de terapia de combinación, aún se considera que los agentes
5 antidiabéticos orales nuevos y establecidos tienen una eficacia no uniforme e incluso limitada. La eficacia de las terapias antidiabéticas orales puede estar limitada, en parte, debido a un control glucémico deficiente o limitado, o a un seguimiento deficiente de la terapia por parte del
10 paciente debido a efectos secundarios inaceptables. Estos efectos secundarios incluyen edema, aumento de peso, o incluso complicaciones más graves. Por ejemplo, en algunos pacientes que toman sulfonilureas se han observado hipoglucemias. El metformina, una biguanida sustituida,
15 puede producir diarrea y molestias gastrointestinales. Finalmente, la administración de algunos agentes antidiabéticos de tiazolidina 2,4 diona se han asociado con edema, aumento de peso y, en algunos casos, hepatotoxicidad. La terapia de combinación usando dos o más
20 de los agentes anteriores es común, pero generalmente solo conduce a mejoras en el control glucémico.

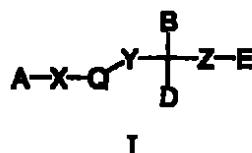
Como resultado, existe la necesidad de agentes antidiabéticos orales que puedan usarse solos o en combinación, y que no produzcan efectos secundarios tales
25 como retención de líquidos, edema periférico, aumento de

peso o complicaciones más graves.

SUMARIO DE LA INVENCION

Estas y otras necesidades se satisfacen por la presente invención, que es un compuesto de fórmula (I)

5



o una sal farmacéuticamente aceptable del mismo, en la que:

10 A es arilo y arilo sustituido,

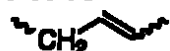
heteroarilo y heteroarilo sustituido,

heteroarilo condensado y heteroarilo condensado sustituido,

cicloalquilo (C₃-C₇) y cicloalquilo sustituido, o

15 heterocicloalquilo y heterocicloalquilo sustituido;

X es una cadena de 2 a 5 átomos de longitud seleccionada entre $\sim\text{CH}_2-\text{O}\sim$, $\sim\text{CH}_2-\text{CH}_2-\text{O}\sim$, $\sim\text{CH}_2-\text{CH}_2-\text{CH}_2\sim$, $\sim\text{CH}_2-\equiv\sim$, 2 o



3, indicando "w" 4 un punto de unión;

Q es arilo o arilo sustituido;

20 heteroarilo o heteroarilo sustituido;

heteroarilo condensado o heteroarilo condensado sustituido; con la condición de que cuando q es un heteroarilo de cinco miembros, el punto de unión de X a Q no está en el heteroátomo del heteroarilo;

25 Y y Z, independientemente, están ausentes o son (CR₁R₂)_n y

(CR₃R₄)_m, siendo cada uno de R₁-R₄ independientemente H, halo, alquilo (C₁-C₆), hidroxilo, alcoxi (C₁-C₆), y siendo cada uno de m y n independientemente 1, 2 ó 3;

B es H, halo, alquilo (C₁-C₆), haloalquilo (C₁-C₆) o alcoxi (C₁-C₆);

D es H, H, -NH-arilo y -NH-arilo sustituido,

alcanoílo (C₁-C₆) y alcanoílo (C₁-C₆) sustituido,

benzoílo y benzoílo sustituido,

arilo y arilo sustituido,

10 heteroarilo y heteroarilo sustituido,

cicloalquilo (C₃-C₇) y cicloalquilo sustituido; o

heterocicloalquilo y heterocicloalquilo sustituido;

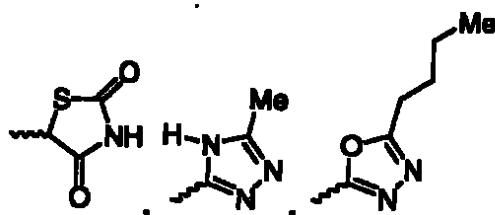
E es COR₅, siendo R₅ alquilo (C₁-C₆), OH, alcoxi (C₁-C₆),

NR₆R₇, siendo cada uno de R₆ y R₇ independientemente H o

15 alquilo (C₁-C₆), o siendo uno de R₆ y R₇ H o alquilo (C₁-C₆)

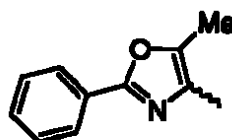
y el otro SO₂R₈, siendo R₈ H o alquilo (C₁-C₆), o E es

heteroarilo sustituido o



; 5 con la

condición de cuando A es

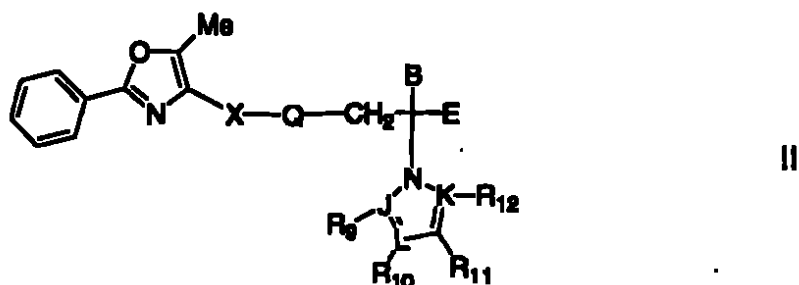


'6 X es $\sim\text{CH}_2\text{CH}_2\text{O}\sim$ 7 Q

20 es fenilo, Y y Z son CH₂, B es H, y E es CO₂H, D no sea

pirrolilo.

La invención también proporciona un compuesto de fórmula (II)



5 o una sal farmacéuticamente aceptable del mismo, en la que:
 X es una cadena de 2 a 5 átomos de longitud seleccionada
 entre $\sim\text{CH}_2\text{O}\sim$, $\sim\text{CH}_2\text{CH}_2\text{O}\sim$, $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$, $\sim\text{CH}_2\equiv\sim$,⁹ o
 $\sim\text{CH}_2\text{CH}=\text{CH}\sim$ ¹⁰ indicando " $\sim$ "¹¹ un punto de unión;

Q es arilo o arilo sustituido;

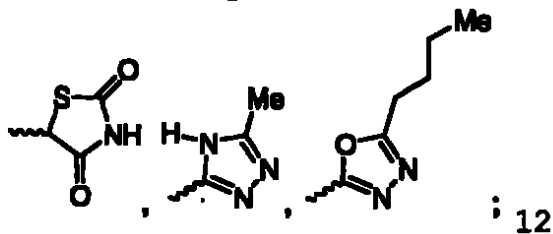
10 heteroarilo o heteroarilo sustituido;

heteroarilo condensado o heteroarilo condensado
 sustituido; con la condición de que cuando q es un
 heteroarilo de cinco miembros, el punto de unión de X a Q
 no está en el heteroátomo del heteroarilo;

15 B es H, halo, alquilo (C₁-C₆), haloalquilo (C₁-C₆) o alcoxi
 (C₁-C₆);

E es COR₅, siendo R₅ alquilo (C₁-C₆), OH, alcoxi (C₁-C₆),
 NR₆R₇, siendo cada uno de R₆ y R₇ independientemente H o
 alquilo (C₁-C₆), o uno de R₆ y R₇ es H o alquilo (C₁-C₆) y el

otro es SO_2R_8 , siendo R_8 H o alquilo ($\text{C}_1\text{-C}_6$), o E es



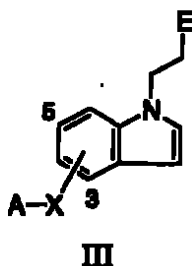
heteroarilo sustituido o

; 12

cada uno de $\text{R}_9\text{-R}_{12}$ es independientemente H, halo, arilo, alquilo ($\text{C}_1\text{-C}_6$), haloalquilo ($\text{C}_1\text{-C}_6$), alcanóilo ($\text{C}_1\text{-C}_6$), halo-alcanóilo ($\text{C}_1\text{-C}_6$), cicloalquilcarbonilo ($\text{C}_3\text{-C}_7$), benzoílo o haloalcanóilo ($\text{C}_2\text{-C}_6$); y uno o dos de J, K y L son N,

con la condición de que cuando J, K o L son N, R_9 , R_{10} , R_{11} o R_{12} esté ausente en esa posición.

10 La invención también proporciona un compuesto de fórmula (III):



15

III

o una sal farmacéuticamente aceptable del mismo, en la que; A es arilo y arilo sustituido,

20 heteroarilo y heteroarilo sustituido,

heteroarilo condensado y heteroarilo condensado sustituido,

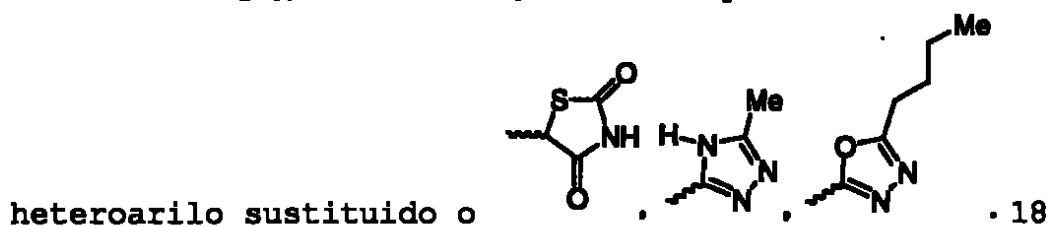
cicloalquilo (C_3-C_7) y cicloalquilo sustituido, o

heterocicloalquilo y heterocicloalquilo sustituido;

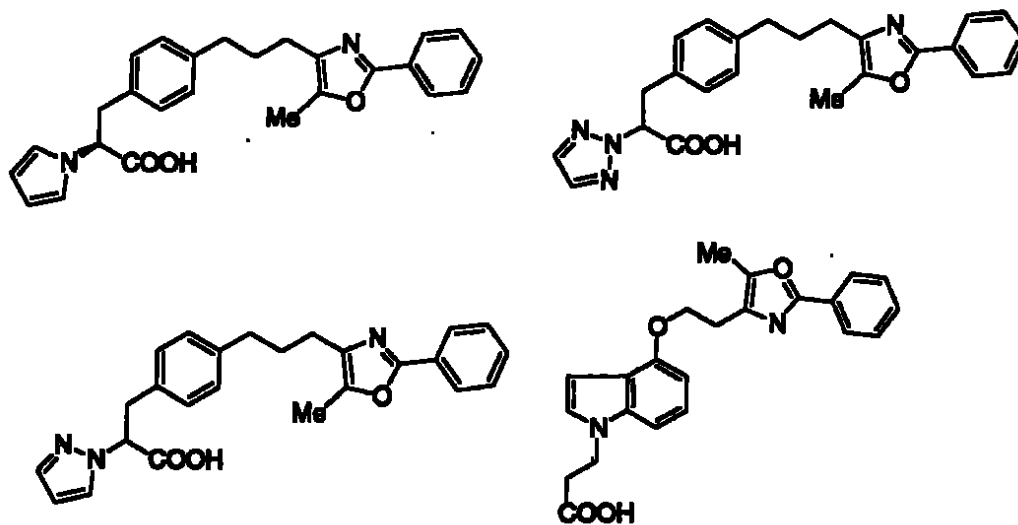
X es una cadena de 2 a 5 átomos de longitud seleccionada entre $\sim CH_2-O \sim$, $\sim CH_2-CH_2-O \sim$, $\sim CH_2-CH_2-CH_2 \sim$, $\sim CH_2-CH_2-O \sim$, 14

5 $\sim CH_2 \equiv \sim$, 15 o $\sim CH_2 \sim$ 16 indicando "wavy" 17 un punto de unión, y pudiendo estar unido -XA a las posiciones 3, 4, 5 ó 6 del núcleo de indolínilo; y

E es COR_5 , siendo R_5 alquilo (C_1-C_6), OH, alcoxi (C_1-C_6), NR_6R_7 , siendo cada uno de R_6 y R_7 independientemente H o 10 alquilo (C_1-C_6), o uno de R_6 y R_7 es H o alquilo (C_1-C_6) y el otro es SO_2R_8 , siendo R_8 H o alquilo (C_1-C_6), o E es

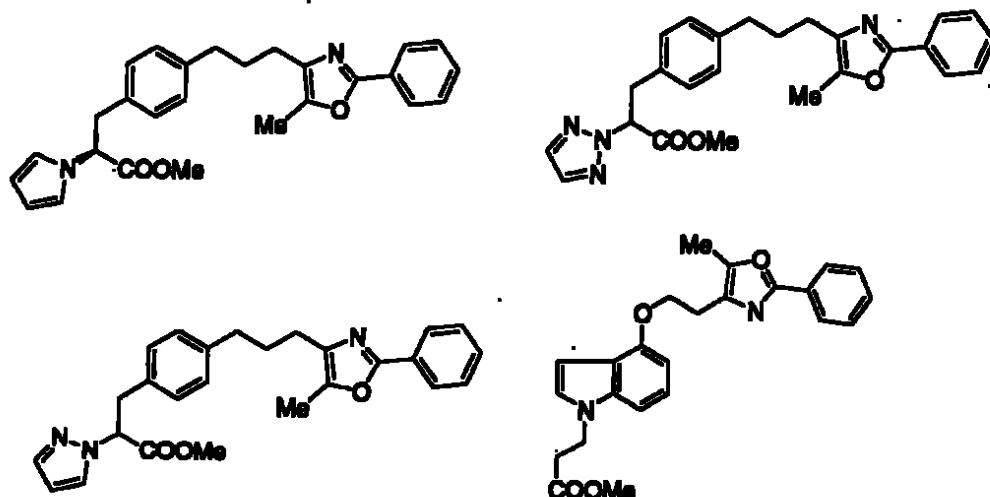


La invención también proporciona un compuesto que es:



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La invención también proporciona un compuesto que es:



La invención también proporciona un compuesto que es:

(R)-2-(2-(4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-5 fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

(R)-2-Etil-5-(2-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(R)-2-(4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

10 Ácido (R)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

(R)-3-Metil-5-(2-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;

15 Ácido (R)-2-(3-bromo-pirrol-1-il)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Ácido (S)-3,3,3-trifluoro-2-{4-[2-(5-metil-2-fenil-

35

oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;

Ácido (R)-3,3,3-trifluoro-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;

Ácido (R)-2-etil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido (S)-2-etil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido (R)-2-propil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

10 Ácido (S)-2-propil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido (S)-3,3,3-trifluoroetil-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;

15 Ácido (R)-3,3,3-trifluoroetil-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;

Ácido (R) 2-fluorometil-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;

Ácido (S) 2-fluorometil-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;

20 Ácido (S)-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-2-fluorometil-2-pirrol-1-il-propiónico;

Ácido (R)-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-2-fluorometil-2-pirrol-1-il-propiónico;

(S)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-
25 pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

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(R)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

(S)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

5 (R)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(S)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

Ácido (R)-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-
10 2-pirrol-1-il-propiónico;

Ácido (S)-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

(R)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;

15 (S)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;

Ácido (R)-2-(3-bromo-pirrol-1-il)-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-propiónico;

Ácido (S)-2-(3-bromo-pirrol-1-il)-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-propiónico;
20

Ácido (S)-3,3,3-trifluoro-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido (R)-3,3,3-trifluoro-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

25 Ácido (R)-2-etil-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-

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fenil}-2-pirrol-1-il-propiónico;

Ácido (S)-2-etil-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-
fenil}-2-pirrol-1-il-propiónico;

Ácido (R)-2-propil-3-{4-[2-(5-etil-piridin-2-il)-
5 etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido (S)-2-propil-3-{4-[2-(5-etil-piridin-2-il)-
etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido (S)-3,3,3-trifluoroetil-3-{4-[2-(5-etil-piridin-
2-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

10 Ácido (R)-3,3,3-trifluoroetil-3-{4-[2-(5-etil-piridin-
2-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido (S)-2-pirrol-1-il-3-[4-(4'-trifluorometil-
bifenil-4-ilmetoxi)-fenil]-propiónico;

Ácido (R)-2-pirrol-1-il-3-[4-(4'-trifluorometil-
15 bifenil-4-ilmetoxi)-fenil]-propiónico;

(R)-2-(2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-
fenil}}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

(S)-2-(2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-
fenil}}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

20 (R)-2-Etil-2-[4-(4'-trifluorometil-bifenil-4-
ilmetoxi)-fenil}}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(S)-2-Etil-2-[4-(4'-trifluorometil-bifenil-4-
ilmetoxi)-fenil}}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(R)-2-2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-
25 fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

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(S)-2-2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-
fenil]-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

Ácido (R)-2-metil-3-[4-(4'-trifluorometil-bifenil-4-
ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;

5 Ácido (S)-2-metil-3-[4-(4'-trifluorometil-bifenil-4-
ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;

(R)-3-Metil-5-(3-[4-(4'-trifluorometil-bifenil-4-
ilmetoxi)-fenil]-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;

(S)-3-Metil-5-(3-[4-(4'-trifluorometil-bifenil-4-
10 ilmetoxi)-fenil]-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;

Ácido (R)-2-(3-bromo-pirrol-1-il)-3-[4-(4'-
trifluorometil-bifenil-4-ilmetoxi)-fenil]-propiónico;

Ácido (R)-2-(3-bromo-pirrol-1-il)-3-[4-(4'-
trifluorometil-bifenil-4-ilmetoxi)-fenil]-propiónico;

15 Ácido (S)-3,3,3-trifluoro-2-[4-(4'-trifluorometil-
bifenil-4-ilmetoxi)-bencil]-2-pirrol-1-il-propiónico;

Ácido (R)-3,3,3-trifluoro-2-[4-(4'-trifluorometil-
bifenil-4-ilmetoxi)-bencil]-2-pirrol-1-il-propiónico;

Ácido (R)-2-etil-3-[4-(4'-trifluorometil-bifenil-4-
20 ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;

Ácido (S)-2-etil-3-[4-(4'-trifluorometil-bifenil-4-
ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;

Ácido (R)-2-propil-3-[4-(4'-trifluorometil-bifenil-4-
ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;

25 Ácido (S)-2-propil-3-[4-(4'-trifluorometil-bifenil-4-

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ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;

Ácido (S)-3,3,3-trifluoroetil-2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-bencil]-2-pirrol-1-il-propiónico;

Ácido (R)-3,3,3-trifluoroetil-2-(4-(4'-trifluorometil-5 bifenil-4-ilmetoxi)-bencil]-2-pirrol-1-il-propiónico;

Ácido (R) 2-fluorometil-2-(4-(4'-trifluorometil-bifenil-4-ilmetoxi)-bencil]-2-pirrol-1-il-propiónico;

Ácido (S) 2-fluorometil-2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-bencil]-2-pirrol-1-il-propiónico;

10 (S)-2-3-{4-[2-(Metil-piridin-2-il-amino)-etoxi]-fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

(R)-2-3-{4-[2-(Metil-piridin-2-il-amino)-etoxi]-fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

(S)-2-Etil-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-15 fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(R)-2-Etil-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(R)-2-2-{4-[2-(Metil-piridin-2-il-amino)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

20 (S)-2-2-{4-[2-(Metil-piridin-2-il-amino)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

Ácido (R)-2-metil-3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido (S)-2-metil-3-{4-[2-(metil-piridin-2-il-amino)-25 etoxi]-fenil}-2-pirrol-1-il-propiónico;

- (R)-3-Metil-5-(3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;
- (S)-3-Metil-5-(3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;
- 5 Ácido (R)-2-(3-bromo-pirrol-1-il)-3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-propiónico;
- Ácido (S)-2-(3-bromo-pirrol-1-il)-3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-propiónico;
- Ácido (S)-3,3,3-trifluoro-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- 10 amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- Ácido (R)-3,3,3-trifluoro-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- Ácido (R)-2-etil-3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- 15 Ácido (S)-2-etil-3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (R)-2-propil-3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (S)-2-propil-3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- 20 etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (S)-3,3,3-trifluoroetil-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- Ácido (R)-3,3,3-trifluoroetil-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- 25 Ácido (R) 2-fluorometil-2-{4-[2-(metil-piridin-2-il-

amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico; o

Ácido (S) 2-fluorometil-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico.

La invención también proporciona un compuesto que es:

5 Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido (S)-2-(2-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Ácido (S)-2-(3-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-10 2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-propiónico;

Ácido (S)-3-{4-[2-(benzooxazol-2-il-metil-amino)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-propiónico;

15 N-(S)-(3-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propionil)-bencenosulfonamida;

N-(S)-(3-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propionil)-metanosulfonamida;

Ácido (S)-2-(3-isobutiril-pirrol-1-il)-3-{4-[2-(5-20 metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Ácido (S)-2-(3-Ciclohexanocarbonil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Ácido (S)-3-{4-[2-(benzooxazol-2-il-metil-amino)-etoxi]-fenil}-2-(3-ciclohexanocarbonil-pirrol-1-il)-

25 propiónico;

Ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-[4-(2-fluoro-benciloxi)-fenil]-propiónico;

Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-5 propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-4-il-propiónico;

2-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-2H-tetrazol;

10 Ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-2-il-propiónico;

N-(2,2-Dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propionil)-metanosulfonamida;

15 N-(2-Fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propionil)-metanosulfonamida;

Ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;

Ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

20 Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-fenil-propiónico;

Ácido (S)-2-(2-acetil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

25 Ácido 3-{4-[2-(benzotiazol-2-ilsulfanil)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

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- Ácido (S)-2-pirrol-1-il-3-{4-[2-(2-trifluorometil-fenil)-etoxi]-fenil}-propiónico;
- Ácido (S)-3-{4-[2-(4-fenil-piperazin-1-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- 5 Ácido (S)-3-{4-[2-(5-metil-2-fenil-tiazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (S)-2-(3-cloro-2,5-dimetil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido (S)-3-(4-{2-[(7-cloro-quinolin-4-il)-metil-10 amino]-etoxi}-fenil)-2-pirrol-1-il-propiónico;
- Ácido (S)-2-(3-acetil-2,5-dimetil-pirrol-1-il)-3-{4-[2-(4-metil-2-fenil-oxazol-5-il)-etoxi]-fenil}-propiónico;
- Ácido (S)-2-[2,5-dimetil-3-(2,2,2-trifluoro-acetil)-pirrol-1-il]-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-15 fenil}-propiónico;
- Ácido 3-{4-[2-(2-bencil-bencimidazol-1-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido 2-(3-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- 20 Ácido 2-(2-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido 2-(2-cloro-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido (S)-2-(2-butiril-pirrol-1-il)-3-{4-[2-(5-metil-25 2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

- Ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-[4-(2-fluoro-benciloxi)-fenil]-propiónico;
- Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(2-metil-5-fenil-pirrol-1-il)-propiónico;
- 5 Ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-10 fenil}-2-tiofen-2-il-propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-3-il-propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;
- 15 Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-trifluorofenil)-propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico; (R)
- Ácido 2-(4-metoxi-fenil)-3-{4-[2-(5-metil-2-fenil-20 oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-fenil}-2-pirrol-1-il-propiónico;
- Ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;
- 25 Ácido 2,2-dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-

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il)-etoxi]-fenil)-propiónico;

Ácido 2-fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-
etoxi]-fenil}-2-fenil-propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
5 fenil}-2-(2-oxo-pirrolidin-1-il)-propiónico;

2-Etil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-
etoxi]-fenil}-1-fenil-etil)-1,3,4-oxadiazol;

Ácido 3-{4-[3-(5-Metil-2-fenil-oxazol-4-il)-
propionil]-fenil}-2-pirrol-1-il-propiónico;

10 Ácido 2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-
piridin-3-il-propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
fenil}-2-fenil-propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
15 fenil}-2-(3-trifluorofenil)-propiónico;

Ácido (R)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-
etoxi]-fenil}-2-fenil-propiónico;

Ácido (S)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-
il)-etoxi]-fenil}-2-pirrol-1-il-propiónico; éster metílico

20 Ácido 3-{5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
indol-1-il}-propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
indol-1-il}-propiónico;

(S)-2-(2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-
25 fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

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(S)-2-Etil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(S)-2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

5 (S)-3-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;

Ácido 2-(3-bromo-pirrol-1-il)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

10 Ácido 3,3,3-trifluoro-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;

Ácido 2-(4-benciloxi-indol-1-il)-propiónico;

Ácido 3-(1-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-bencil}-1H-pirrol-2-il)-propiónico;

15 Ácido (1-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-1H-indol-5-iloxi)-fenil-acético;

Ácido 2-(1-metil-1H-indol-3-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Ácido 3-(4-[3-(5-metil-2-fenil-oxazol-4-il)-propoxi]-indol-1-il)-propiónico;

20 Ácido 2-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il)-propiónico;

Ácido 3-(4-[2-(2-trifluorometil-fenil)-etoxi]-indol-1-il)-propiónico;

25 Ácido (4-[3-(5-metil-2-fenil-oxazol-4-il)-propoxi]-indol-1-il)-acético;

Ácido 4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-acético;

Ácido 4-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-butírico;

5 Ácido 3-(3-fluoro-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-(S)-pirrol-1-il-propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-4-il-propiónico;

2-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-2H-tetrazol;

1-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-1H-tetrazol;

Ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-2-il-propiónico;

15 Ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-3-il-propiónico;

N-(2,2-dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propionil)-metanosulfonamida;

N-(2-Fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propionil)-metanosulfonamida;

Ácido 3-{3-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-isoxazol-5-il}-2-pirrol-1-il-propiónico;

Ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;

25 Ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[2-(5-

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metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-propiónico;

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-
fenil}-2-fenil-propiónico;

Ácido 3-{4-[3-(5-metil-2-feniloxazol-4-il)-propil]-
5 fenil}-2-fenilpropiónico;

Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
piridin-3-il}-2-pirrol-1-il-propiónico;

Ácido 3-{6-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-
piridin-3-il}-2-fenilpropiónico;

10 Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
piridin-3-il}-2-fenilpropiónico;

Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
piridin-3-il}-2-tiofen-2-il-propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
15 fenil}-2-fenil-acrílico;

Ácido {4-[2-(5-metil-2-fenil-oxazol-4-il)-
etoxi]bencilamino}fenilacético;

Ácido metil-{4-[2-(5-metil-2-fenil-oxazol-4-il)-
etoxi]-bencilamino}-fenilacético;

20 Ácido 6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
naftaleno-2-carboxílico;

Ácido 3-{5-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-
naftalen-1-il}-2-pirrol-1-il-propiónico;

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-
25 fenil}-2-1,2,3-triazol-1-il-propiónico; éster etílico;

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Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-
fenil}-2-1,2,3-triazol-1-il-propiónico;

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-
fenil}-2-pirazol-1-il-propiónico;

5 Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-
fenil}-2-1,2,4-triazol-1-il-propiónico;

5-metil-2-fenil-4-prop-2-eniloxazol;

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-
inil]-fenil}-2-piridin-3-il-propiónico;

10 Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-
fenil}-2-piridin-3-il-propiónico;

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-
fenil}-2-piridin-3-il-propiónico;

Ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-
15 4-il)-propil]-fenil}-propiónico;

Ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-
4-il)-prop-1-inil]-fenil}-propiónico;

Ácido 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-
4-il)-prop-1-inil]-fenil}-propiónico;

20 Ácido 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-
4-il)-propil]-fenil}-propiónico;

Ácido 2-(5-metil-isoxazol-3-il)-3-{4-[3-(5-metil-2-
fenil-oxazol-4-il)-propil]-fenil}-propiónico;

Ácido 2-(3-metil-isoxazol-5-il)-3-{4-[3-(5-metil-2-
25 fenil-oxazol-4-il)-propil]-fenil}-propiónico;

Ácido (S)-3-(4-([(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico;

Ácido (S)-3-(4-([acetil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico;

5 Ácido (S)-3-(4-([metil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico;

Ácido (S)-3-(4-([2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-metil)-fenil)-2-pirrol-1-il-propiónico;

Ácido (S)-3-[4-([bencil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino]-metil)-fenil]-2-pirrol-1-il-propiónico;

Ácido (S)-3-[4-([Benzoil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino]-metil)-fenil]-2-pirrol-1-il-propiónico;

Ácido (S)-3-[4-([acetil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino]-metil)-fenil]-2-pirrol-1-il-propiónico;

15 Ácido 4-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-butírico;

Ácido 3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-piperidin-4-il}-2-pirrol-1-il-propiónico;

Ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil}-2-pirrol-1-il-propiónico;

Ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propiónico;

Ácido 3-{3-metoxi-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

25 Ácido butano-1-sulfónico; 3-{4-[3-(5-metil-2-fenil-

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oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propionil)-amida;

N-(3-{4-[3-(5-Metil-2-fenil-oxazol-4-il)-propil]-
fenil}-2-pirrol-1-il-propionil)-metanosulfonamida;

Ácido 3-{3-yodo-4-[2-(5-metil-2-fenil-oxazol-4-il)-
5 etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-3-
prop-1-inil-fenil}-2-pirrol-1-il-propiónico;

Ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-
etoxi]-fenil}-2-pirrol-1-il-propiónico;

10 Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
bifenil-3-il}-2-pirrol-1-il-propiónico;

Ácido 4-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-
fenil}-2-pirrol-1-il-butírico;

Ácido 2-pirrol-1-il-4-(4-trifluorometanosulfonil-
15 fenil)-butírico; éster metílico

Ácido 3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-
piperidin-4-il}-2-pirrol-1-il-propiónico;

Ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-
propenil]-fenil}-2-pirrol-1-il-propiónico;

20 Ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-
propil]-fenil}-2-pirrol-1-il-propiónico;

Ácido 3-{3-metoxi-4-[2-(5-metil-2-fenil-oxazol-4-il)-
etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido butano-1-sulfónico; (3-{4-[3-(5-metil-2-fenil-
25 oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propionil)-amida;

N-(3-{4-[3-(5-Metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propionil)-metanosulfonamida;

Ácido 3-{3-yodo-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

5 Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-3-prop-1-inil-fenil}-2-pirrol-1-il-propiónico;

Ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-10 bifenil-3-il}-2-pirrol-1-il-propiónico;

La invención también proporciona un compuesto que es:

éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido (S)-2-(2-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-15 propiónico;

Éster metílico del ácido (S)-2-(3-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

20 Éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-propiónico;

Éster metílico del ácido (S)-3-{4-[2-(benzooxazol-2-il-metil-amino)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-25 propiónico;

N-(S)-(3-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propionil)-bencenosulfonamida;

N-(S)-(3-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propionil)-metanosulfonamida;

5 Éster metílico del ácido (S)-2-(3-isobutiril-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

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Éster metílico del ácido (S)-3-{4-[2-(Benzooxazol-2-il-metil-amino)-etoxi]-fenil}-2-(3-ciclohexanocarbonil-pirrol-1-il)-propiónico;

Éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-[4-(2-fluoro-benciloxi)-fenil]-propiónico;

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Éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-4-il-propiónico;

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2-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-2H-tetrazol;

Éster metílico del ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-2-il-propiónico;

25 N-(2,2-Dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-

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etoxi]-fenil)-propionil)-metanosulfonamida;

N-(2-Fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-
etoxi]-fenil}-2-fenil-propionil)-metanosulfonamida;

Éster metílico del ácido 2-(5-metil-2-fenil-oxazol-4-
5 il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-
propiónico;

Éster metílico del ácido 2-(5-metil-2-fenil-oxazol-4-
il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-
propiónico;

10 Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-
oxazol-4-il)-propil]-fenil}-2-fenil-propiónico;

Éster metílico del ácido (S)-2-(2-acetil-pirrol-1-il)-
3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-
propiónico;

15 Éster metílico del ácido 3-{4-[2-(benzotiazol-2-
ilsulfanil)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido (S)-2-pirrol-1-il-3-{4-[2-(2-
trifluorometil-fenil)-etoxi]-fenil}-propiónico;

Éster metílico del ácido (S)-3-{4-[2-(4-fenil-
20 piperazin-1-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido (S)-3-{4-[2-(5-Metil-2-fenil-
tiazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido (S)-2-(3-cloro-2,5-dimetil-
pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-
25 fenil}-propiónico;

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Éster metílico del ácido (S)-3-(4-{2-[(7-cloro-quinolin-4-il)-metil-amino]-etoxi}-fenil)-2-pirrol-1-il-propiónico;

Éster metílico del ácido (S)-2-(3-acetil-2,5-dimetil-5 pirrol-1-il)-3-{4-[2-(4-metil-2-fenil-oxazol-5-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido (S)-2-[2,5-dimetil-3-(2,2,2-trifluoro-acetil)-pirrol-1-il]-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

10 Éster metílico del ácido 3-{4-[2-(2-fenil-bencimidazol-1-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 2-(3-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido 2-(2-bromo-pirrol-1-il)-3-{4-15 [2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido 2-(2-cloro-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido (S)-2-(2-butil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-20 propiónico;

Éster metílico del ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-[4-(2-fluoro-benciloxi)-fenil]-propiónico;

Éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(2-metil-5-fenil-pirrol-1-il)-25 propiónico;

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Éster metílico del ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-2-il-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-3-il-propiónico;

10 Éster metílico del ácido 3-{4-(2-(5-metil-2-fenil-oxazol-4-il)-etoxi)-fenil}-2-fenil-propiónico;

éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-trifluorofenil)-propiónico;

15 éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico; (R)

Éster metílico del ácido 2-(4-metoxi-fenil)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-fenil}-2-pirrol-1-il-propiónico;

20 Éster metílico del ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;

Éster metílico del ácido 2,2-dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

25 Éster metílico del ácido 2-fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;

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Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(2-oxo-pirrolidin-1-il)-propiónico;

2-Etil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-1,3,4-oxadiazol;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-3-il-propiónico;

10 Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-trifluorofenil)-propiónico;

Éster metílico del ácido (R)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;

15 éster metílico del ácido (S)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico; éster metílico

Éster metílico del ácido 3-{5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-propiónico;

20 Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-propiónico;

(S)-2-(2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

25 (S)-2-Etil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-

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etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(S)-2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-]-pirrol-]-il-etil)-1,3,4-oxadiazol;

(S)-3-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-5 etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;

Éster metílico del ácido 2-(3-bromo-pirrol-1-il)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido 3,3,3-Trifluoro-2-{4-[2-(5-10 metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 2-(4-benciloxi-indol-1-il)-propiónico;

Éster metílico del ácido 3-(1-{4-[3-(5-metil-2-fenil-15 oxazol-4-il)-propil]-bencil}-1H-pirrol-2-il)-propiónico;

Éster metílico del ácido (1-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-1H-indol-5-iloxi)-fenil-acético;

Éster metílico del ácido 2-(1-metil-1H-indol-3-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-20 propiónico;

Éster metílico del ácido 3-(4-[3-(5-metil-2-fenil-oxazol-4-il)-propoxi]-indol-1-il)-propiónico;

Éster metílico del ácido 2-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il)-propiónico;

25 Éster metílico del ácido 3-(4-[2-(2-trifluorometil-

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fenil)-etoxi]-indol-1-il)-propiónico;

Éster metílico del ácido (4-[3-(5-metil-2-fenil-oxazol-4-il)-propoxi]-indol-1-il)-acético;

Éster metílico del ácido 4-[2-(5-metil-2-fenil-oxazol-5 4-il)-etoxi]-indol-1-il)-acético;

Éster metílico del ácido 4-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il)-butírico;

Éster metílico del ácido 3-(3-fluoro-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-(5)-pirrol-1-il-10 propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-piridin-4-il)-propiónico;

2-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-1-fenil-etil)-2H-tetrazol;

15 1-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-1-fenil-etil)-1H-tetrazol;

Éster metílico del ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-tiofen-2-il)-propiónico;

Éster metílico del ácido 2-Metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-tiofen-3-il)-propiónico;

N-(2,2-Dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-propionil)-metanosulfonamida;

N-(2-Fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-fenil-propionil)-metanosulfonamida;

25 Éster metílico del ácido 3-{3-[2-(5-metil-2-fenil-

30

oxazol-4-il)-etoxi]-isoxazol-5-il}-2-pirrol-1-il-
propiónico;

Éster metílico del ácido 2-(5-metil-2-fenil-oxazol-4-
il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-
5 propiónico;

Éster metílico del ácido 2-(5-metil-2-fenil-oxazol-4-
il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-
propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-
10 oxazol-4-il)-propil]-fenil}-2-fenil-propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-
feniloxazol-4-il)-propil]-fenil}-2-fenilpropiónico;

Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-
oxazol-4-il)-etoxi]-piridin-3-il}-2-pirrol-1-il-propiónico;

15 Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-
oxazol-4-il)-etoxi]-piridin-3-il}-2-fenilpropiónico;

Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-
oxazol-4-il)-etoxi]-piridin-3-il}-2-fenilpropiónico;

Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-
20 oxazol-4-il)-etoxi]-piridin-3-il}-2-tiofen-2-il-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-
oxazol-4-il)-etoxi]-fenil}-2-fenil-acrílico;

Éster metílico del ácido {4-[2-(5-metil-2-fenil-
oxazol-4-il)-etoxi]-bencilamino}-fenilacético;

25 Éster metílico del ácido {4-[2-(5-metil-2-fenil-

oxazol-4-il)-etoxi]-bencilamino}-fenilacético; éster
metílico

Éster metílico del ácido metil-{4-[2-(5-metil-2-fenil-
oxazol-4-il)-etoxi]-bencilamino}-fenilacético;

5 Éster metílico del ácido 6-[2-(5-metil-2-fenil-oxazol-
4-il)-etoxi]-naftaleno-2-carboxílico;

Éster metílico del ácido 3-{5-[3-(5-metil-2-fenil-
oxazol-4-il)-propil]-naftalen-1-il}-2-pirrol-1-il-
propiónico;

10 Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-
oxazol-4-il)-propil]-fenil}-2-1,2,3-triazol-1-il-
propiónico; éster etílico

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-
oxazol-4-il)-propil]-fenil}-2-1,2,3-triazol-1-il-

15 propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-
oxazol-4-il)-propil]-fenil}-2-pirazol-1-il-propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-
oxazol-4-il)-propil]-fenil}-2-1,2,4-triazol-1-il-

20 propiónico;

5-Metil-2-fenil-4-prop-2-eniloxazol;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-
oxazol-4-il)-prop-1-inil]-fenil}-2-piridin-3-il-propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-
25 oxazol-4-il)-propil]-fenil}-2-piridin-3-il-propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-piridin-3-il-propiónico;

Éster metílico del ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;

5 Éster metílico del ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-propiónico;

Éster metílico del ácido 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-propiónico;

10 Éster metílico del ácido 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;

Éster metílico del ácido 2-(5-metil-isoxazol-3-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;

15 Éster metílico del ácido 2-(3-metil-isoxazol-5-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;

Éster metílico del ácido (S)-3-(4-{[(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil}-fenil)-2-pirrol-1-il-propiónico;

20 Éster metílico del ácido (S)-3-(4-{[acetil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil}-fenil)-2-pirrol-1-il-propiónico;

25 Éster metílico del ácido (S)-3-(4-{[metil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil}-fenil)-2-pirrol-1-il-propiónico;

Éster metílico del ácido (S)-3-(4-([2-(5-metil-2-fenil-oxazol-4-il)-etilamino)-metil]-fenil)-2-pirrol-1-il-propiónico;

Éster metílico del ácido (S)-3-[4-({bencil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil)-2-pirrol-1-il-propiónico;

Éster metílico del ácido (S)-3-[4-({benzoil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil)-2-pirrol-1-il-propiónico;

10 Éster metílico del ácido (S)-3-[4-({acetil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil)-2-pirrol-1-il-propiónico;

Éster metílico del ácido 4-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-2-pirrol-1-il-butírico;

15 Éster metílico del ácido 3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-piperidin-4-il)-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil)-2-pirrol-1-il-propiónico;

20

Éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{3-metoxi-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-pirrol-1-il-propiónico;

25 Éster metílico del ácido butano-1-sulfónico; (3-{4-[3-

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(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propionil)-amida;

N-(3-{4-[3-(5-Metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propionil)-metanosulfonamida;

5 Éster metílico del ácido 3-{3-yodo-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-3-prop-1-inil-fenil}-2-pirrol-1-il-propiónico;

10 Éster metílico del ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bifenil-3-il}-2-pirrol-1-il-propiónico;

15 Éster metílico del ácido 4-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-butírico;

Éster metílico del ácido 2-pirrol-1-il-4-(4-trifluorometanosulfonil-fenil)-butírico; éster metílico

Éster metílico del ácido 3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-piperidin-4-il}-2-pirrol-1-il-

20 propiónico;

Éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil}-2-pirrol-1-il-propiónico;

25 Éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propiónico;

45

Éster metílico del ácido 3-{3-metoxi-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido butano-1-sulfónico; 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-5 propionil)-amida;

N-(3-{4-[3-(5-Metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propionil)-metanosulfonamida;

Éster metílico del ácido 3-{3-yodo-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

10 Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-3-prop-1-inil-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

15 Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bifenil-3-il}-2-pirrol-1-il-propiónico;

La invención también proporciona una composición farmacéutica que comprende un compuesto de fórmula I, II o III mezclado con un vehículo, diluyente o excipiente.

20 La invención también proporciona un procedimiento para tratar, prevenir o controlar la diabetes mellitus no dependiente de insulina en un mamífero, que comprende administrar al mamífero en necesidad del mismo una cantidad eficaz de un compuesto de fórmula I, II o III.

25 La invención también proporciona un procedimiento para

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tratar, prevenir o controlar la obesidad en un mamífero, que comprende administrar al mamífero en necesidad del mismo una cantidad eficaz de un compuesto de fórmula I, II o III.

5 La invención también proporciona un procedimiento para reducir el peso corporal en un mamífero obeso, que comprende administrar al mamífero en necesidad del mismo una cantidad eficaz de un compuesto de fórmula I, II o III.

La invención también proporciona un procedimiento para
10 tratar, prevenir o controlar la hiperglucemia en un mamífero, que comprende administrar al mamífero en necesidad del mismo una cantidad eficaz de un compuesto de fórmula I, II o III.

La invención también proporciona un procedimiento para
15 tratar, prevenir o controlar la hiperlipidemia en un mamífero, que comprende administrar al mamífero en necesidad del mismo una cantidad eficaz de un compuesto de fórmula I, II o III.

La invención también proporciona un procedimiento para
20 tratar, prevenir o controlar la hipercolesterolemia en un mamífero, que comprende administrar al mamífero en necesidad del mismo una cantidad eficaz de un compuesto de fórmula I, II o III.

La invención también proporciona un procedimiento para
25 tratar, prevenir o controlar la aterosclerosis en un

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mamífero, que comprende administrar al mamífero en necesidad del mismo una cantidad eficaz de un compuesto de fórmula I, II o III.

La invención también proporciona un procedimiento para 5 tratar, prevenir o controlar la hipertrigliceridemia en un mamífero, que comprende administrar al mamífero en necesidad del mismo una cantidad eficaz de un compuesto de fórmula I, II o III.

La invención también proporciona un procedimiento para 10 tratar, prevenir o controlar la hiperinsulinemia en un mamífero, que comprende administrar al mamífero en necesidad del mismo una cantidad eficaz de un compuesto de fórmula I, II o III.

La invención también proporciona un procedimiento para 15 tratar a un paciente que sufre alguna anormalidad de insulina y/o indicios de trastornos de la glucosa asociados con glucocorticoides circulantes, hormona de crecimiento, catecolaminas, glucagón u hormona paratiroidea, que comprende administrar al paciente una cantidad 20 terapéuticamente eficaz de un compuesto de fórmula I, II o III.

La invención también proporciona un procedimiento de tratamiento del síndrome de resistencia a insulina en seres humanos que comprende administrar a un paciente en 25 necesidad de tratamiento una composición de fórmula I, II o

III.

La invención también proporciona un procedimiento para modular la actividad de PPAR en un mamífero, que comprende administrar al mamífero una cantidad eficaz de un modulador 5 de PPAR de fórmula I, II o III.

La invención también proporciona un procedimiento para reducir la glucosa en sangre en un mamífero, que comprende administrar a un mamífero una cantidad eficaz de un compuesto de fórmula I, II o III.

10 La invención también proporciona un procedimiento para modular la diferenciación de células adiposas en un mamífero, que comprende administrar al mamífero una cantidad eficaz de un compuesto de fórmula I, II o III.

La invención también proporciona un procedimiento para 15 preparar un compuesto de fórmula I, en la que:

A es arilo y arilo sustituido,
heteroarilo y heteroarilo sustituido,
heteroarilo condensado y heteroarilo condensado sustituido,

20 cicloalquilo (C₃-C₇) y cicloalquilo sustituido, o heterocicloalquilo y heterocicloalquilo sustituido;

X es una cadena de 2 a 5 átomos de longitud seleccionada entre $\sim\text{CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\equiv\sim$, 21 o

$\sim\text{CH}_2\text{-CH=CH}\sim$ 22, indicando " $\sim$ " 23 un punto de unión;

25 Q es arilo o arilo sustituido;

38d

heteroarilo o heteroarilo sustituido;

heteroarilo condensado o heteroarilo condensado sustituido; con la condición de que cuando q es un heteroarilo de cinco miembros, el punto de unión de X a Q 5 no está en el heteroátomo del heteroarilo;

Y y Z, independientemente, están ausentes o son $(CR_1R_2)_n$ y $(CR_3R_4)_m$, siendo cada uno de R_1-R_4 independientemente H, halo, alquilo (C_1-C_6), hidroxilo, alcoxi (C_1-C_6), y siendo cada uno de m y n independientemente 1, 2 ó 3;

10 B es H, halo, alquilo (C_1-C_6), haloalquilo (C_1-C_6) o alcoxi (C_1-C_6);

D es H, H, -NH-arilo y -NH-arilo sustituido,

alcanoílo (C_1-C_6) y alcanoílo (C_1-C_6) sustituido,

benzoílo y benzoílo sustituido,

15 arilo y arilo sustituido,

heteroarilo y heteroarilo sustituido,

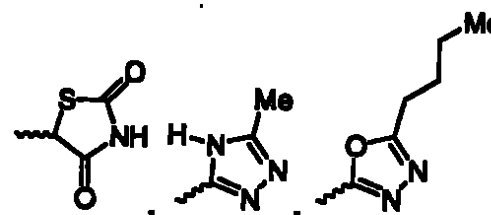
cicloalquilo (C_3-C_7) y cicloalquilo sustituido; o

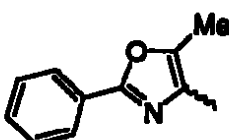
heterocicloalquilo y heterocicloalquilo sustituido;

E es COR_5 , siendo R_5 alquilo (C_1-C_6), OH, alcoxi (C_1-C_6),

20 NR_6R_7 , siendo cada uno de R_6 y R_7 independientemente H o alquilo (C_1-C_6), o siendo uno de R_6 y R_7 H o alquilo (C_1-C_6) y el otro SO_2R_8 , siendo R_8 H o alquilo (C_1-C_6), o E es

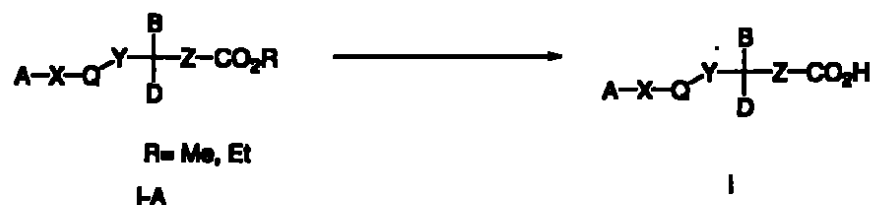
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heteroarilo sustituido o  ; 24 con la

condición de cuando A es  '25 X es $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$ 26
 5 Q es fenilo, Y y Z son CH₂, B es H, y E es CO₂H, D no sea pirrolilo.

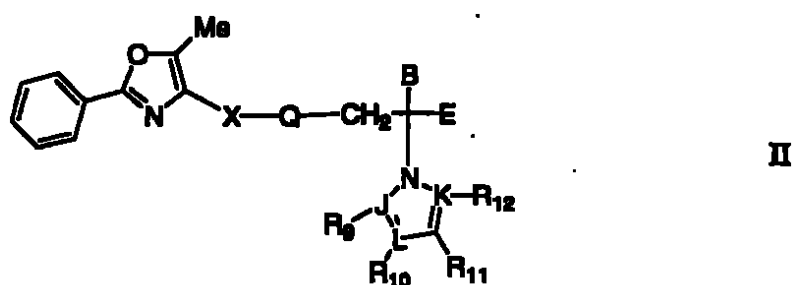
que comprende:

(a) hidrolizar el resto éster del compuesto de fórmula I-A para obtener un resto ácido en condiciones básicas.



La invención también proporciona un procedimiento para
 15 preparar un compuesto de fórmula II,

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en la que:

X es una cadena de 2 a 5 átomos de longitud seleccionada entre $\sim\text{CH}_2\text{O}\sim$, $\sim\text{CH}_2\text{CH}_2\text{O}\sim$, $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$, $\sim\text{CH}_2\equiv\sim$,²⁹ o

$\sim\text{CH}_2\text{CH}=\sim$ ³⁰ indicando "o" ³¹ un punto de unión;

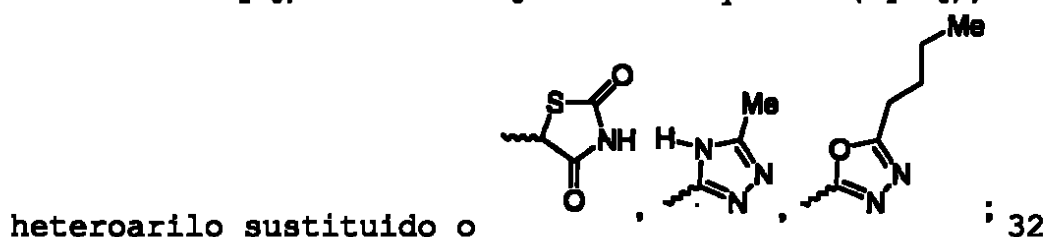
5 Q es arilo o arilo sustituido;

heteroarilo o heteroarilo sustituido;

heteroarilo condensado o heteroarilo condensado sustituido; con la condición de que cuando q es un heteroarilo de cinco miembros, el punto de unión de X a Q no está en el heteroátomo del heteroarilo;

B es H, halo, alquilo (C₁-C₆), haloalquilo (C₁-C₆) o alcoxi (C₁-C₆);

E es COR₅, siendo R₅ alquilo (C₁-C₆), OH, alcoxi (C₁-C₆), NR₆R₇, siendo cada uno de R₆ y R₇ independientemente H o 15 alquilo (C₁-C₆), o uno de R₆ y R₇ es H o alquilo (C₁-C₆) y el otro es SO₂R₈, siendo R₈ H o alquilo (C₁-C₆), o E es



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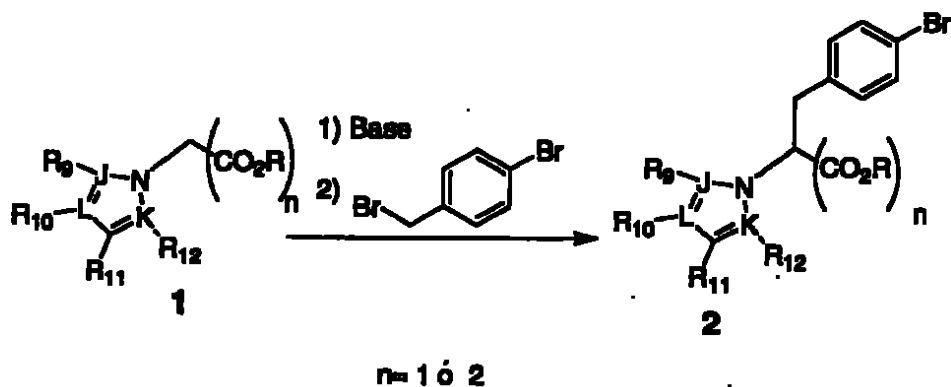
cada uno de R_9-R_{12} es independientemente H, halo, arilo, alquilo (C_1-C_6), haloalquilo (C_1-C_6), alcanoilo (C_1-C_6), halo-alcanoilo (C_1-C_6), cicloalquilcarbonilo (C_3-C_7), benzoilo o haloalcanoilo (C_2-C_6); y

5 uno o dos de J, K y L son N,

con la condición de que cuando J, K o L son N, R_9 , R_{10} , R_{11} o R_{12} esté ausente en esa posición.

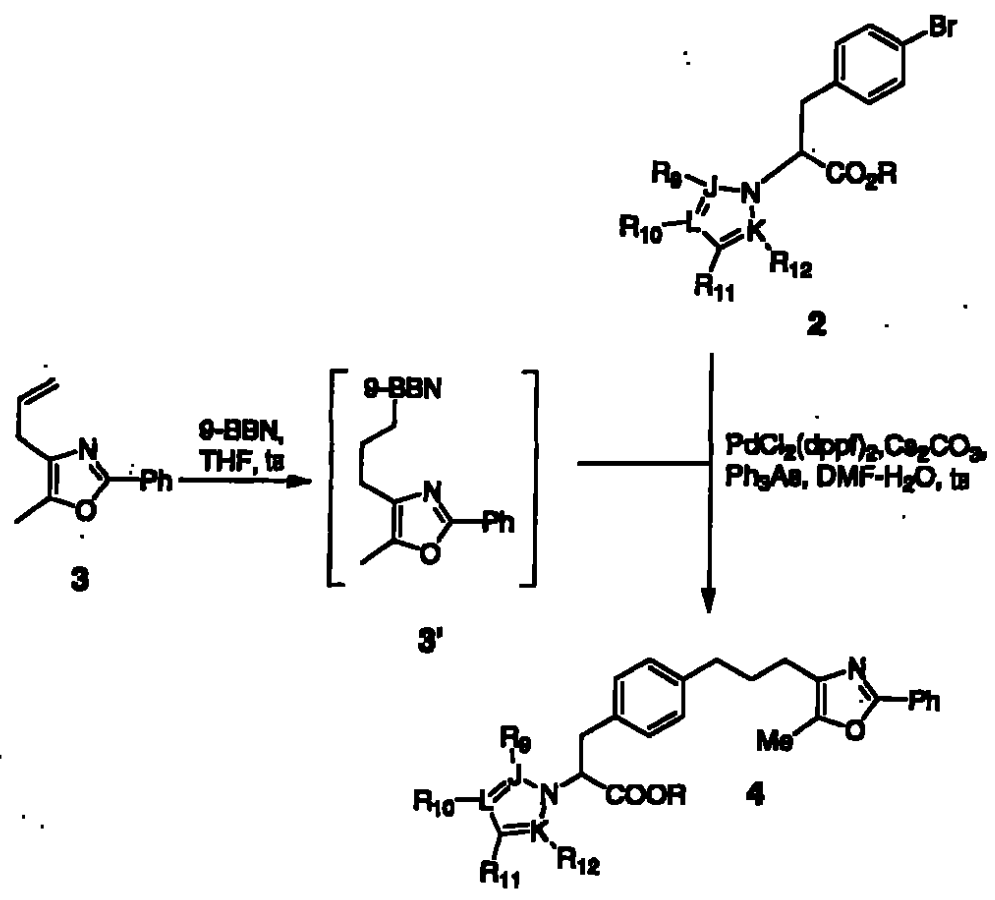
que comprende:

(a) alquilar 1 con 2 y descarboxilar 2 cuando $n=2$;



10 (b) acoplar 2 con 3' para formar 4;

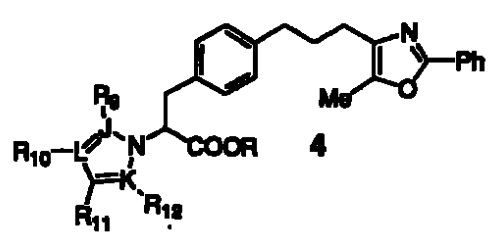
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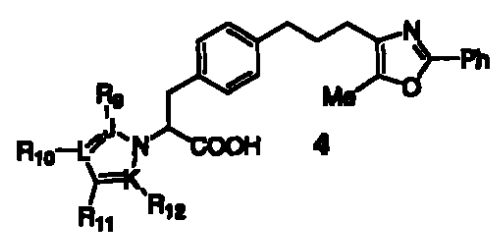
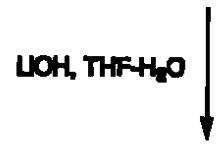
(c) hidrolizar el resto de éster en 4 para formar un 5 compuesto de la invención.

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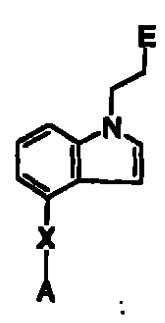
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10

La invención también proporciona un procedimiento para preparar un compuesto de fórmula (III)

15



III

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en la que A es arilo y arilo sustituido,
heteroarilo y heteroarilo sustituido,
heteroarilo condensado y heteroarilo condensado
sustituido,
cicloalquilo (C₃-C₇) y cicloalquilo (C₃-C₇) sustituido,

25 o

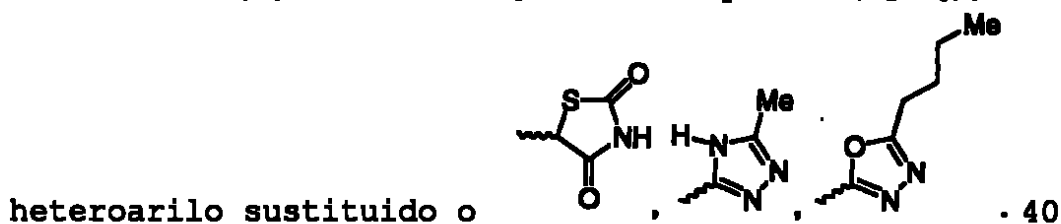
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heterocicloalquilo y heterocicloalquilo sustituido;

X es una cadena de 2 a 5 átomos de longitud seleccionado entre $\sim\text{CH}_2\text{O}\sim$, $\sim\text{CH}_2\text{CH}_2\text{O}\sim$, $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$, $\sim\text{CH}_2\equiv\sim$, 37 o

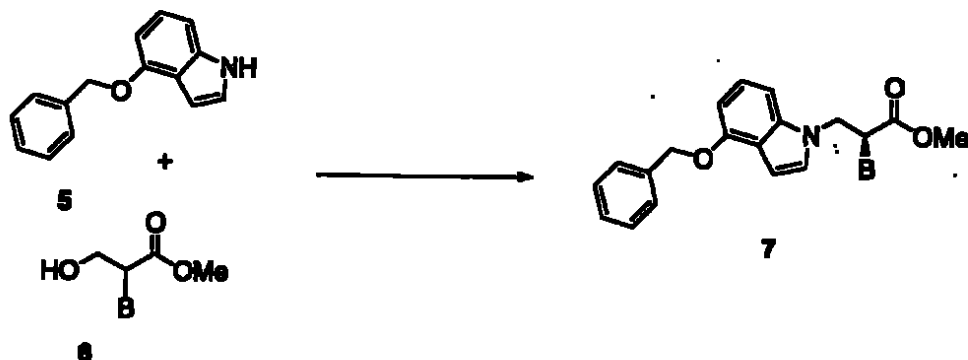
$\sim\text{CH}_2\text{CH}=\sim$, 38 indicando " " 39 un punto de unión; y

5 E es COR_5 , siendo R_5 alquilo ($\text{C}_1\text{-C}_6$), OH, alcoxi ($\text{C}_1\text{-C}_6$), NR_6R_7 , siendo cada uno de R_6 y R_7 independientemente H o alquilo ($\text{C}_1\text{-C}_6$), o uno de R_6 y R_7 es H o alquilo ($\text{C}_1\text{-C}_6$) y el otro es SO_2R_8 , siendo R_8 H o alquilo ($\text{C}_1\text{-C}_6$), o E es



10 que comprende:

(a) preparar un compuesto 6 por acoplamiento del beta hidroxí éster 6 con un derivado de indol 5:



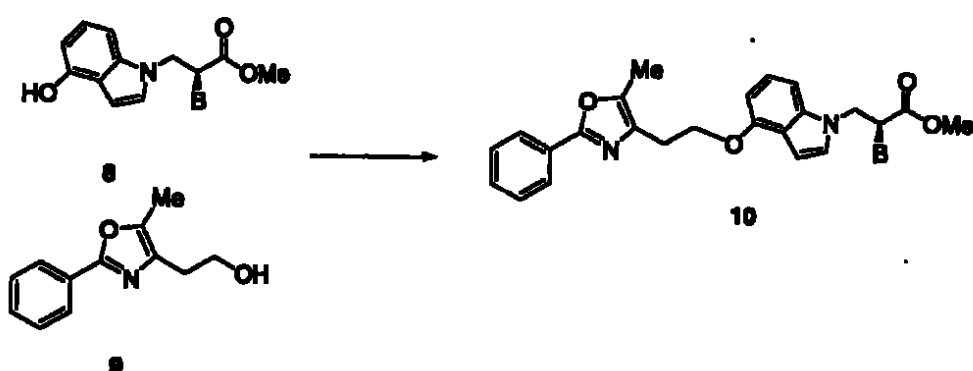
15 (b) retirar el grupo bencilo en 7 para proporcionar

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8;



(c) acoplar 8 con 9 para proporcionar 10;



(d) hidrolizar el resto éster en 10 para formar un 5 compuesto de la invención.

DESCRIPCIÓN DETALLADA DE LA INVENCION

Se usan las siguientes definiciones a menos que se describa otra cosa: halo es fluoro, cloro, bromo o yodo. Alquilo, alcoxi, alquenilo, alquinilo, etc. se refieren a 10 grupos tanto lineales como ramificados; pero la referencia a un radical individual tal como "propilo" incluye sólo el radical de cadena lineal, haciéndose referencia específicamente a un isómero de cadena ramificada, tal como "isopropilo".

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La expresión "alquilo (C_1-C_6)" se refiere a un radical hidrocarburo lineal o ramificado que tiene de 1 a 6 átomos de carbono e incluye, por ejemplo, metilo, etilo, n-propilo, isopropilo, n-butilo, sec-butilo, isobutilo, terc-5 butilo, n-pentilo y n-hexilo.

La expresión "heterocicloalquilo" se refiere a un sistema de anillo heterocíclico monocíclico, condensado, enlazado o espiro bicíclico. Los anillos heterocíclicos monocíclicos contienen de aproximadamente 3 a 12 átomos de 10 anillo, con de 1 a 5 heteroátomos seleccionados entre N, O y S, y preferiblemente de 3 a 7 átomos, en el anillo. Los heterociclicos bicíclicos contienen de 7 a 17 átomos, preferiblemente de 7 a 12 átomos, en el anillo. Los heterociclicos bicíclicos contienen de aproximadamente 7 a 15 aproximadamente 17 átomos de anillo, preferiblemente de 7 a 12 átomos de anillo. Los anillos heterocíclicos bicíclicos pueden ser sistemas de anillo condensados, espiro o enlazados. Los ejemplos de grupos heterocíclicos incluyen éteres cíclicos (oxiranos) tales como óxido de etileno, 20 tetrahidrofurano, dioxano y éteres cíclicos sustituidos, siendo los sustituyentes los descritos anteriormente para los grupos alquilo y cicloalquilo. Los éteres cíclicos sustituidos típicos incluyen óxido de propileno, feniloxirano (óxido de estireno), óxido de cis-2-buteno 25 (2,3-dimetiloxirano), 3-clorotetrahidrofurano, 2,6-dimetil-

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1,4-dioxano, y similares. Son grupos heterocicloalilo que contienen nitrógeno grupos tales como pirrolidina, piperidina, piperazina, tetrahidrotriazina, tetrahidropirazol y grupos sustituidos tales como 3-5 aminopirrolidina, 4-metilpiperazin-1-ilo y similares. Los heterociclos típicos que contienen azufre incluyen tetrahidrotiofeno, dihidro-1,3-ditio-2-ilo y hexahidrotiepin-4-ilo. Otros heterociclos empleados comúnmente incluyen dihidro-oxatio-4-ilo, tetrahidro-10 oxazolilo, tetrahidro-oxadiazolilo, tetrahidro-dioxazolilo, tetrahidro-oxatiazolilo, hexahidrotriazinilo, tetrahidro-oxazinilo, morfolinilo, tiomorfolinilo, tetrahidropirimidinilo, dioxolinilo, octahidrobenzofuranilo, octahidrobenzoimidazolilo y 15 octahidrobenzotiazolilo. Para los heterociclos que contienen azufre, también se incluyen los heterociclos de azufre oxidados que contienen grupos SO o SO₂. Los ejemplos incluyen las formas sulfóxido y sulfona de tetrahidrotiofeno.

20 El término "arilo" se refiere a un anillo aromático cíclico o policíclico que tiene de 5 a 12 átomos de carbono, y que está sin sustituir o sustituido con hasta 3 de los grupos sustituyentes mencionados anteriormente para alquilo, alquenilo y alquinilo. Los ejemplos de grupos 25 arilo incluyen fenilo, 2,6-diclorofenilo, 3-metoxifenilo,

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naftilo, 4-tionaftilo, tetralinilo, antracinilo, fenantrenilo, benzonafteño, fluorenilo, 2-acetamidofluoren-9-ilo y 4'-bromobifenilo.

El término "heteroarilo" se refiere a un anillo cíclico aromático o policíclico condensado que tiene de 1 a 8 heteroátomos seleccionado entre N, O y S. Los grupos heteroarilo o grupos heteroarilo condensados pueden estar sin sustituir o sustituidos con 1 a 3 sustituyentes seleccionados entre los descritos anteriormente para alquilo, alqueno y alquino, por ejemplo, cianotienilo y formilpirrolilo.

Los grupos heteroarilo típicos incluyen 2- o 3-tienilo, 2- o 3-furilo, 2- o 3-pirrolilo, 2-, 4- o 5-imidazolilo, 3-, 4- o 5-pirazolilo, 2-, 4- o 5-tiazolilo, 3-, 4- o 5-isotiazolilo, 2-, 4- o 5-oxazolilo, 3-, 4- o 5-isoxazolilo, 3- o 5-1,2,4-triazolilo, 4- o 5-1,2,3-triazolilo, tetrazolilo, 2-, 3- o 4-piridilo, 3- o 4-piridazinilo, 3-, 4- o 5-pirazinilo, 2-pirazinilo, y 2-, 4- o 5-pirimidinilo.

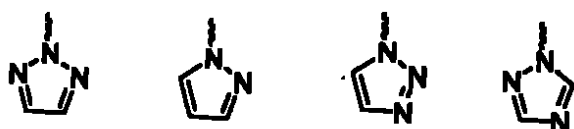
Los grupos heteroarilo aromáticos condensados de 8 a 20 átomos incluyen, pero sin limitación, 1-, 2-, 3-, 5-, 6-, 7- o 8-indolizínico, 1-, 3-, 4-, 5-, 6- o 7-isoindolilo, 2-, 3-, 4-, 5-, 6- o 7-indolilo, 2-, 3-, 4-, 6- o 7-indazolilo, 2-, 4-, 5-, 6-, 7- o 8-purinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8- o 9-quinolizínico, 2-, 3-, 4-, 5-, 6-, 7- o 8-

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quinolilo, 1-, 3-, 4-, 5-, 6-, 7- o 8-isoquinolinilo, 1-,
 4-, 5-, 6-, 7- o 8-ftalazinilo, 2-, 3-, 4-, 5- o 6-
 naftiridinilo, 2-, 3-, 5-, 6-, 7- o 8-quinazolinilo, 3-, 4-
 , 5-, 6-, 7- o 8-cinolinilo, 2-, 4-, 6- o 7-pteridinilo, 1-
 5 , 2-, 3-, 4-, 5-, 6-, 7- o 8-4aH carbazolilo, 1-, 2-, 3-,
 4-, 5-, 6-, 7- o 8-carbazolilo, 1-, 3-, 4-, 5-, 6-, 7-, 8-
 o 9-carbolinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9- o 10-
 fenantridinilo, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- o 9-
 acridinilo, 1-, 2-, 4-, 5-, 6-, 7-, 8- o 9-pirimidinilo, 2-
 10 , 3-, 4-, 5-, 6-, 8-, 9- o 10-fenantrolinilo, 1-, 2-, 3-,
 4-, 6-, 7-, 8- o 9-fenazinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8-,
 9- o 10-fenotiazinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9- o 10-
 fenoxazinilo, 2-, 3-, 4-, 5-, 6- o 1-, 3-, 4-, 5-, 6-, 7-,
 8-, 9- o 10-benzoisoquinolinilo, 2-, 3-, 4- o tieno[2,3-
 15 b]furanilo, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10- o 11-7H-
 pirazino[2,3-c]carbazolilo, 2-, 3-, 5-, 6- o 7-2H-furo[3,2-
 b]-piranilo, 2-, 3-, 4-, 5-, 7- o 8-5H-pirido[2,3-d]-o-
 oxazinilo, 1-, 3- o 5-1H-pirazolo[4,3-d]-oxazolilo, 2-, 4-
 o 5-4H-imidazo[4,5-d]tiazolilo, 3-, 5- o 8-pirazino[2,3-
 20 d]piridazinilo, 2-, 3-, 5- o 6-imidazo[2,1-b]tiazolilo, 1-,
 3-, 6-, 7-, 8- o 9-furo[3,4-c]cinolinilo, 1-, 2-, 3-, 4-,
 5-, 6-, 8-, 9-, 10- o 11-4H-pirido[2,3-c]carbazolilo, 2-,
 3-, 6- o 7-imidazo[1,2-b][1,2,4]triazinilo, 7-
 benzo[b]tienilo, 2-, 4-, 5-, 6- o 7-benzoxazolilo, 2-, 4-,
 25 5-, 6- o 7-benzoimidazolilo, 2-, 4-, 5-, 6- o 7-

benzotiazolilo, 1-, 2-, 4-, 5-, 6-, 7-, 8- o 9-benzoxapinilo, 2-, 4-, 5-, 6-, 7- o 8-benzoxazinilo, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10- o 11-1H-pirrólo[1,2-b][2]benzazapinilo. Los grupos heteroarilo condensados 5 típicos incluyen, pero sin limitación, 2-, 3-, 4-, 5-, 6-, 7- o 8-quinolinilo, 1-, 3-, 4-, 5-, 6-, 7- o 8-isoquinolinilo, 2-, 3-, 4-, 5-, 6- o 7-indolilo, 2-, 3-, 4-, 5-, 6- o 7-benzo[b]tienilo, 2-, 4-, 5-, 6- o 7-benzoxazolilo, 2-, 4-, 5-, 6- o 7-benzoimidazolilo, y 2-, 10 4-, 5-, 6- o 7-benzotiazolilo.

Otros grupos heteroarilo incluyen los siguientes grupos, en los que "~~~~" 44 indica el punto de unión.



15

Los grupos alquilo, cicloalquilo, heterocicloalquilo, arilo y heteroarilo pueden sustituirse con 1 a 4 grupos seleccionados entre halo, hidroxilo, ciano, alcoxi C₁-C₆, nitro, nitroso, amino, alquil C₁-C₆-amino, di-alquil C₁-C₆-20 amino, carboxi, alcanóilo C₁-C₆, alcoxi C₁-C₆-carbonilo, aminocarbonilo, halometilo, dihalometilo, trihalometilo, haloetilo, dihaloetilo, trihaloetilo, tetrahaloetilo, pentahaloetilo, tiol, alquil (C₁-C₄)sulfanilo, alquil (C₁-C₄)sulfinilo y aminosulfonilo. Los ejemplos de grupos 25 alquilo sustituidos incluyen fluorometilo, tribromometilo,

hidroximetilo, 3-metoxipropilo, 3-carboxipentilo, 3,5-dibromo-6-aminocarbonildecilo y 4-etilsulfiniloctilo.

El término "profármaco" se refiere a un compuesto que se convierte *in vivo* en un compuesto activo. La expresión
5 "grupo de profármaco" se refiere a un resto que se convierte *in vivo* en el compuesto activo de fórmula I en la que E es heteroarilo sustituido o $-CO_2H$. Tales grupos generalmente se conocen en la técnica e incluyen grupos formadores de éster, que forman un profármaco de éster,
10 tales como benciloxi, di-alquil (C_1-C_6)-aminoetiloxi, acetoximetilo, pivaloiloximetilo, ftalidoilo, etoxycarboniloxietilo, 5-metil-2-oxo-1,3-dioxol-4-il metilo y alcoxi (C_1-C_6) opcionalmente sustituido con N-morfolino y grupos formadores de amida tales como dialquil (C_1-C_6)-
15 amino. Otros grupos de profármaco incluyen alcoxi C_1-C_6 , y O^-M^+ , representando M^+ un catión. Los cationes preferidos incluyen sodio, potasio y amonio. Otros cationes incluyen magnesio y calcio. Otros grupos de profármaco incluyen O^-M^{++} , siendo M^{++} un catión divalente tal como magnesio o
20 calcio.

El término "diabetes" se refiere a un trastorno metabólico en el que la utilización de la glucosa está alterada induciendo hiperglucemia. Está disponible una visión general de la patogénesis y morfología de la
25 diabetes y sus complicaciones a largo plazo,

particularmente la NIDDM, para los especialistas en la técnica, por ejemplo, en Pathologic Basis of Disease (5ª Ed. páginas 910-922) de Robins. Otros trastornos metabólicos asociados con la alteración de la utilización 5 de la glucosa y la resistencia a la insulina incluyen el IRS, descrito previamente. Además de las principales complicaciones a largo plazo de la NIDDM (angiopatía diabética, aterosclerosis, nefropatía diabética, neuropatía diabética y complicaciones oculares diabéticas tales como 10 retinopatía, formación de cataratas y glaucoma), muchas otras afecciones están asociadas con la NIDDM, incluyendo la dislipidemia, resistencia a la insulina inducida por glucocorticoides, dislipidemia, síndrome de ovarios poliquísticos, obesidad, hiperglucemia, hiperlipidemia, 15 hipercolesterolemia, hipertrigliceridemia, hiperinsulinemia e hipertensión. Están disponibles breves definiciones de estas afecciones en cualquier diccionario médico, por ejemplo, en Stedman's Medical Dictionary (Xª Ed.).

Como se usa en este documento, el término "modular" 20 significa cambiar (algo tal como una acción o un proceso); para que sea más adecuado para su situación. Cambridge Dictionaries Online ([http:// dictionary.cambridge.org/define. asp?key=modulate*2+0](http://dictionary.cambridge.org/define.asp?key=modulate*2+0) última visita 20 de junio de 2002).

25 Los especialistas en la técnica apreciarán que los

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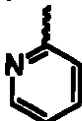
compuestos de la invención que tienen un centro quiral pueden existir y estar en formas ópticamente activas y racémicas. Algunos compuestos pueden presentar polimorfismo. Se entenderá que la presente invención 5 incluye cualquier forma racémica, ópticamente activa, polimórfica o estereoisomérica, o mezclas de los mismos, de un compuesto de la invención, que posee las propiedades útiles descritas en este documento, siendo bien conocido en la técnica cómo preparar formas ópticamente activas (por 10 ejemplo, por resolución de la forma racémica por técnicas de recristalización, por síntesis a partir de materiales de partida ópticamente activos, por síntesis quiral o por separación cromatográfica usando una fase estacionaria quiral) y cómo determinar la actividad o citotoxicidad 15 usando los ensayos convencionales descritos en este documento, o usando otros ensayos similares que son bien conocidos en la técnica.

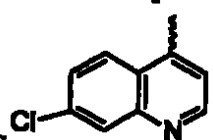
Los valores específicos y preferidos mencionados más adelante para los radicales, sustituyentes e intervalos, 20 son solamente ilustrativos; no excluyen otros valores definidos ni otros valores dentro de intervalos definidos para los radicales y sustituyentes.

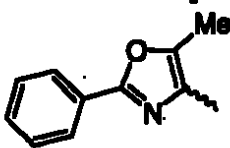
Específicamente, alquilo (C_1-C_6) puede ser metilo, etilo, propilo, isopropilo, butilo, iso-butilo, sec-butilo, 25 pentilo, 3-pentilo, o hexilo; alcoxi (C_1-C_6) puede ser

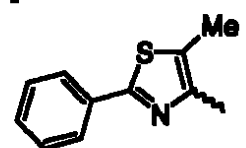
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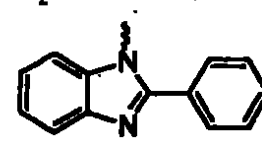
metoxi, etoxi, propoxi, isopropoxi, butoxi, iso-butoxi, sec-butoxi, pentoxi, 3-pentoxi o hexiloxi; halo-alquilo (C₁-C₆) puede ser yodometilo, bromometilo, clorometilo, fluorometilo, triclorometilo, trifluorometilo, 2-5 cloroetilo, 2-fluoroetilo, 2,2,2-trifluoroetilo o pentafluoroetilo; heterocicloalquilo (C₃-C₇) puede ser pirrolidinilo, piperidinilo, furanilo, piranilo, tiofuranilo, y tiopiranilo; y heteroarilo puede ser furilo, imidazolilo, triazolilo, triazinilo, oxazolilo, 10 isoxazolilo, tiazolilo, isotiazolilo, pirazolilo, pirrolilo, pirazinilo, tetrazolilo, piridilo (o su N-óxido), tienilo, pirimidinilo (o su N-óxido), indolilo, isoquinolilo (o su N-óxido) o quinolilo (o su N-óxido).

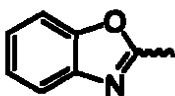
Un valor específico para A es  .46 Otro valor

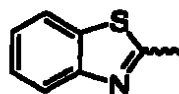
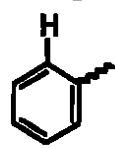
15 específico para A es  47 indicando "~~~~" 48 un punto

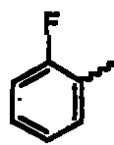
de unión. Otro valor específico para A es  .49

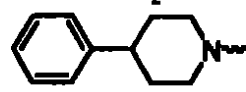
Otro valor específico para A es  .50 Otro valor

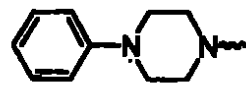
específico para A es  .51 Otro valor específico

para A es  .52 Otro valor específico para A es

 .53 Otro valor específico para A es  .54 Otro

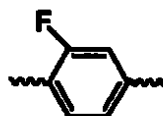
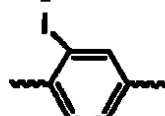
valor específico para A es  .55 Otro valor específico

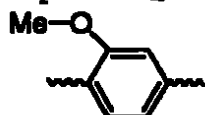
para A es  .56 Otro valor más, específico para A

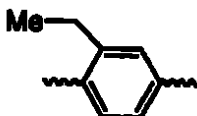
5 es  .57

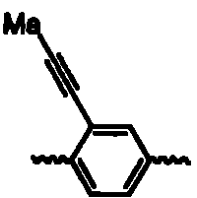
Un valor específico para X es $\sim\text{CH}_2\text{-O}\sim$ 58 indicando
 " " 59 un punto de unión. Otro valor específico para X es
 $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$.60 Otro valor específico para X es
 $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$.61 Otro valor específico para X es
 10 $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$.62 Otro valor específico para X es $\sim\text{CH}_2\text{-}\equiv\sim$.63
 Otro valor más, específico para X es $\sim\text{CH}_2\text{-CH=CH}\sim$.64

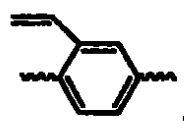
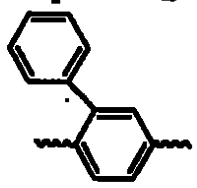
Un valor específico para Q es  65 indicando
 " " 66 un punto de unión. Otro valor específico para Q es

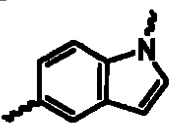
 .67 Otro valor específico para Q es  .68

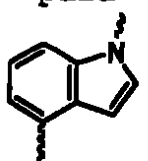
15 Otro valor específico para Q es  .69 Otro valor

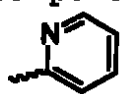
específico para Q es  .70 Otro valor específico

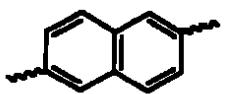
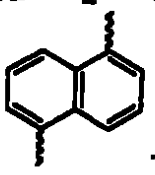
para Q es  .71 Otro valor específico para Q es

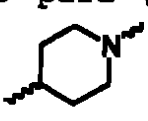
 .72 Otro valor específico para Q es  .73

Otro valor específico para Q es  .74 Otro valor

específico para Q es  .75 Otro valor específico para

5 Q es  .76 Otro valor específico para Q es

 .77 Otro valor específico para Q es  78

Otro valor más, específico para Q es  .79

Un valor específico para X es CH₂.

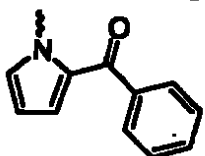
Un valor específico para Y es CH₂.

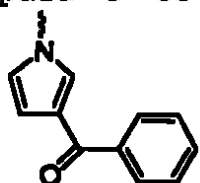
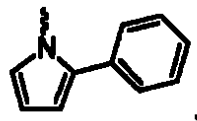
10 Un valor específico para B es H. Otro valor específico para B es F. Otro valor específico para B es metilo. Otro valor específico para B es metoxi.

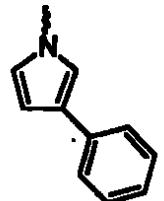
Un valor específico para D es H. Otro valor específico

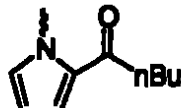
para D es Me. Otro valor específico para D es  80

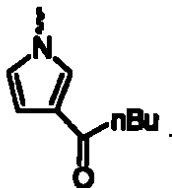
indicando "81" un punto de unión. Otro valor específico

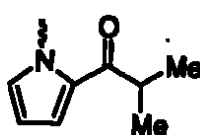
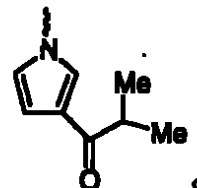
para D es  .82 Otro valor específico para D es

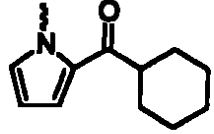
 .83 Otro valor específico para D es  .84

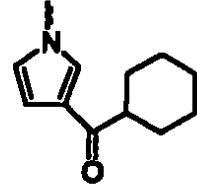
Otro valor específico para D es  .85 Otro valor

5 específico para D es  .86 Otro valor específico

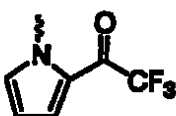
para D es  .87 Otro valor específico para D es

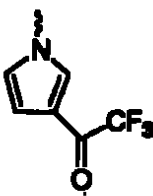
 .88 Otro valor específico para D es  89

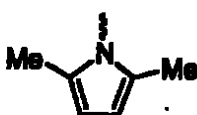
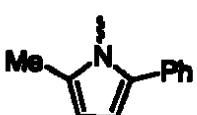
Otro valor específico para D es  .90

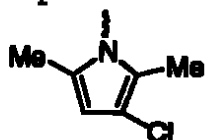
Otro valor específico para D es  .91 Otro valor

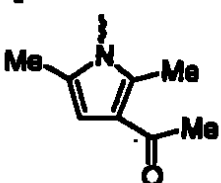
65

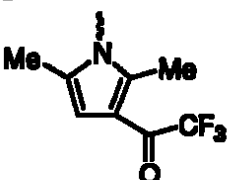
específico para D es  .92 Otro valor específico

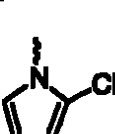
para D es  .93 Otro valor específico para D es

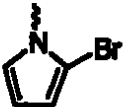
 .94 Otro valor específico para D es  .95

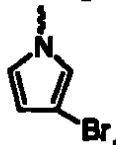
Otro valor específico para D es  .96 Otro valor

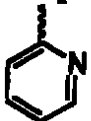
5 específico para D es  .97 Otro valor específico

para D es  .98 Otro valor específico para D es

 .99 Otro valor específico para D es  .100 Otro

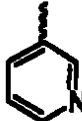
valor específico para D es  .101 Otro valor específico

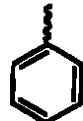
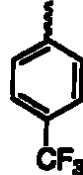
para D es  .102 Otro valor específico para D es

10  .103 Otro valor específico para D es  .104 Otro

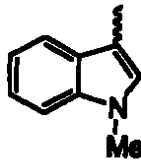
410

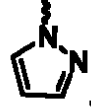
66

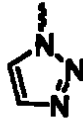
valor específico para D es .105 Otro valor específico

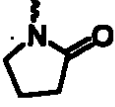
para D es .106 Otro valor específico para D es .107

Otro valor específico para D es .108 Otro valor

específico para D es .109 Otro valor específico para

5 D es .110 Otro valor específico para D es .111 Otro

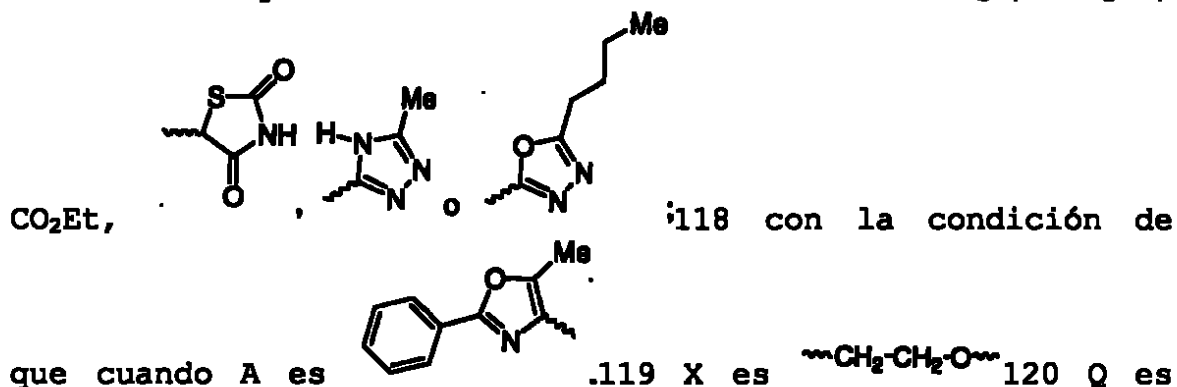
valor específico para D es .112 Otro valor

más, específico para D es .113 o .114

Un grupo de compuestos de la invención son compuestos de fórmula I en la que A es arilo o arilo sustituido, 10 heteroarilo o heteroarilo sustituido, heteroarilo condensado o heteroarilo condensado sustituido o heterocicloalquilo y heterocicloalquilo sustituido; X es una cadena de 2 a 5 átomos de longitud seleccionada entre $\sim\text{CH}_2\text{-O}\sim$,115

15 $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\text{-}\equiv\sim$, o $\sim\text{CH}_2\text{-CH=CH}\sim$,116 indicando

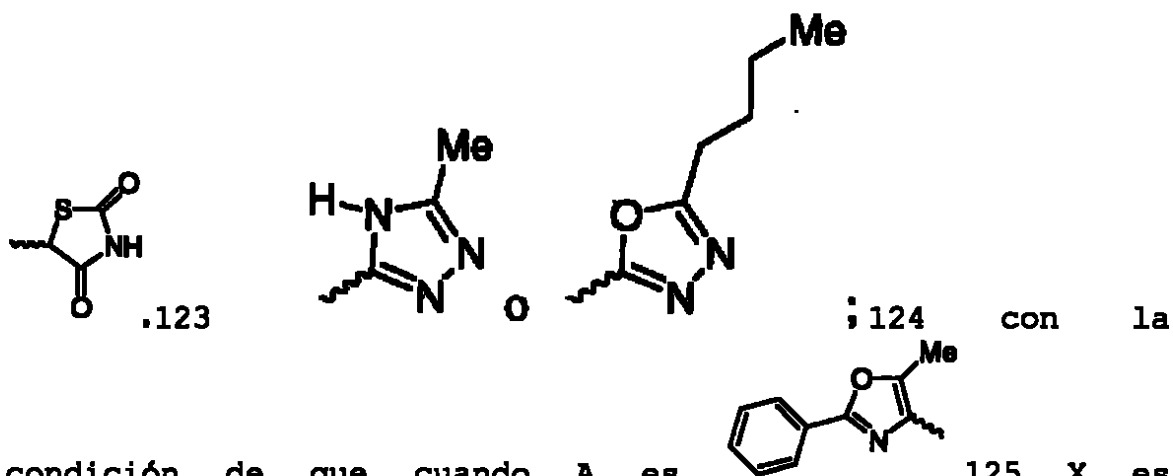
"117 un punto de unión; Q es arilo o arilo sustituido;
 heteroarilo o heteroarilo sustituido; heteroarilo
 condensado o heteroarilo condensado sustituido; con la
 condición de que cuando Q es un heteroarilo de cinco
 5 miembros, el punto de unión de X a Q no sea un heteroátomo
 del heteroarilo; Y y Z están independientemente ausentes o
 son $(CR_1R_2)_n$ y $(CR_3R_4)_m$, siendo cada uno de R_1-R_4
 independientemente H, halo, alquilo (C_1-C_6), hidroxilo, alcoxi
 (C_1-C_6), y cada uno de m y n es independientemente 1, 2, ó
 10 3; B es H, halo, alquilo (C_1-C_6), halo-alquilo (C_1-C_6) o
 alcoxi (C_1-C_6); D es H, arilo y arilo sustituido, o
 heteroarilo y heteroarilo sustituido; E es CO_2H , CO_2Me ,



15 fenilo, B es H y E es CO_2H , D no sea pirrolilo.

Otro grupo de compuestos de la invención son
 compuestos de fórmula I en la que A es arilo o arilo
 sustituido, heteroarilo o heteroarilo sustituido,
 heteroarilo condensado o heteroarilo condensado sustituido,
 20 o heterocicloalquilo y heterocicloalquilo sustituido; S es
 una cadena de 2 a 5 átomos de longitud seleccionado entre

$\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\text{-}\equiv\sim$, o $\sim\text{CH}_2\text{-}\text{CH}=\text{CH}\sim$, 121 indicando
 "122 un punto de unión; Q es arilo o arilo sustituido;
 heteroarilo o heteroarilo sustituido; heteroarilo
 condensado o heteroarilo condensado sustituido; con la
 5 condición de que cuando Q es un heteroarilo de cinco
 miembros, el punto de unión entre X y Q no esté en el
 heteroátomo del heteroarilo; Y y Z están independientemente
 ausentes o son CH_2 , B es H, halo, alquilo ($\text{C}_1\text{-C}_6$), halo-
 alquilo ($\text{C}_1\text{-C}_6$), o alcoxi ($\text{C}_1\text{-C}_6$); D es H, heteroarilo o
 10 heteroarilo sustituido; y E es CO_2H , CO_2Me , CO_2Et ,



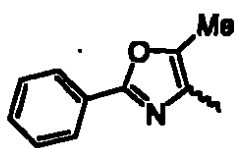
condición de que cuando A es 124 con la
 126 Q es fenilo, Y y Z son CH_2 , B es H, y E es
 CO_2H , D no sea pirrolilo.

15 Otro grupo de compuestos de la invención son
 compuestos de fórmula I en la que A es arilo o arilo
 sustituido, heteroarilo o heteroarilo sustituido,
 heteroarilo condensado o heteroarilo condensado sustituido,
 o heterocicloalquilo y heterocicloalquilo sustituido; X es

una cadena de 2 a 5 átomos de longitud seleccionada entre $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\text{-}\equiv\sim$, o $\sim\text{CH}_2\text{-}\text{CH}=\text{CH}\sim$,¹²⁷ indicando " $\sim$ "¹²⁸ un punto de unión; Q es fenilo o fenilo sustituido, naftilo o naftilo sustituido, indolilo o indolilo sustituido, piridilo o piridilo sustituido, o piperidinilo o piperidinilo sustituido; Y y Z están independientemente ausentes o son CH_2 ; B es H, F, metilo o metoxi, D es H, pirrolilo sustituido, piridilo, fenilo sustituido, diazolilo o triazolilo; y E es CO_2H , CO_2Me o CO_2Et .

10 Otro grupo de compuestos de la invención son compuestos de fórmula I en la que A es arilo o arilo sustituido, heteroarilo o heteroarilo sustituido, heteroarilo condensado o heteroarilo condensado sustituido, o heterocicloalquilo y heterocicloalquilo sustituido; X es
15 una cadena de 2 a 5 átomos de longitud seleccionada entre $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$, $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$, $\sim\text{CH}_2\text{-}\equiv\sim$, o $\sim\text{CH}_2\text{-}\text{CH}=\text{CH}\sim$,¹²⁹ indicando " $\sim$ "¹³⁰ un punto de unión; Q es fenilo o fenilo sustituido, naftilo o naftilo sustituido, indolilo o indolilo sustituido, piridilo o piridilo sustituido, o piperidinilo
20 o piperidinilo sustituido; Y y Z están independientemente ausentes o son CH_2 ; B es H, F, metilo o metoxi; D es H, pirrolilo sustituido, piridilo, fenilo sustituido, diazolilo o triazolilo; y E es CO_2H , CO_2Me o CO_2Et .

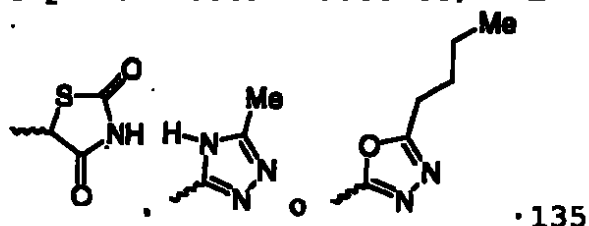
Otro grupo de compuestos de la invención son

compuestos de fórmula I en la que A es .131

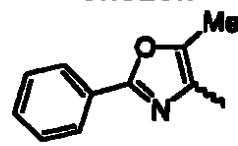
indicando "~~~~"132 el punto de unión; X es $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$, $\sim\text{CH}_2\text{CH}_2\text{O}\sim$, $\sim\text{CH}_2\equiv\sim$.133 o $\sim\text{CH}_2\text{CH}=\sim$.134 Q es

arilo o arilo sustituido, heteroarilo o heteroarilo sustituido, o heteroarilo condensado o heteroarilo condensado sustituido; con la condición de que cuando Q es un heteroarilo de cinco miembros, el punto de unión de X a Q no esté en el heteroátomo del heteroarilo; B es H, halo, alquilo ($\text{C}_1\text{-C}_6$), halo-alquilo ($\text{C}_1\text{-C}_6$) o alcoxi ($\text{C}_1\text{-C}_6$);

10 D es heteroarilo o heteroarilo sustituido; Y es CH_2 ; Z es CH_2 o está ausente; E es CO_2H , CO_2Me o CO_2Et ,



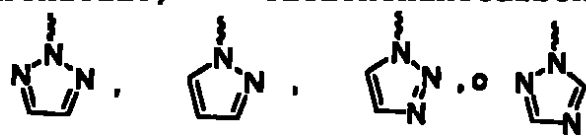
Otro grupo de compuestos de la invención son

compuestos de fórmula I, en la que A es .136

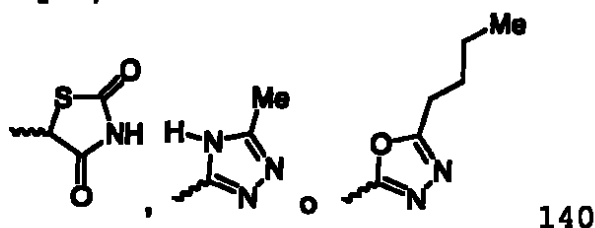
15 indicando "~~~~"137 el punto de unión; X es $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$, o $\sim\text{CH}_2\text{CH}_2\text{O}\sim$.138 Q es arilo o arilo sustituido, heteroarilo o heteroarilo sustituido, o heteroarilo condensado o heteroarilo condensado sustituido; con la condición de que cuando Q es un heteroarilo de cinco

415

miembros, el punto de unión de X a Q no está en el heteroátomo del heteroarilo; B es H; Y es CH₂; Z es CH₂ o está ausente; D es fenilo o pirrolilo sin sustituir o pirrolilo sustituido con 1, 2, 3, ó 4 grupos seleccionados entre metilo, bromo, cloro, acetilo, trifluoroacetilo, benzoílo, ciclohexanocarbonilo y propionilo; o

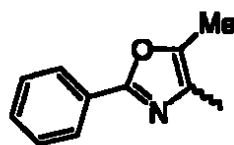


;139 y E es CO₂H, CO₂Me, CO₂Et,



10

Otro grupo de compuestos de la invención son



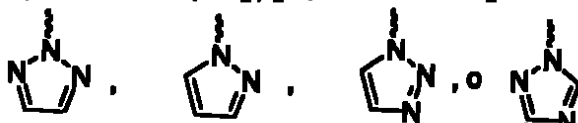
compuestos de fórmula I en la que A es ;141

indicando "wavy"142 el punto de unión; X es ~CH₂-CH₂-CH₂~143

o -(CH₂)₂-O-; Q es fenilo, indolinilo, pirrolilo o

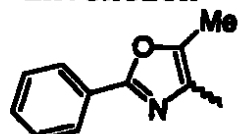
15 piridinilo, pudiendo estar sustituido o no sustituido

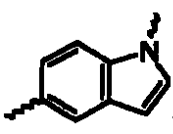
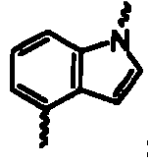
cualquiera de ellos; Y es -(CH₂)₂-; Z es CH₂ o está ausente;



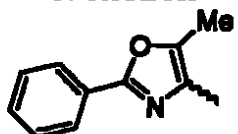
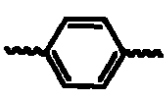
B es H, D es H, ;144 y E es CO₂H, CO₂Me; CO₂Et.

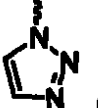
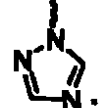
Otro grupo de compuestos de la invención son

compuestos de fórmula I en la que A es .145
indicando "~~~~"146 el punto de unión; X es ~~~CH₂-CH₂-CH₂~147 o

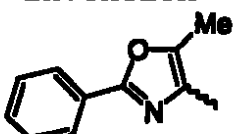
-(CH₂)₂-O-; Q es 148 o ;149 Y es -(CH₂)₂-; Z
5 es CH₂; B es H; D es H; y E es CO₂H, CO₂Me, CO₂Et.

Otro grupo de compuestos de la invención son

compuestos de fórmula I, en la que A es .150
indicando "~~~~"151 el punto de unión; X es
~~~CH<sub>2</sub>-CH<sub>2</sub>-O~, α ~~~CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>~152 Q es 153 Y es CH<sub>2</sub>; Z

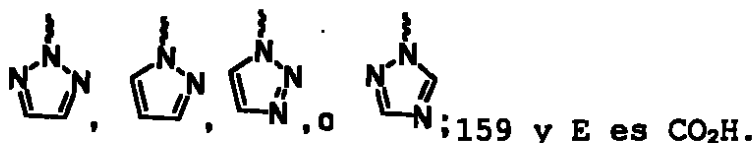
10 está ausente; B es H; D es , , , o ;154 y E  
es CO<sub>2</sub>H, CO<sub>2</sub>Me o CO<sub>2</sub>Et.

Otro grupo de compuestos de la invención son

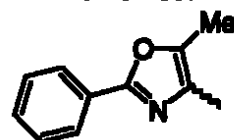
compuestos de fórmula I, en la que A es .155  
indicando "~~~~"156 el punto de unión; X es ~~~CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>~157 Q

15 es ;158 Y es CH<sub>2</sub>; Z está ausente; B es H; D es

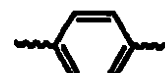
217



Otro grupo de compuestos de la invención son compuestos de fórmula I, en la que A es



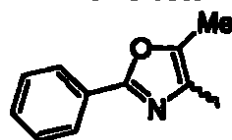
indicando "—" 161 el punto de unión; X es —CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>— 162 Q

5 es  ;163 ; Y es CH<sub>2</sub>; Z está ausente; B es H; D es



Otro grupo de compuestos de la invención son

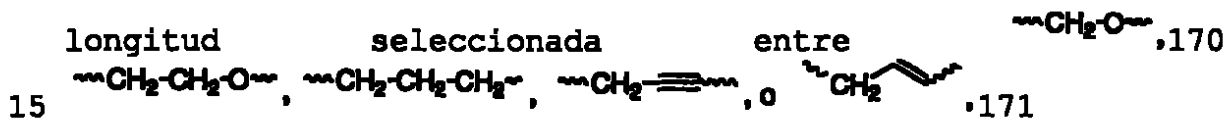
compuestos de fórmula I, en la que A es



indicando "—" 166 el punto de unión; X es —CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>— 167 Q

10 es  ;168 Y es CH<sub>2</sub>; B es H, D es  ;169 y E es CO<sub>2</sub>H.

Un grupo de compuestos de la invención son compuestos de fórmula II en la que X es una cadena de 2 a 5 átomos de longitud seleccionada entre

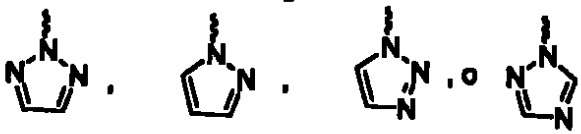


indicando "—" 172 un punto de unión; Q es arilo o arilo sustituido; heteroarilo o heteroarilo sustituido; heteroarilo condensado o heteroarilo condensado sustituido;

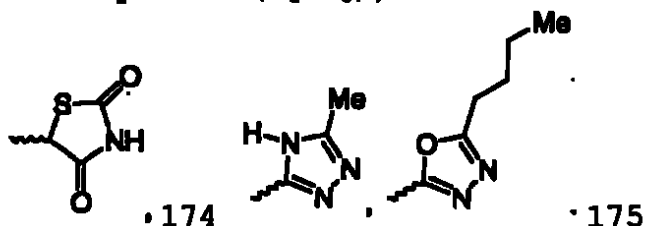
418

con la condición de que cuando Q es un heteroarilo de cinco miembros, el punto de unión de X a Q no esté en el heteroátomo del heteroarilo; B es H, halo, alquilo (C<sub>1</sub>-C<sub>6</sub>), halo-alquilo (C<sub>1</sub>-C<sub>6</sub>) o alcoxi (C<sub>1</sub>-C<sub>6</sub>); y uno o dos de tres de

5 J, K y L son N para formar

;173 y E es COR<sub>5</sub>, siendo R<sub>5</sub> alquilo (C<sub>1</sub>-C<sub>6</sub>), OH, alcoxi (C<sub>1</sub>-C<sub>6</sub>), NR<sub>6</sub>R<sub>7</sub>, siendo cada uno de R<sub>6</sub> y R<sub>7</sub> independientemente H o alquilo (C<sub>1</sub>-C<sub>6</sub>), o uno de R<sub>6</sub> y R<sub>7</sub> es H o alquilo (C<sub>1</sub>-C<sub>6</sub>) y el otro es SO<sub>2</sub>R<sub>8</sub>, siendo R<sub>8</sub> H

10 o alquilo (C<sub>1</sub>-C<sub>6</sub>), o E es heteroarilo sustituido o



Otro grupo de compuestos de la invención son compuestos de fórmula II en la que X es una cadena de 2 a 5 átomos de longitud seleccionada entre  $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$ ,176

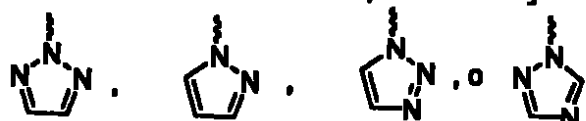
15  $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$ ,  $\sim\text{CH}_2\text{-}\equiv\sim$ , o  $\sim\text{CH}_2\text{-}\text{CH}=\text{CH}\sim$ ,177 indicando " $\sim$ "178 un punto de unión; Q es arilo o arilo sustituido; heteroarilo o heteroarilo sustituido; heteroarilo condensado o heteroarilo condensado sustituido; con la condición de

20 cuando Q es un heteroarilo de cinco miembros, el punto de unión de X a Q no esté en el heteroátomo del heteroarilo; B es H, fluoro, metilo, trifluorometilo o metoxi; uno o dos

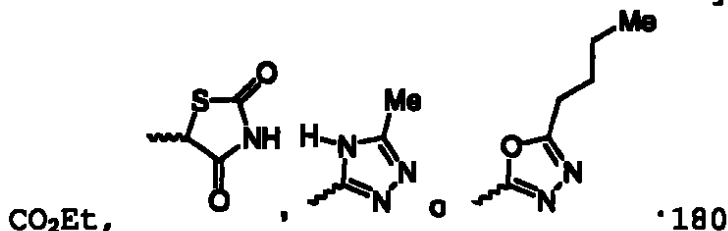


4A

de tres de J, K y L son N, para formar



179 y E es CO<sub>2</sub>H, CO<sub>2</sub>Me,



CO<sub>2</sub>Et,

180

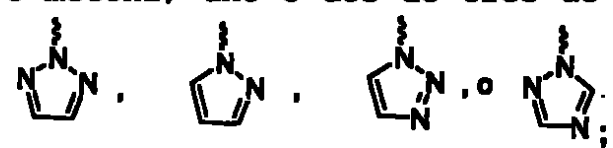
Otro grupo de compuestos de la invención son 5 compuestos de fórmula II en la que X es una cadena de 2 a 5 átomos de longitud seleccionada entre  $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$ , 181  $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$ ,  $\sim\text{CH}_2\text{-}\equiv\sim$ , o  $\sim\text{CH}_2\text{-}\text{CH}=\text{CH}\sim$ , 182 indicando " $\sim$ " 183 un punto de unión; Q es arilo o arilo sustituido; heteroarilo o heteroarilo sustituido; heteroarilo condensado o 10 heteroarilo condensado sustituido; con la condición de que cuando Q es un heteroarilo de cinco miembros, el punto de unión de X a Q no esté en el heteroátomo del heteroarilo; B es H, fluoro, metilo, trifluorometilo o metoxi; uno o dos de tres de J, K y L son N para formar

15 184 y E es CO<sub>2</sub>H, CO<sub>2</sub>Me o CO<sub>2</sub>Et.

Otro grupo de compuestos de la invención son compuestos de fórmula II en la que X es una cadena de 2 a 5 átomos de longitud seleccionada entre  $\sim\text{CH}_2\text{-CH}_2\text{-CH}_2\sim$  185 o 20  $\sim\text{CH}_2\text{-CH}_2\text{-O}\sim$ , 186 indicando " $\sim$ " 187 un punto de unión; Q es

420

arilo o arilo sustituido; B es H, fluoro, metilo, trifluorometilo o metoxi; uno o dos de tres de J, K y L son

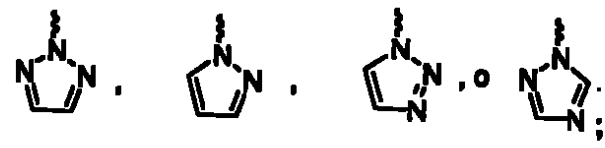


N para formar  $\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{Me}$  o  $\text{CO}_2\text{Et}$ .

5 Otro grupo de compuestos de la invención son compuestos de fórmula II en la que X es una cadena de 2 a 5 átomos de longitud seleccionada entre  $\text{---CH}_2\text{---CH}_2\text{---CH}_2\text{---}$  189 o  $\text{---CH}_2\text{---CH}_2\text{---O---}$  190 indicando "wavy" 191

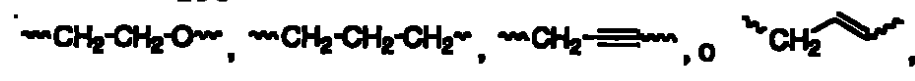
un punto de unión; Q es arilo o arilo sustituido; B es H;

10 uno o dos de tres de J, K y L son N para formar



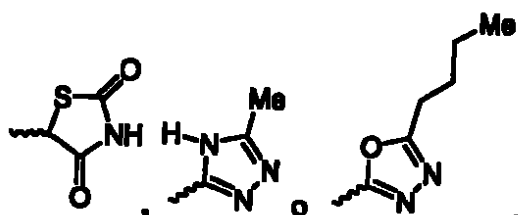
192 y E es  $\text{CO}_2\text{H}$ .

Un grupo de compuestos de la invención son compuestos de fórmula III en la que A es arilo o arilo sustituido; heteroarilo o heteroarilo sustituido; heteroarilo condensado o heteroarilo condensado sustituido, o heterocicloalquilo y heterocicloalquilo sustituido; X es una cadena de 2 a 5 átomos de longitud seleccionada entre  $\text{---CH}_2\text{---O---}$  193



194 indicando

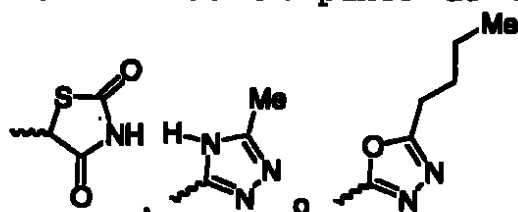
20 "wavy" 195 un punto de unión; y E es  $\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{Me}$ ,  $\text{CO}_2\text{Et}$ ,



196

Otro grupo de compuestos de la invención son compuestos de fórmula III en la que A es arilo o arilo sustituido; heteroarilo o heteroarilo sustituido; 5 heteroarilo condensado o heteroarilo condensado sustituido, o heterocicloalquilo y heterocicloalquilo sustituido; X es una cadena de 2 a 5 átomos de longitud seleccionada entre  $\sim\text{CH}_2\text{CH}_2\text{O}\sim$ ,  $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$ ,  $\sim\text{CH}_2\equiv\sim$ , o  $\sim\text{CH}_2\sim$ , 197

indicando " " 198 un punto de unión; y E es  $\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{Me}$ ,



10  $\text{CO}_2\text{Et}$ ,

199

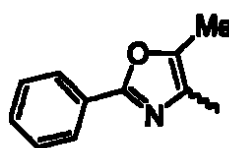
Otro grupo de compuestos de la invención son compuestos de fórmula III en la que A es arilo o arilo sustituido; heteroarilo o heteroarilo sustituido; heteroarilo condensado o heteroarilo condensado sustituido, 15 o heterocicloalquilo y heterocicloalquilo sustituido; X es una cadena de 2 a 5 átomos de longitud seleccionada entre  $\sim\text{CH}_2\text{CH}_2\text{O}\sim$ ,  $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$ , 200 indicando " " 201 un punto de unión; y E es  $\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{Me}$ ,  $\text{CO}_2\text{Et}$ .

Otro grupo de compuestos de la invención son

422

compuestos de fórmula III en la que A es heteroarilo o heteroarilo sustituido, X es una cadena de 2 a 5 átomos de longitud seleccionada entre  $\sim\text{CH}_2\text{CH}_2\text{O}\sim$ ,  $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$ ,<sup>202</sup> indicando "—" <sup>203</sup> un punto de unión; y E es CO<sub>2</sub>H, CO<sub>2</sub>Me o 5 CO<sub>2</sub>Et.

Otro grupo de compuestos de la invención son

compuestos de fórmula III en la que A es  <sup>204</sup> indicando "—" <sup>205</sup> un punto de unión; X es  $\sim\text{CH}_2\text{CH}_2\text{O}\sim$ ,  $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$ ,<sup>206</sup> y E es CO<sub>2</sub>H.

10 Se proporcionan procedimientos e intermedios nuevos para preparar compuestos de fórmula I como realizaciones adicionales de la invención y se ilustran por los siguientes procedimientos en los que los significados de los radicales genéricos son como se han proporcionado  
15 anteriormente a menos que se indique otra cosa. Ciertos compuestos de fórmula I son útiles como intermedios para preparar otros compuestos de fórmula I.

También se indica que los compuestos de fórmula I pueden prepararse usando grupos protectores. Debe indicarse  
20 que el uso y la elección apropiados de grupos protectores es bien conocida por un especialista en la técnica, y no se limita a los ejemplos específicos mostrados a continuación. También debe indicarse que tales grupos no sólo sirven para

proteger sitios químicamente reactivos, sino también para mejorar la solubilidad o cambiar de otra forma las propiedades físicas. Una buena referencia general para la preparación y desprotección de grupos protectores es 5 "Protecting Groups in Organic Synthesis" por T.W. Green y P.G. Wuts. Varias reacciones generales tales como oxidaciones y reducciones etc. no se muestran con detalle, pero pueden realizarse por procedimientos entendidos por un especialista en la técnica. Las transformaciones generales 10 se revisan bien en "Comprehensive Organic Transformation" por Richard Larock, y en la serie "Compendium of Organic Synthetic Methods" publicada por Wiley-Interscience. En general, los materiales de partida se obtienen a partir de fuentes comerciales a menos que se indique otra cosa.

15 Los especialistas en la técnica apreciarán que los compuestos de la invención que tienen uno o más centros quirales pueden existir y aislarse en formas ópticamente activas y racémicas. Algunos compuestos pueden presentar polimorfismo. Se entenderá que la presente invención 20 incluye cualquier forma racémica, ópticamente activa, polimórfica, geométrica o estereoisomérica, o mezclas de las mismas, de un compuesto de la invención, que posea las propiedades útiles descritas en este documento, siendo bien conocido en la técnica cómo preparar formas ópticamente 25 activas (por ejemplo, por resolución de la forma racémica

1424

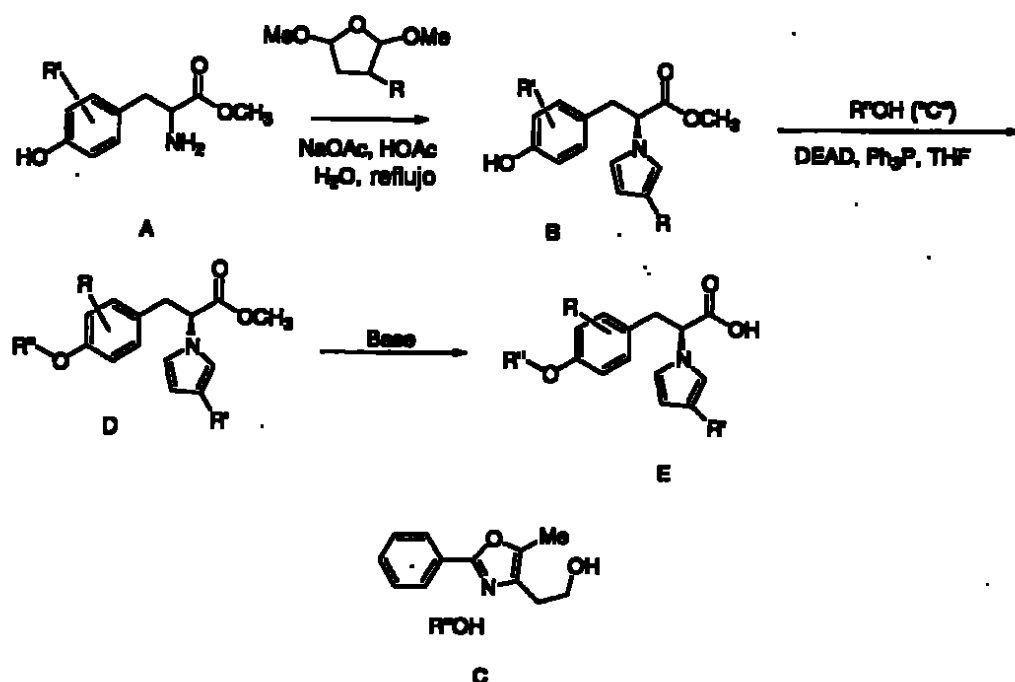
por técnicas de recristalización, por síntesis a partir de materiales de partida ópticamente activos, por síntesis quiral o por separación cromatográfica usando una fase estacionaria quiral) y cómo determinar la actividad o  
5 citotoxicidad usando los ensayos convencionales descritos en este documento, o usando otros ensayos similares que son bien conocidos en la técnica.

También se apreciará por los especialistas en la técnica que los siguientes esquemas representan la síntesis  
10 de compuestos en los que A, X, Q, Y, B, D, Z o E son como se han definido. Sin embargo, se entenderá que pueden prepararse compuestos de la invención distintos a los descritos específicamente, usando las estrategias representadas en los esquemas.

15 El Esquema 1 representa un procedimiento general para la preparación de compuestos de Fórmula I en la que el grupo pirrolilo está sin sustituir.

Esquema 1

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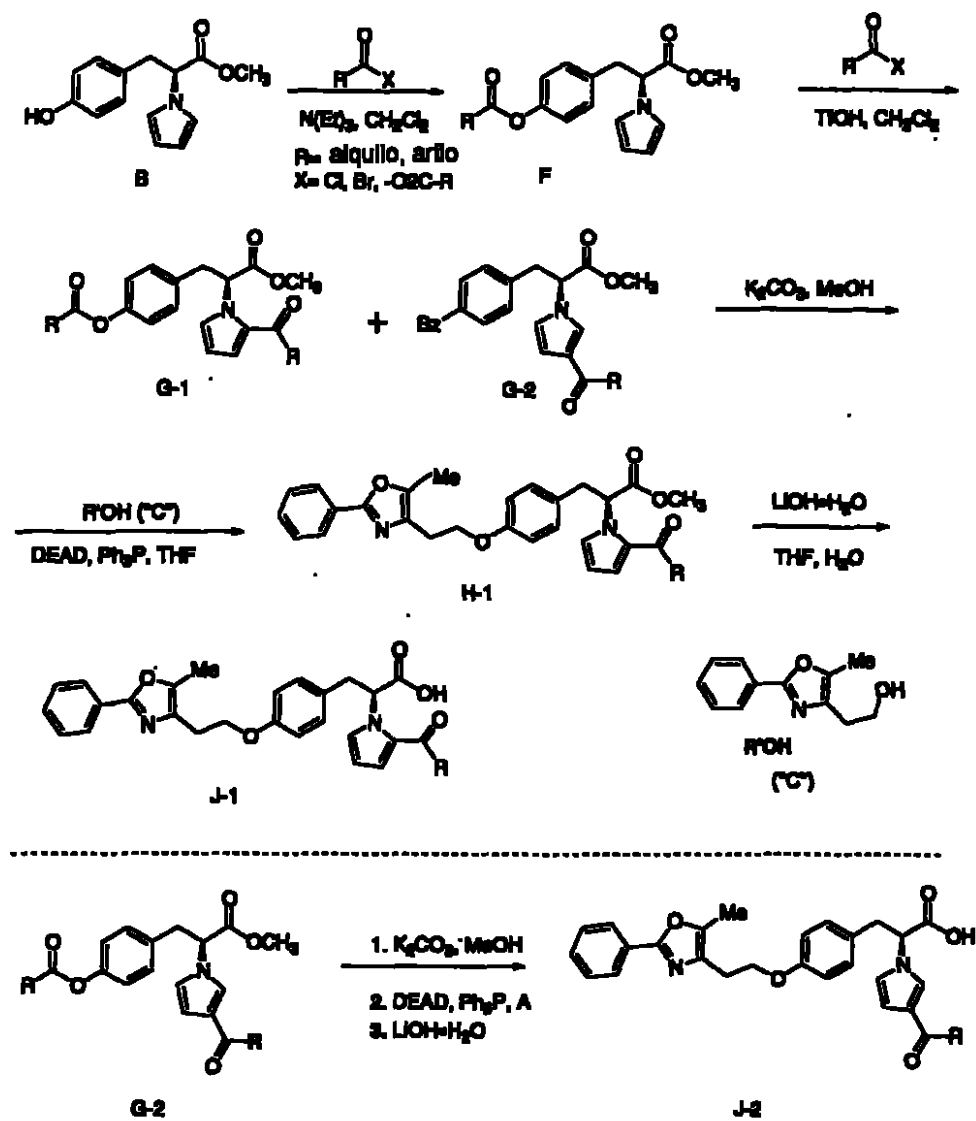


En el Esquema 1, primero se prepara el éster de pirrolotirosina B dejando que el éster de tirosina A experimente una reacción con 2,5 dimetoxi tetrahidrofurano en presencia de una base. En el Esquema 1 se representa el 5 éster metílico, pero es posible usar otros ésteres. El acoplamiento de un análogo de éster de pirrolotirosina con un compuesto que lleva un alcohol primario o secundario en condiciones de tipo de Mitsunobu o similares proporciona un derivado del éster metílico de pirrolotirosina D. La 10 hidrólisis del éster metílico de pirrolotirosina D en condiciones básicas proporciona el compuesto de la invención E.

El Esquema 2 representa la preparación de compuestos de Fórmula I en la que el grupo pirrol lleva un sustituyente alquil o aril carbonilo.



Esquema 2

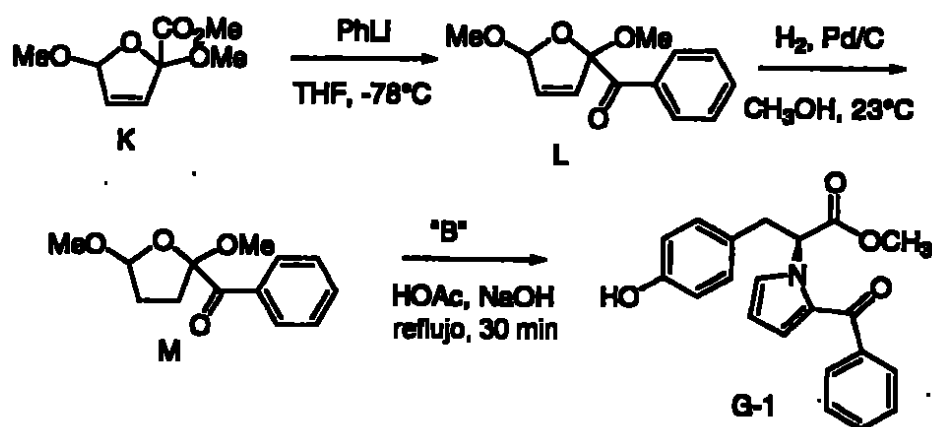


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De acuerdo con el Esquema 2, primero se protege el grupo fenol del éster de pirrolotirosina B usando un haluro o anhídrido de ácido usando procedimientos conocidos por los especialistas en la técnica. Después, se deja que el 5 éster metílico de pirrolotirosina E protegido reaccione con un haluro de ácido tal como cloruro de benzoílo, aunque pueden usarse otros haluros o anhídridos de ácido. La acilación se produce en la posición 2 ó 3 del anillo de pirrol para proporcionar una mezcla de los derivados de 10 benzoílo 2- y 3-sustituidos G-1 y G-2, que pueden separarse usando técnicas convencionales. La desprotección del grupo benzoílo del derivado de pirrolotirosina G-1 o G-2, y el posterior acoplamiento de Mitsunobu, proporciona el penúltimo éster metílico H-1 o H-2. La hidrólisis del éster 15 metílico proporciona el compuesto de la invención J-1 o J-2.

En el Esquema 3 se proporciona un procedimiento alternativo para la preparación del derivado de pirrolotirosina G-1 sustituido.

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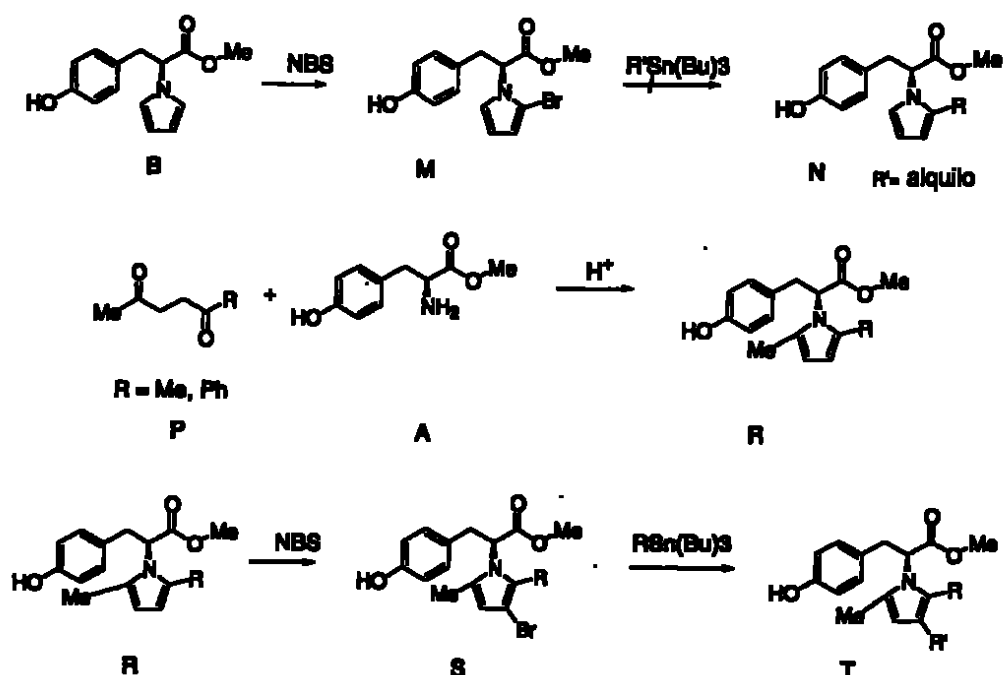


Por consiguiente, el 2,5-dihidro-2,5-dimetoxi-2-furan carboxilato de metilo K experimenta una reacción con fenil litio para proporcionar el derivado de benzoílo L. El derivado de benzoílo L después experimenta una reacción con 5 éster metílico de tirosina B para proporcionar el compuesto G-1. El compuesto G-1 puede convertirse en el compuesto de la invención de acuerdo con las etapas proporcionadas anteriormente.

El Esquema 4 proporciona otra ruta para los compuestos 10 de la invención en la que el grupo pirrol lleva más de un sustituyente.

Esquema 4

W30



De esta forma, La Fila 1 del Esquema 4 representa la síntesis de derivados de éster metílico de pirrolotirosina que llevan un sustituyente en la posición 2 del pirrolilo. El éster metílico de pirrolotirosina **B** experimenta una 5 reacción con N-bromosuccinimida o un agente similar para proporcionar el derivado de éster metílico de 2-bromo pirrolotirosina **M**. El derivado de éster metílico de 2-bromo pirrolotirosina **M** puede experimentar acoplamiento con un alcohol **C** e hidrólisis para proporcionar un compuesto de la 10 invención. Como alternativa, el derivado de éster metílico de 2-bromo-pirrolotirosina **M** puede experimentar reacción con un reactivo de alquil estaño en condiciones conocidas en la técnica para proporcionar el derivado de éster

metílico de 2-alquil pirrolotirosina N, que puede experimentar acoplamiento e hidrólisis para proporcionar otros compuestos de la invención.

La Fila 2 del Esquema 4 representa la síntesis de 5 derivados de éster metílico de pirrolotirosina disustituidos. De esta forma, la dicetona P experimenta reacción con éster metílico de tirosina A en presencia de un ácido para proporcionar el derivado del éster metílico de pirrolotirosina P, en el que las posiciones 2 y 5 del 10 anillo de pirrolilo llevan sustituyentes alquilo o arilo. El derivado de éster metílico de pirrolotirosina P puede acoplarse con el alcohol C o un alcohol alternativo en condiciones del tipo de Mitsunobu, seguido de hidrólisis de éster, para proporcionar un compuesto de la invención R.

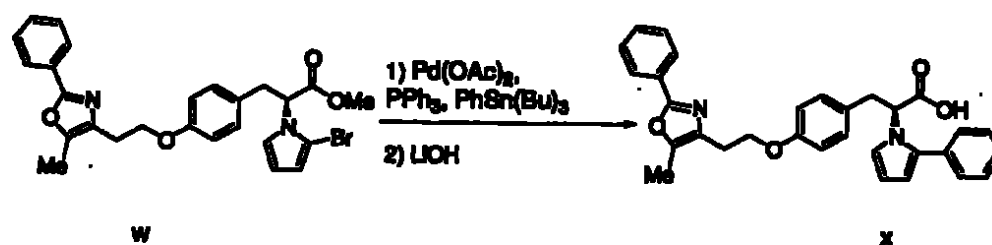
15 Como alternativa, el derivado de éster metílico de pirrolotirosina R puede usarse para proporcionar otros compuestos de la invención en los que el anillo de pirrolilo está trisustituido. De esta forma, como se representa en la Fila 3 del Esquema 4, la bromación del 20 éster metílico de pirrolotirosina R usando N-bromosuccinimida o un agente similar proporciona el compuesto bromado S. El compuesto bromado S puede experimentar acoplamiento e hidrólisis como se ha descrito anteriormente para proporcionar un compuesto de la 25 invención. El compuesto bromado S también puede

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experimentar una reacción con un reactivo de alquil estaño para proporcionar derivados trisustituídos tales como V.

El Esquema 5 representa una síntesis alternativa de compuestos de la invención en los que el anillo de 5 pirrolilo está sustituido en la posición 2.

Esquema 5



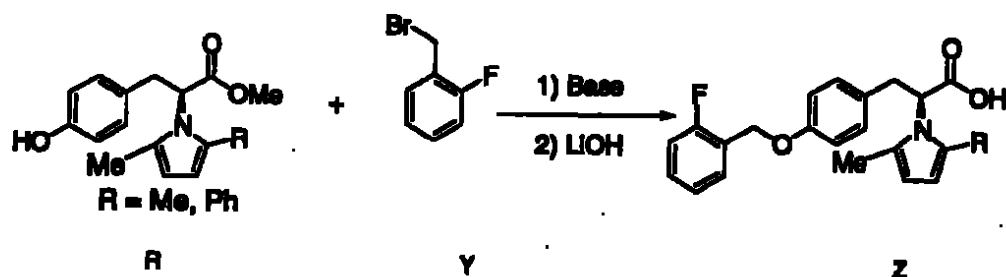
Como indica el Esquema 5, el éster metílico W, preparado por acoplamiento del derivado del éster metílico de 2-bromopirrolotirosina M con el alcohol C, puede  
 10 experimentar acoplamiento de alquilo o arilo catalizado con paladio para proporcionar el derivado metílico de pirrolotirosina 2-aril sustituido X. El derivado metílico de pirrolotirosina 2-alquil o aril sustituido (derivado de arilo X representado). Tras la hidrólisis, el derivado de  
 15 arilo X proporciona un compuesto de la invención.

El Esquema 6 proporciona compuestos de la invención derivados del derivado de éster metílico de pirrolotirosina disustituido R.

Esquema 6

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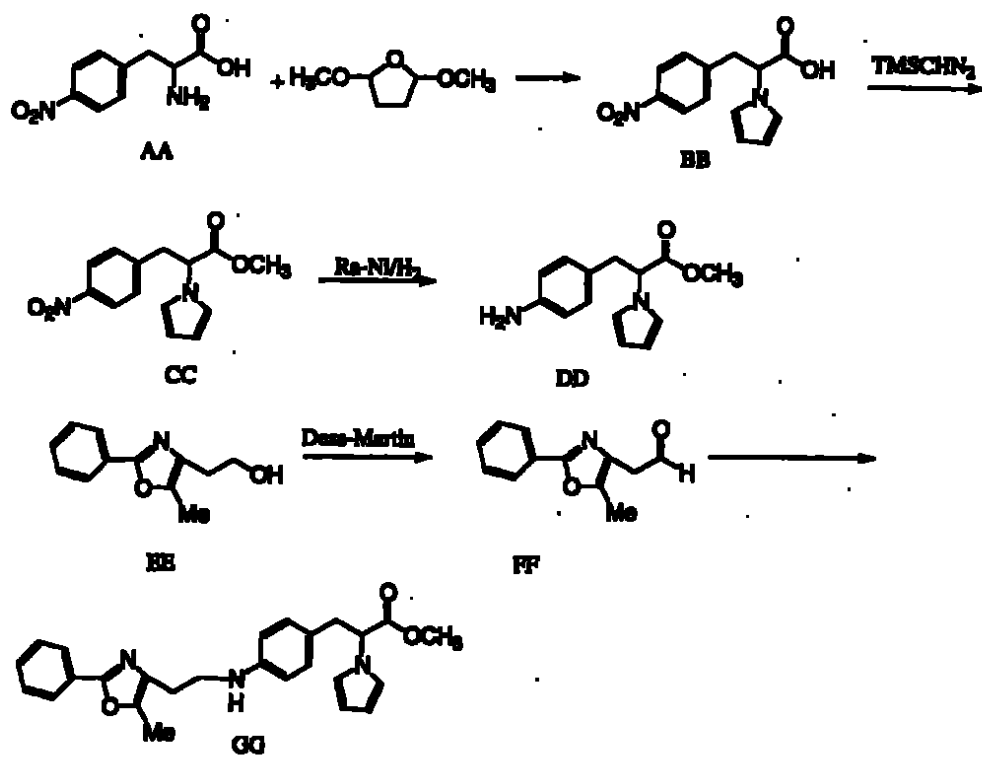
Después del tratamiento con una base para generar fenóxido, el derivado del éster metílico de pirrolotirosina R puede experimentar una reacción con una amplia diversidad de agentes alquilantes conocidos en la técnica (Véanse, por 5 ejemplo, los agentes alquilantes mencionados en Aldrich Handbook of Fine Chemicals (2000-2001)). En el Esquema 6, el fenóxido del derivado del éster metílico de pirrolotirosina R experimenta una reacción con bromuro de 2-fluorobencilo Y, seguido de hidrólisis para proporcionar 10 el compuesto de la invención Z.

El Esquema 7 representa la síntesis de compuestos de Fórmula I en la que X es  $-\text{CH}_2\text{CH}_2\text{NH}-$ .

Esquema 7

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HPB

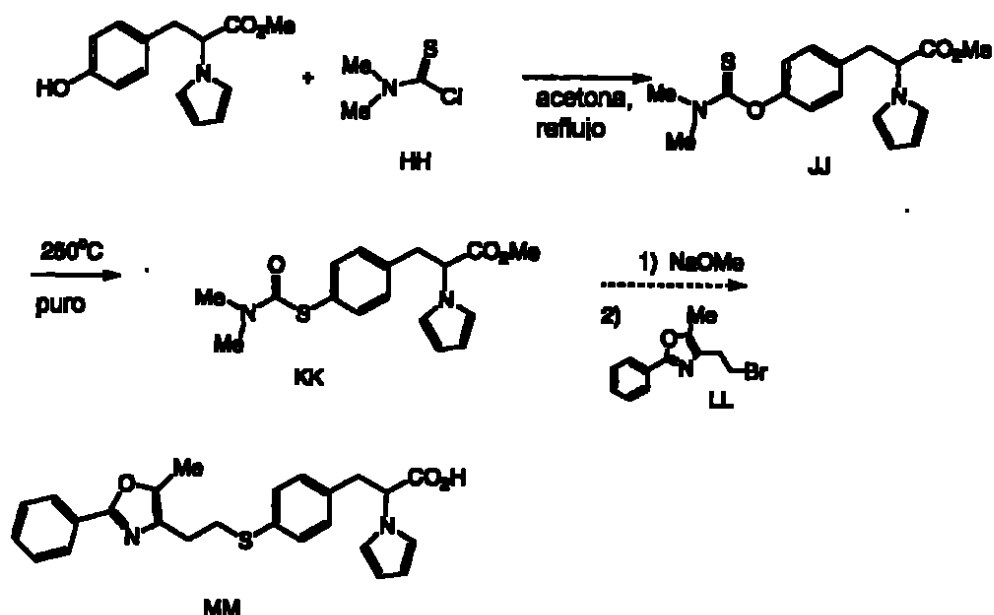
De esta forma, el compuesto nitro AA experimenta una reacción con 2,5-dimetoxi tetrahidrofurano para 5 proporcionar el derivado de pirrolo BB. El derivado de pirrolo BB después se esterifica usando azida de trimetilsililo para proporcionar el éster metílico CC. La reducción del grupo nitro en el éster CC usando níquel Raney en presencia de hidrógeno proporciona el compuesto de 10 amina DD. La adición del compuesto de amina DD al aldehído FF (generado a partir del alcohol EE por oxidación) seguido de reducción, proporciona la amina GG. La amina GG se hidroliza como se ha descrito previamente para proporcionar el compuesto de la invención.

15 El Esquema 8 representa la síntesis de compuestos de Fórmula I en la que X es  $-\text{CH}_2\text{CH}_2\text{S}-$ .

Esquema 8

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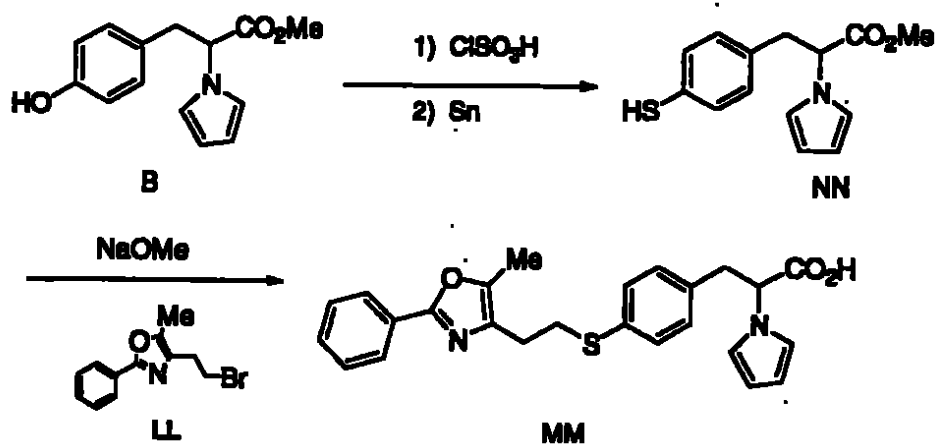
92



De esta forma, el éster metílico de pirrolotirosina B experimenta una reacción con cloruro de dimetiltiocarbamoilo para proporcionar el compuesto JJ. 5 Cuando se calienta a  $250^\circ\text{C}$ , el compuesto JJ experimenta redistribución para proporcionar el compuesto KK. El tratamiento de KK con una base genera el tiofenóxido, que experimenta una reacción con el haluro de alquilo representado LL, para proporcionar el compuesto de fórmula 10 I tio-variante MM.

En el Esquema 9 se representa una preparación alternativa de un compuesto de Fórmula I tio-variante.

Esquema 9



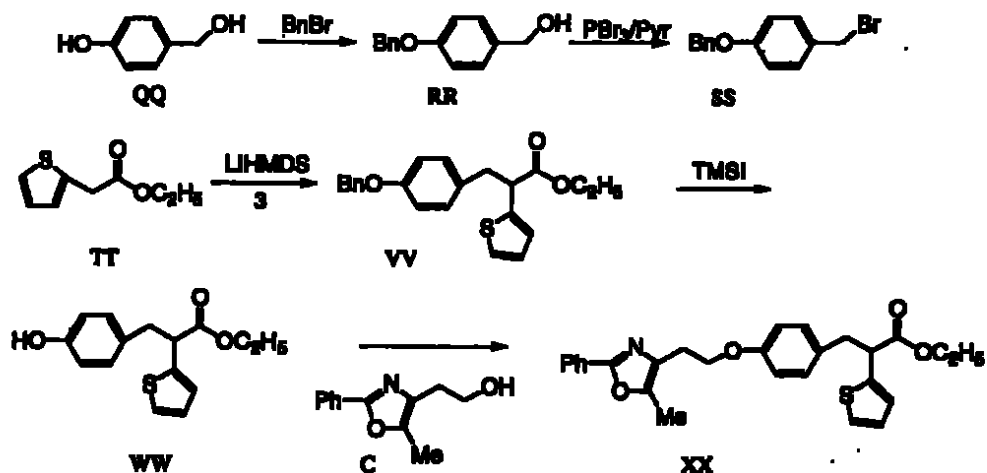
5

De esta forma, el éster metílico de pirrolotirosina B puede experimentar una reacción con ácido clorosulfónico en presencia de estaño elemental para proporcionar el tiofenol 10 NN. La alquilación de NN y la hidrólisis del éster puede proporcionar el compuesto de la invención MM.

El Esquema 10 representa la síntesis de compuestos adicionales de la invención en los que el grupo pirrol se reemplaza por un grupo tiopirrolilo.

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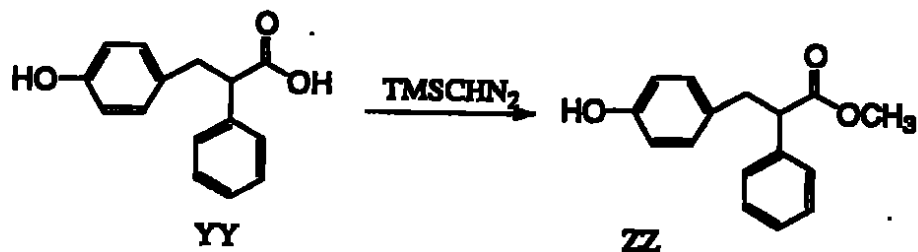
Esquema 10



De esta forma, el 4-hidroxibencil alcohol QQ experimenta una reacción con bromuro de bencilo para proporcionar el alcohol RR. El alcohol RR se convierte en el bromuro SS por tratamiento con tribromo fosfina en presencia de piridina. El bromuro SS experimenta una reacción con el tiopirrol VV en condiciones de alquilación convencionales seguido de desprotección para proporcionar el compuesto WW. El acoplamiento de tipo Mitsunobu de WW con el alcohol C proporciona el éster XX. La hidrólisis del éster XX proporciona un compuesto de la invención.

El Esquema 11 representa la síntesis de compuestos de la invención en la que el grupo pirrol se reemplaza por otro grupo arilo, tal como un grupo fenilo fenil-15 sustituido.

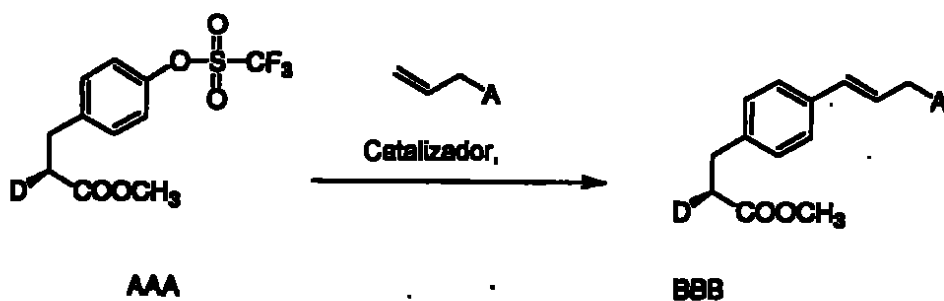
Esquema 11



De esta forma, la esterificación de 4-hidroxifenilalanina YY proporciona el éster metílico ZZ. El 5 acoplamiento de tipo Mitsunobu y la hidrólisis de éster del compuesto ZZ proporciona un compuesto de la invención.

El Esquema 12 representa la síntesis de compuestos de la invención en la que X es  $-\text{CH}-\text{CH}=\text{CH}-$  y D es heteroarilo.

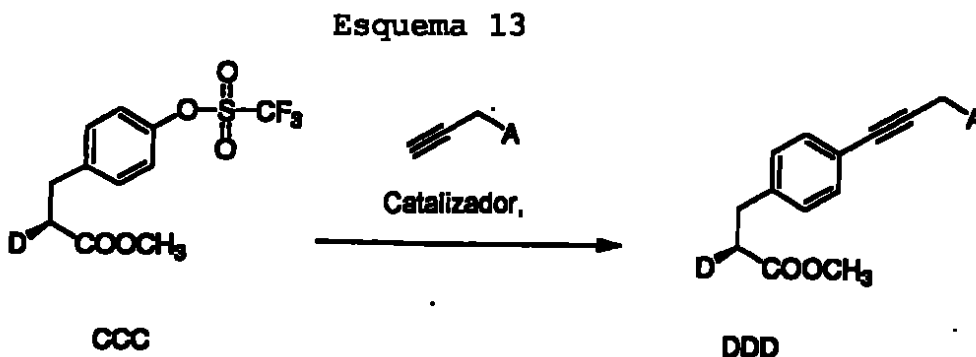
Esquema 12



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En el Esquema 12, el acoplamiento del triflato AAA con un compuesto de vinilo en presencia de un catalizador organometálico proporciona el éster vinílico BB. La 5 hidrólisis del resto éster en BBB como se ha descrito anteriormente proporciona un compuesto de la invención en el que R es alquilo o alquilo sustituido, arilo o arilo sustituido, heteroarilo o heteroarilo sustituido, heterocicloalquilo o heterocicloalquilo sustituido, o 10 heteroalquilo o heteroalquilo sustituido.

El Esquema 13 representa la síntesis de compuestos adicionales de la invención en los que X es  $-C\equiv C-CH_2-$  y D es heteroarilo.



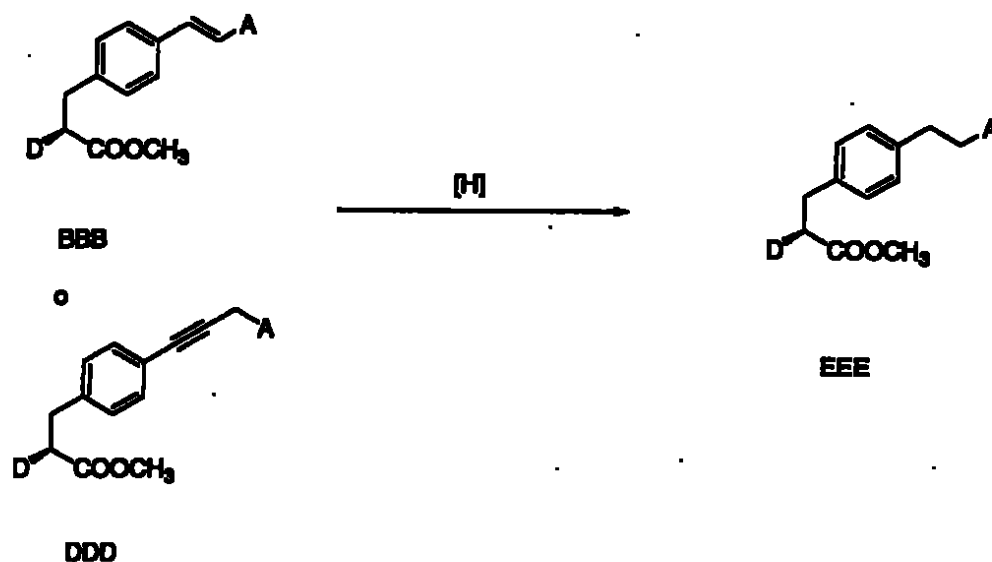
441

En el Esquema 13, el acoplamiento del triflato AAA con un compuesto de alquinilo CCC en presencia de un catalizador organometálico proporciona el alquinil éster 5 DDD. La hidrólisis del resto éster en DDD como se ha descrito anteriormente proporciona un compuesto de la invención en el que R es alquilo o alquilo sustituido, arilo o arilo sustituido, heteroarilo o heteroarilo sustituido, heterocicloalquilo y heterocicloalquilo 10 sustituido o heteroalquilo o heteroalquilo sustituido.

El Esquema 14 representa la síntesis de compuestos de la invención en la que X es  $-(CH_2)_3-$  y D es heteroarilo.

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Esquema 14



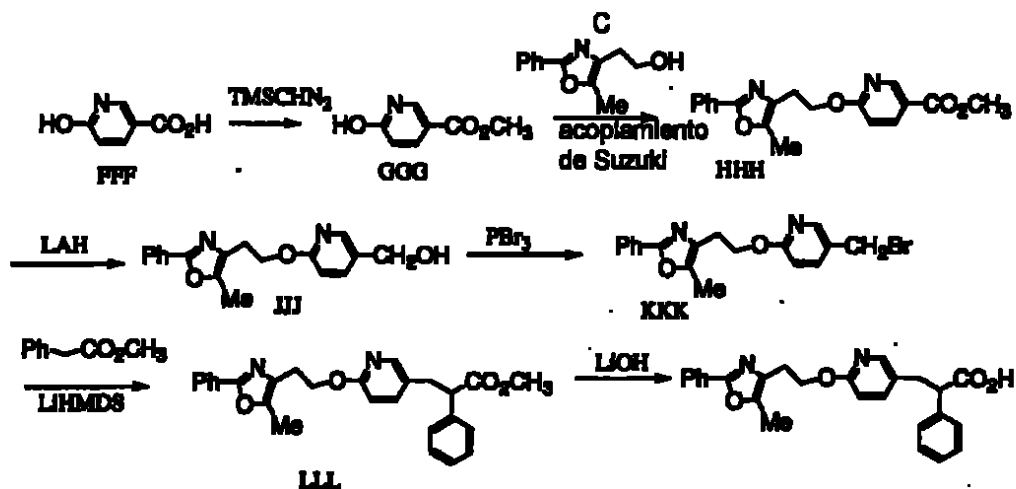
El Esquema 14 indica que el compuesto de vinilo BBB o el compuesto de alquinilo DDD pueden reducirse en 5 condiciones conocidas en la técnica para proporcionar la variante saturada EEE.

El Esquema 15 representa un procedimiento para preparar compuestos de la invención en la que Q es heteroarilo o heteroarilo sustituido.



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Esquema 15

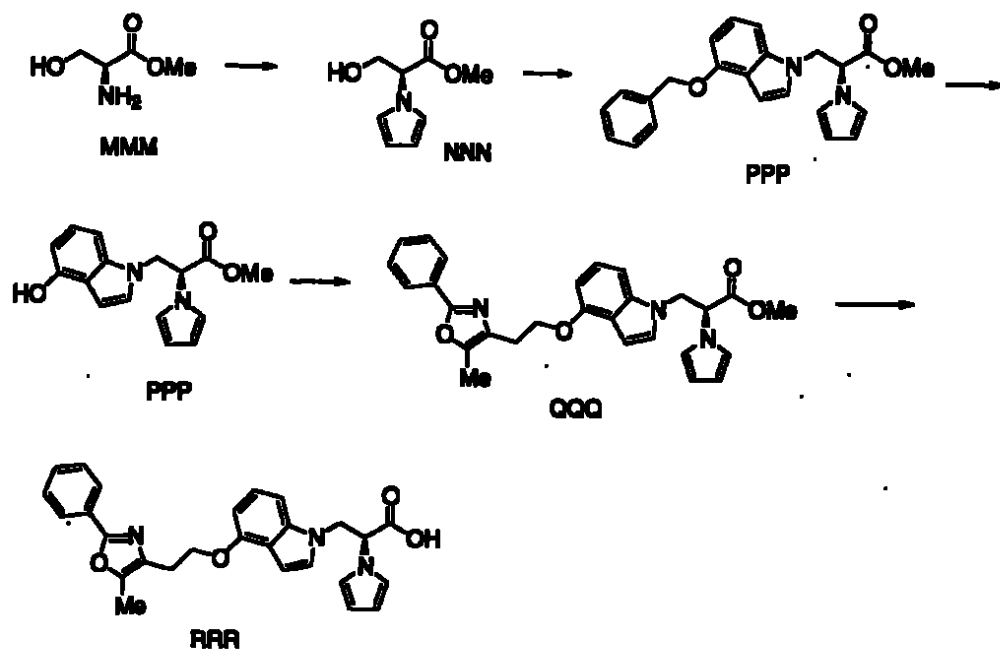


De esta forma, el ácido nicotínico FFF se esterifica para proporcionar GGG. GGG se acopla a C como se ha descrito anteriormente para dar HHH. El resto éster en HHH 5 se reduce para dar el alcohol JJJ, que después se convierte en el haluro KKK usando técnicas convencionales. La alquilación del ácido metil estero f fenil acético usando KKK proporciona el producto LLL. LLL se hidroliza a un compuesto de la invención en las condiciones descritas 10 previamente.

El Esquema 16 representa un compuesto de la invención en el que B es H.

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Esquema 16



El derivado de indol 5-sustituido se prepara de la misma forma, con la excepción de que se usa 5-benciloxiindol en la segunda etapa.

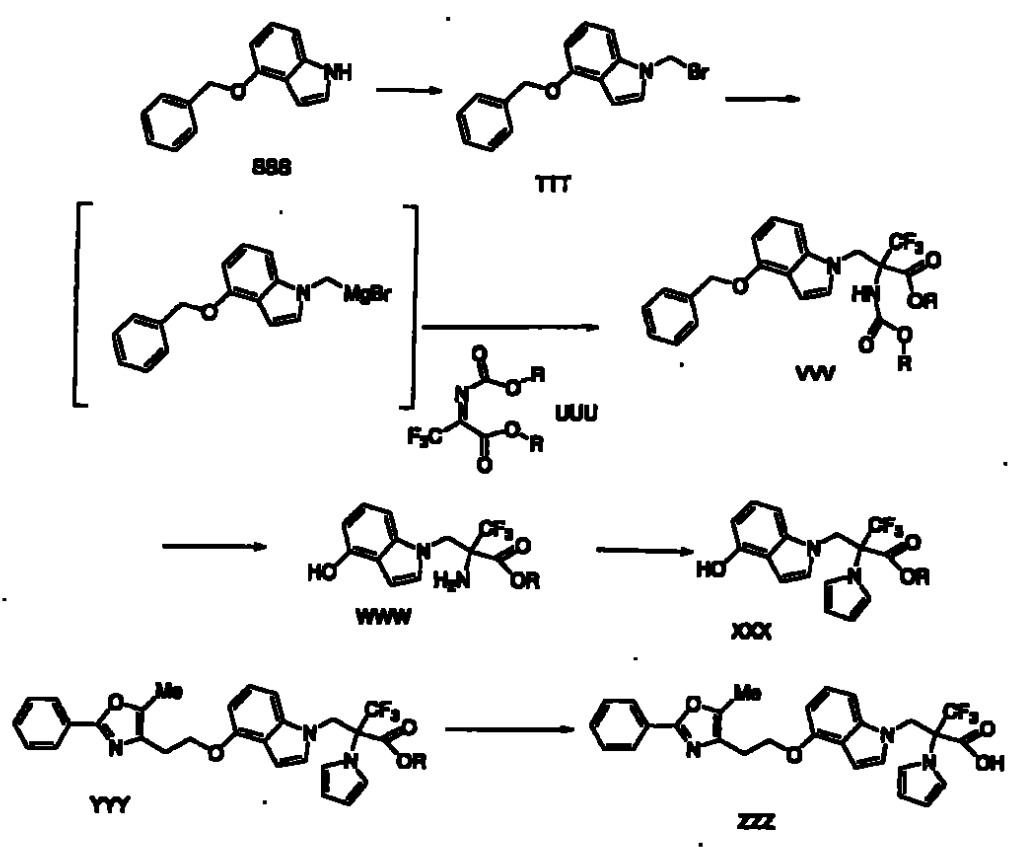
5 De esta forma, MMM se convierte en el derivado de pirrol NNN como se ha indicado anteriormente. El grupo hidroxí del compuesto NNN se convierte en un grupo saliente, tal como bromuro, mesilato, tosilato o similares, y después experimenta la adición del derivado de 10 hidroxíindol bencil-sustituido en la posición N para dar OOO. La eliminación del grupo protector de bencilo en OOO, seguida del acoplamiento con C como se ha indicado anteriormente, da QQQ. La saponificación del resto de éster

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en QQQ da el compuesto de la invención RRR.

El Esquema 17 representa la síntesis de un compuesto de la invención en el que B es haloalquilo.

Esquema 17



5 De esta forma, el derivado de benciloxi indol SSS se  
 convierte en el compuesto de bromometilo TTT, por  
 tratamiento con formaldehído o su equivalente, seguido de  
 halogenación usando condiciones convencionales. El  
 compuesto TTT después se convierte en el reactivo de  
 10 Grignard, que después experimenta 1,2-adición con la imina  
 UUU para proporcionar VVV. El resto amida en VVV se

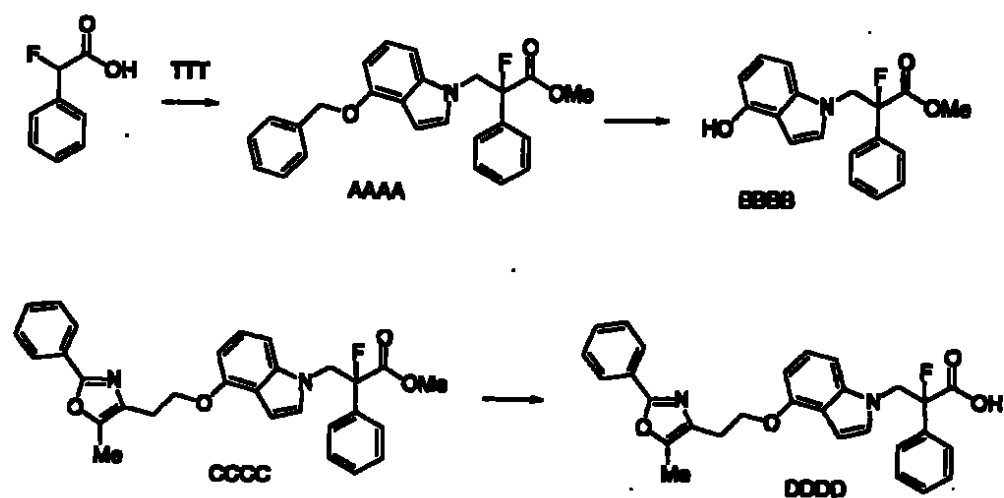
2486

hidroliza para proporcionar WWW. El acoplamiento de WWW con C como se ha indicado anteriormente da XXX. La construcción del anillo pirrolilo para proporcionar XXX y la saponificación del resto éster en YYY como se ha indicado 5 anteriormente, da el compuesto de la invención ZZZ.

El Esquema 18 representa la síntesis de un compuesto de la invención en el que B es F.

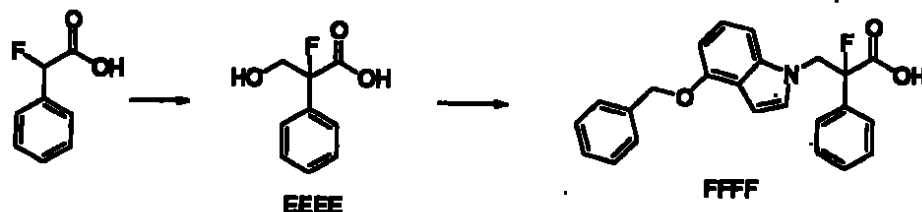
Esquema 18

**Procedimiento 1**



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Procedimiento 2



5

10 El derivado de indol 5-sustituido se prepara de la misma forma, con la excepción de que se usa 5-benciloxiindol.

En el Procedimiento 1 del Esquema 18, se desprotona ácido 1-fluoro-2-fenilacético seguido del tratamiento con 15 TTT para proporcionar AAA. En el Procedimiento 2 del Esquema 18, el reactivo de Grignard derivado de TTT se combina con el derivado de hidroximetilo EEE para proporcionar FFFF.

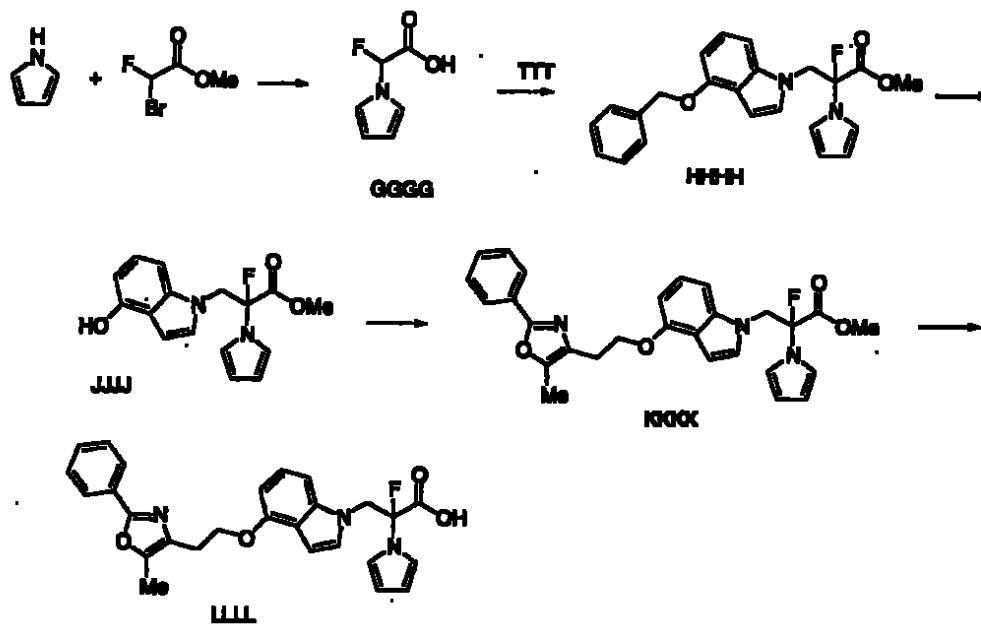
El Esquema 19 representa síntesis alternativas de un 20 compuesto de la invención en el que B es F. La diferencia entre los Procedimientos 1 y 2 en el Esquema 19 es la ruta

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por medio de la cual se usa el pirrol (GGGG o QQQQ).

Esquema 19

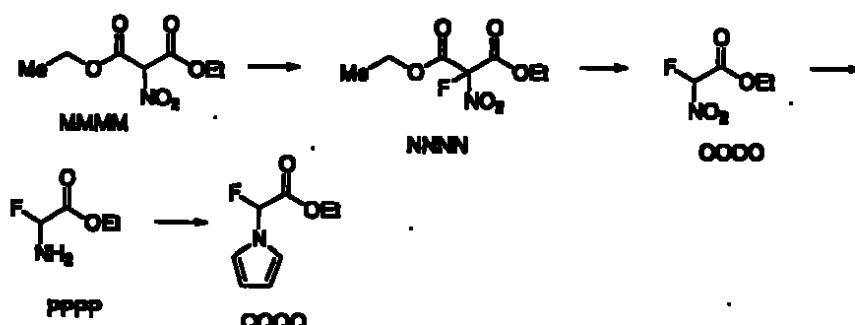
Procedimiento 1



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El derivado de indol 5-sustituido se prepara de la misma forma, con la excepción de que se usa 5-benciloxiindol

Procedimiento 2



5 De esta forma, en el Procedimiento 1, el derivado de pirrol requerido GGGG se acopla con TTT como se indica en el Esquema 17 para proporcionar HHHH. El acoplamiento de HHHH a C, seguido de saponificación, proporciona el compuesto de la invención LLLL. En el Procedimiento 2, el  
 10 pirrol requerido QQQQ se prepara a partir de MMMM mediante fluoración, descarboxilación y reducción. QQQQ después se usa como en el Procedimiento 1 para proporcionar el compuesto de la invención.

Algunos de los compuestos de Fórmula I pueden formar  
 15 sales de adición de ácidos y/o bases farmacéuticamente aceptables. Todas estas formas están dentro del alcance de la presente invención.

Las sales de adición de ácidos farmacéuticamente aceptables de los compuestos de Fórmula I incluyen sales

VSD

derivadas de ácidos inorgánicos no tóxicos tales como clorhídrico, nítrico, fosfórico, sulfúrico, bromhídrico, yodhídrico, fluorhídrico, fosforoso y similares, así como las sales derivadas de ácidos orgánicos no tóxicos tales  
5 como ácidos mono- y dicarboxílicos alifáticos, ácidos alcanoicos fenil-sustituidos, ácidos hidroxialcanoicos, ácidos alcanodioicos, ácidos aromáticos, ácidos alifáticos y aromático sulfónicos, etc. De esta manera, tales sales incluyen sulfato, piro sulfato, bisulfato, sulfito,  
10 bisulfito, nitrato, fosfato, fosfato monoácido, fosfato diácido, metafosfato, pirofosfato, acetato, trifluoroacetato, propionato, caprilato, isobutirato, oxalato, malonato, succinatos, suberato, sebacato, fumarato, maleato, mandelato, benzoato, clorobenzoato,  
15 metilbenzoato, dinitrobenzoato, ftalato, bencenosulfonato, toluenosulfonato, fenilacetato, citrato, lactato, maleato, tartrato, metanosulfonato y similares. También se contemplan sales de aminoácidos tales como arginato y similares y gluconato, galacturonato (véase, por ejemplo,  
20 Berge S.M. y col., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 1977; 66:1-19).

Las sales de adición de ácidos de los compuestos básicos se preparan poniendo en contacto la forma de base libre con una cantidad suficiente del ácido deseado para  
25 producir la sal de una forma convencional.



Las sales de adición de bases farmacéuticamente aceptables se forman con metales o aminas, tales como metales alcalinos o alcalinotérreos o aminas orgánicas. Son ejemplos de metales usados como cationes el sodio, potasio, 5 magnesio, calcio y similares. Son ejemplos de aminas adecuadas N,N'-dibenciletilendiamina, cloroprocaína, colina, dietanolamina, diciclohexilamina, etilendiamina, N-metilglucamina y procaína (véase, por ejemplo, Berge S.M., supra., 1977).

10 Las sales de adición de bases de los compuestos ácidos se preparan poniendo en contacto la forma de ácido libre con una cantidad suficiente de la base deseada para producir la sal de la manera convencional.

Ciertos de los compuestos de la presente invención 15 pueden existir en formas no solvatadas así como en formas solvatadas, incluyendo formas hidratadas. En general, las formas solvatadas, incluyendo las formas hidratadas, son equivalentes a las formas no solvatadas y pretenden incluirse dentro del alcance de la presente invención.

20 Ciertos de los compuestos de la presente invención poseen uno o más centros quirales y cada centro puede existir en la configuración R(D) o S(L). La presente invención incluye todas las formas enantioméricas y epiméricas, así como las mezclas apropiadas de las mismas.

25 Los compuestos de fórmula I pueden formularse como

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composiciones farmacéuticas y administrarse a un hospedador mamífero, tal como un paciente humano, en una diversidad de formas adaptadas a la vía de administración elegida, es decir, por vía oral o parenteral, por vía intravenosa, 5 intramuscular, tópica o subcutánea.

De esta manera, los presentes compuestos pueden administrarse sistémicamente, por ejemplo, por vía oral, en combinación con un vehículo farmacéuticamente aceptable tal como un diluyente inerte o un vehículo comestible 10 asimilable. Pueden encerrarse en cápsulas de gelatina dura o blanda, pueden comprimirse en comprimidos, o pueden incorporarse directamente con los alimentos de la dieta del paciente. Para la administración terapéutica oral, el compuesto activo puede combinarse con uno o más excipientes 15 y usarse en forma de comprimidos ingeribles, comprimidos bucales, trociscos, cápsulas, elixires, suspensiones, jarabes, obleas y similares. Tales composiciones y preparaciones deben contener al menos un 0,1% de compuesto activo. El porcentaje de las composiciones y preparaciones, 20 por supuesto, puede variar y puede estar comprendido convenientemente entre aproximadamente un 2 y aproximadamente un 60% del peso de una forma de dosificación unitaria dada. La cantidad de compuesto activo en tales composiciones terapéuticamente útiles será tal que 25 se obtenga un nivel de dosificación eficaz.

Los comprimidos, trociscos, píldoras, cápsulas y similares también pueden contener lo siguiente: aglutinantes tales como goma de tragacanto, goma arábiga, almidón de maíz o gelatina; excipientes tales como fosfato 5 dicálcico; un agente disgregante tal como almidón de maíz, almidón de patata, ácido algínico y similares; un lubricante tal como estearato de magnesio; y un agente edulcorante tal como sacarosa, fructosa, lactosa o aspartamo, o un agente aromatizante tal como menta, aceite 10 de gualteria o aromatizante de cerezas. Cuando la forma de dosificación unitaria es una cápsula, puede contener, además de materiales del tipo anterior, un vehículo líquido, tal como un aceite vegetal o un polietilenglicol. Otros diversos materiales pueden estar presentes como 15 recubrimientos o para modificar de otra forma la forma física de la forma de dosificación unitaria sólida. Por ejemplo, pueden recubrirse comprimidos, píldoras o cápsulas con gelatina, cera, goma laca o azúcar y similares. Un jarabe o elixir puede contener el compuesto activo, 20 sacarosa o fructosa como agente edulcorante, metil y propilparabenos como conservante, un colorante y un aromatizante tal como aroma de cerezas o de naranja. Por supuesto, cualquier material usado en la preparación de cualquier forma de dosificación unitaria debe ser 25 farmacéuticamente aceptable y sustancialmente no tóxico en

WJH

las cantidades empleadas. Además, el compuesto activo puede incorporarse en preparaciones y dispositivos de liberación sostenida.

El compuesto activo también puede administrarse por  
5 vía intravenosa o intraperitoneal por infusión o inyección. Pueden prepararse soluciones del compuesto activo o sus sales en agua, opcionalmente mezclada con un tensioactivo no tóxico. También pueden prepararse dispersiones en glicerol, polietilenglicoles líquidos, triacetina y mezclas  
10 de los mismos, y en aceites. En las condiciones de almacenamiento y uso habituales, estas preparaciones contienen un conservante para prevenir el crecimiento de los microorganismos.

Las formas de dosificación farmacéuticas adecuadas  
15 para inyección o infusión pueden incluir soluciones o dispersiones acuosas estériles o polvos estériles que comprenden el ingrediente activo, que están adaptados para la preparación extemporánea de soluciones o dispersiones estériles inyectables o infundibles, opcionalmente  
20 encapsuladas en liposomas. En todos los casos, la forma de dosificación final debe ser estéril, fluida y estable en las condiciones de fabricación y almacenamiento. El excipiente o vehículo líquido puede ser un disolvente o medio de dispersión líquido que comprende, por ejemplo,  
25 agua, etanol, un poliol (por ejemplo, glicerol,

VSS

propilenglicol, polietilenglicoles líquidos y similares), aceites vegetales, ésteres de glicerilo no tóxicos, y mezclas adecuadas de los mismos. La fluidez apropiada puede mantenerse, por ejemplo, por la formación de liposomas, por 5 el mantenimiento del tamaño de partículas requerido en el caso de dispersiones o por el uso de tensioactivos. La prevención de la acción de los microorganismos puede conseguirse por diversos agentes antibacterianos y antifúngicos, por ejemplo, parabenos, clorobutanol, fenol, 10 ácido sórbico, timerosal y similares. En muchos casos, será preferible incluir agentes isotónicos, por ejemplo, azúcares, tampones o cloruro sódico. La absorción prolongada de las composiciones inyectables puede realizarse por medio del uso en las composiciones de 15 agentes para retrasar la absorción, por ejemplo, monoestearato de aluminio y gelatina.

Las soluciones inyectables estériles se preparan por la incorporación del compuesto activo en la cantidad requerida en el disolvente apropiado con diversos de los 20 demás ingredientes indicados anteriormente, cuando se requiera, seguido de esterilización por filtración. En el caso de polvos estériles para la preparación de soluciones inyectables estériles, los procedimientos de preparación preferidos son secado al vacío y técnicas de liofilización, 25 que producen un polvo del ingrediente activo más cualquier

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ingrediente deseado adicional presente en las soluciones filtradas de forma estéril previamente.

Para la administración tópica, los presentes compuestos pueden aplicarse en forma pura, es decir, cuando  
5 son líquidos. Sin embargo, generalmente será deseable administrarlos en la piel como composiciones o formulaciones, en combinación con un vehículo dermatológicamente aceptable, que puede ser un sólido o un líquido.

10 Los vehículos sólidos útiles incluyen sólidos finamente divididos tales como talco, arcilla, celulosa microcristalina, sílice, alúmina y similares. Los vehículos líquidos útiles incluyen agua, alcoholes o glicoles, o mezclas de agua-alcohol/glicol, en las que los presentes  
15 compuestos pueden disolverse o dispersarse a niveles eficaces, opcionalmente con la ayuda de tensioactivos no tóxicos. Pueden añadirse adyuvantes tales como aromas y otros agentes antimicrobianos para optimizar las propiedades para un uso dado. Las composiciones líquidas  
20 resultantes pueden aplicarse desde capas absorbentes, usadas para impregnar vendas y otras telas, o pulverizarse sobre el área afectada usando pulverizadores de tipo de bomba o aerosol.

También pueden emplearse espesantes tales como  
25 polímeros sintéticos, ácidos grasos, sales y ésteres de

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ácidos grasos, alcoholes grasos, celulosas modificadas o materiales minerales modificados, junto con vehículos líquidos para formar pastas untables, geles, pomadas, jabones y similares, para aplicación directa en la piel del 5 usuario.

En la técnica se conocen ejemplos de composiciones dermatológicas útiles que pueden usarse para suministrar los compuestos de fórmula I en la piel; por ejemplo, véase Jacquet y col. (Patente de Estados Unidos No. 4.608.392), 10 Geria (Patente de Estados Unidos No. 4.992.478), Smith y col. (Patente de Estados Unidos No. 4.559.157) y Wortzman (Patente de Estados Unidos No. 4.820.508).

Las dosis útiles de los compuestos de fórmula I pueden determinarse por comparación de su actividad in vitro y su 15 actividad in vivo en modelos animales. En la técnica se conocen procedimientos para la extrapolación de dosis eficaces en ratones, y otros animales, a los seres humanos; por ejemplo, véase la Patente de Estados Unidos No. 4.938.949.

20 Generalmente, la concentración del o de los compuestos de fórmula I en una composición líquida, tal como una loción, será de aproximadamente un 0,1 a un 25% en peso, preferiblemente de aproximadamente un 0,5 a un 10% en peso. La concentración en una composición sólida o semisólida tal 25 como un gel o un polvo será de aproximadamente un 0,1 a un

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5% en peso, preferiblemente de aproximadamente un 0,5 a un 2,5% en peso.

La cantidad del compuesto, o una sal activa o derivado del mismo, requerida para uso en el tratamiento variará no sólo con la sal particular seleccionada, sino también con la vía de administración, la naturaleza de la afección a tratar y la edad y estado del paciente, y finalmente estará a la discreción del médico correspondiente.

Sin embargo, en general, una dosis adecuada estará en el intervalo de aproximadamente 0,005 a aproximadamente 100 mg/kg, por ejemplo, de aproximadamente 0,1 a aproximadamente 75 mg/kg de peso corporal al día, tal como de 0,03 a aproximadamente 50 mg por kilogramo de peso corporal del receptor al día, preferiblemente en el intervalo de 0,06 a 90 mg/kg/día, y aún más preferiblemente en el intervalo de 0,15 a 60 mg/kg/día.

El compuesto puede administrarse convenientemente en una forma de dosificación unitaria; por ejemplo, que contiene de 0,05 a 1000 mg, convenientemente de 0,1 a 750 mg, aún más convenientemente de 0,5 a 500 mg de ingrediente activo por forma de dosificación unitaria.

Idealmente, el ingrediente activo debe administrarse para conseguir concentraciones máximas en plasma del compuesto activo de aproximadamente 0,005 a aproximadamente 75  $\mu$ M, preferiblemente de aproximadamente 0,01 a 50  $\mu$ M, aún



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más preferiblemente de aproximadamente 0,02 a aproximadamente 30  $\mu$ M. Esto puede conseguirse, por ejemplo, por medio de la inyección intravenosa de una solución del 0,0005 al 5% del ingrediente activo, opcionalmente en 5 solución salina o administrada por vía oral como un bolo que contiene de aproximadamente 0,01 a 1 mg del ingrediente activo. Pueden mantenerse niveles en sangre deseados por medio de una infusión continua para proporcionar de aproximadamente 0,0001 a 5 mg/kg/h o por medio de 10 infusiones intermitentes que contienen de aproximadamente 0,004 a 15 mg/kg de los ingredientes activos.

La dosis deseada puede presentarse convenientemente en una sola dosis o como dosis divididas administradas a los intervalos apropiados, por ejemplo, como dos, tres, cuatro 15 o más subdosis al día. La propia subdosis puede dividirse adicionalmente, por ejemplo, en varias administraciones discretas separadas holgadamente; tales como inhalaciones múltiples desde un insuflador o por la aplicación de una pluralidad de gotas en el ojo.

20 La capacidad contra la diabetes de un compuesto de la invención se demuestra usando modelos farmacéuticos que son bien conocidos en la técnica, por ejemplo, usando modelos tales como los ensayos descritos más adelante.

ENSAYO A - Ensayo de Diferenciación de Adipocitos 3T3-L1  
25 (ADPDIFF)

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Este ensayo se usa para determinar la capacidad de supuestos ligandos de PPAR- $\gamma$  de inducir la diferenciación de adipocitos. Se estableció un procedimiento cuantitativo para determinar la capacidad de ligandos potenciales de 5 PPAR- $\gamma$  de promover la adipogénesis de preadipocitos 3T3-L1. Los preadipocitos 3T3-L1 se cultivan en placas de 96 pocillos (20.000 células por pocillo). Tras la confluencia, los compuestos que se consideraron inicialmente positivos en los ensayos de desplazamiento de ligandos de PPAR- $\gamma$  y en 10 los ensayos de transcripción del receptor quimérico PPAR- $\gamma$  se añadieron durante 4 días a las concentraciones finales de 2,5, 5,0 y 10  $\mu$ M (n=3). Cada placa contiene controles positivos (BRL 49653 5  $\mu$ M y Troglitazona 5  $\mu$ M) y un vehículo de control (DMSO). Las células se rellenan con 15 medio que contiene FBS en el día 5 después del tratamiento con fármaco y se incuban durante otros 4-6 días más. Las células se tiñen con BODIPY, un colorante lipófilo fluorescente para cuantificar el contenido de lípidos de las células. El ensayo se optimiza para un formato de placa 20 de 96 pocillos. Aproximadamente 10 días después del tratamiento con el fármaco, las células se fijan en una solución de formalina al 3% durante 15 minutos seguido de tinción con BODIPY (80  $\mu$ g/ml) durante 20 minutos a temperatura ambiente. La placa después se pone a través del 25 instrumento CYTOFLUOR para medir la fluorescencia de BODIPY

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(excitación = 485/20; emisión = 530/25). Se crea una plantilla en una hoja de análisis para calcular el valor medio de las mediciones BODIPY y se presentan como % de BRL 49653 a 5  $\mu$ M.

#### 5 ENSAYO B - Ensayo de Transcripción de Antagonistas ANTCV1

El ensayo de transcripción ANTCV1 es un ensayo *in vitro* en el que células CV-1, una línea celular de riñón de mono verde africano, se transfectan con una construcción de indicador de luciferasa compuesta de un fragmento del  
10 promotor de la proteína de unión a ácidos grasos (FATP) localizado cadena arriba de la secuencia TK TATA. La eficacia de la transfección se controla por co-transfección del plásmido de referencia CMV  $\beta$ -galactosidasa. Los ADN se transfectan transitoriamente en las células por  
15 electroporación y las células se cultivan en placas de 96 pocillos. Los compuestos de ensayo se diluyen a una concentración final de 25  $\mu$ M en pocillos individuales que contienen BRL 300 nM. Los pocillos de control incluyen el vehículo de control de DMSO al 0,5%, el antagonista PD  
20 0157724-0000 a una concentración 25  $\mu$ M y BRL 300 nM, o BRL 300 nM solo. Las células se incuban con los dos fármacos durante 48 horas y después se recogen. Los lisados se miden con respecto a las actividades de luciferasa y  $\beta$ -galactosidasa usando el kit de luciferasa dual de Tropix en  
25 un luminómetro EG&G Berthold MicroLumat LB96P. El número de

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veces que aumenta la activación de BRL 49653 en cada ensayo debe ser mayor de 4 para que el ensayo se considere válido.

Los números de partida se transfieren a una hoja de cálculo Excel y se determinan las relaciones luciferasa/ $\beta$ -galactosidasa para cada compuesto. El porcentaje de inhibición de BRL49653 para cada compuesto se calcula dividiendo la relación de luciferasa/ $\beta$ -galactosidasa para cada compuesto por la relación de luciferasa/ $\beta$ -galactosidasa del vehículo de control DMSO. Este número  
10 después se introduce en la siguiente ecuación: % de inhibición de BRL = (activación de BRL en veces - activación de compuesto de ensayo en veces & BRL/activación de BRL en veces - 1) x 100.

#### ENSAYO C - ENSAYO DE TRANSCRIPCIÓN DE RECEPTORES NATIVOS

15 CV-1 (MKNRCV1)

El objetivo de este ensayo es identificar ligandos que activan receptores nucleares endógenos en células CV-1. Protocolo: se cotransfectan células CV-1 con un indicador de luciferasa que contiene un fragmento del promotor FATP  
20 cadena arriba de la secuencia TK TATA y un plásmido de la beta-galactosidasa de CMV. Las células transfectadas se incuban con ligandos de ensayo durante 48 horas. Los lisados celulares se recogen y se determinan las actividades luciferasa y beta-galactosidasa. Descripción:  
25 Las actividades luciferasa y beta-galactosidasa en los

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lisados celulares se miden usando un luminómetro Berthold EG&G. Estos valores se introducen en una hoja de cálculo Excel que calcula las relaciones de luciferasa a beta-galactosidasa y expresa los datos como actividad en 5 porcentaje del compuesto de referencia, BRL 49653.

#### ENSAYO D - MEDICIÓN DE GLUCOSA EN SANGRE (GLUCOSA $\Delta$ )

La glucosa se obtiene 4 horas después de la dosificación por medio de un pinchazo de la vena de la cola (5  $\mu$ l de sangre entera), en estado de vigilia, en animales 10 que han permanecido en ayunas durante 4 horas. La sangre se extrae por acción capilar en una cubeta de glucosa y se lee en un HemoCue Glucose Analyzer (Ryan Diagnostics). La sangre se diluye 1:2 con solución salina si los niveles de glucosa son mayores de 400 mg/dl (límite superior del 15 medidor) y los resultados se multiplican por dos.

#### ENSAYO E - ENSAYO DE INDICADOR TRANSITORIO

Este ensayo se usa para determinar el potencial de supuestos ligandos de PPAR- $\gamma$  de activar el promotor/potenciador del gen  $\alpha$ P2 murino. Se cultivan 20 preadipocitos 3T3-L1 en placas recubiertas con colágeno en DMEM que contiene un 10% de suero de ternero durante 48 horas después de la confluencia. Las células después se cultivan durante aproximadamente 3 días en DMEM que contiene un 10% de Suero Bovino Fetal (FBS), metil 25 isobutilxantina 0,5 mM, dexametasona 0,25  $\mu$ M y 1  $\mu$ g/ml de

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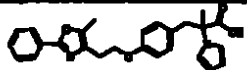
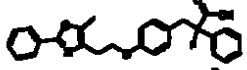
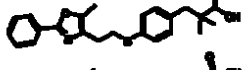
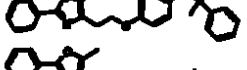
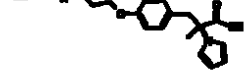
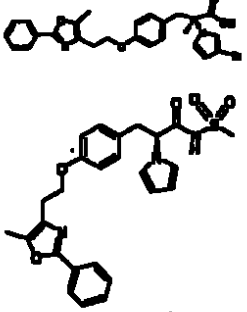
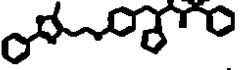
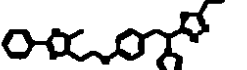
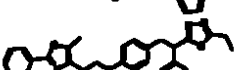
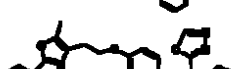
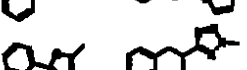
insulina. Las células se separan de las placas con Tripsina-EDTA y se resuspenden en Solución Salina Tamponada con Fosfato (PBS).

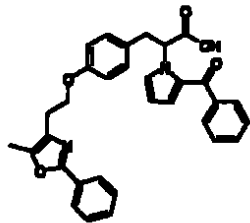
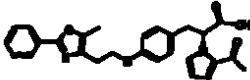
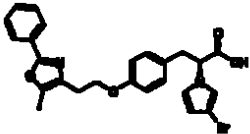
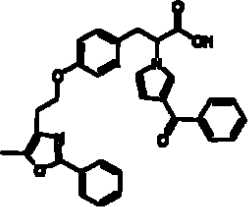
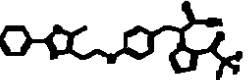
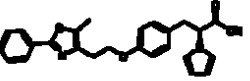
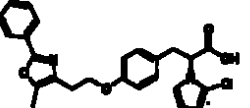
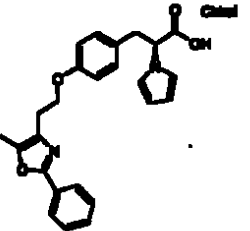
La construcción del indicador usada en este ensayo 5 comprende la región 5' flanqueante de -5,4 kb del gen *ap2* murino insertado en el sitio de clonación del vector de la luciferasa TKpGL3. La eficacia de la transfección se controla por cotransfección del plásmido de referencia CMV- $\beta$ -galactosidasa. La construcción del indicador y el 10 plásmido de referencia se cotransfectan transitoriamente en las células por electroporación. Las células transfectadas se cultivan en placas de 96 pocillos recubiertas de colágeno y se cultivan durante una noche. Las células después se incuban durante 48 horas con los compuestos de 15 ensayo y después se recogen. Los lisados se miden con respecto a las actividades de luciferasa y  $\beta$ -galactosidasa usando el kit de luciferasa Dual-Light® de Tropix en un luminómetro EG&G Berthold MicroLumat LB96P.

Los datos se resumen en las Tablas 1-3.

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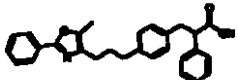
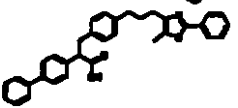
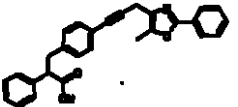
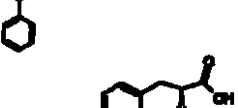
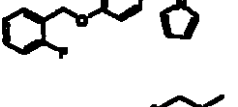
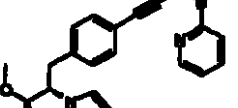
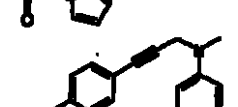
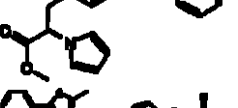
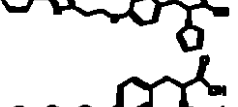
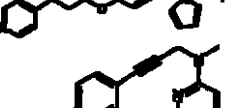
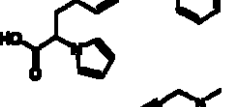
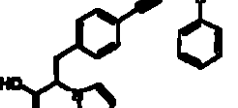
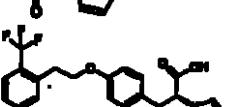
TABLA 1

| Compuesto                                                                           | ADPDIF<br>%BRL<br>@ 5 $\mu$ M | Glucose $\Delta$ | %BRL  | MKNRCV1<br>CE 50 | MKNRCV1<br>%BRL<br>@ 25 $\mu$ M | ANTCV1<br>INHIB<br>@ 25 $\mu$ M |
|-------------------------------------------------------------------------------------|-------------------------------|------------------|-------|------------------|---------------------------------|---------------------------------|
|    | 117                           |                  |       | 2                | 87                              | -80.3333                        |
|    | 122                           |                  |       | 9.5              | 63                              | 37                              |
|    | 131                           |                  |       |                  | 34                              | 59                              |
|    | 99                            |                  |       | 13               | 44                              | 65                              |
|    |                               |                  |       | 1.4              | 83 @ 5 $\mu$ M                  | -22                             |
|   | 110                           |                  |       | 3.2              | 97                              | -30                             |
|  | 90                            |                  |       | 3.3              | 101                             | -117                            |
|  | 94                            |                  |       |                  | 0                               | 84                              |
|  | 88                            | 46.5             | -20.0 | 2000             | 12                              | 53.8                            |
|  | 161                           |                  |       |                  | 61                              | 47                              |
|  | 45                            |                  |       |                  | 37 @ 5 $\mu$ M                  | 49                              |
|  |                               |                  |       |                  |                                 |                                 |
|  |                               |                  |       |                  |                                 |                                 |

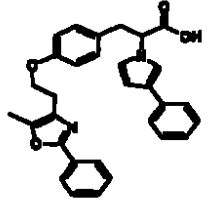
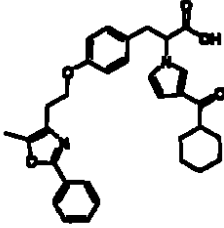
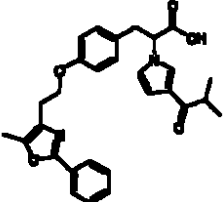
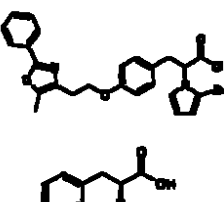
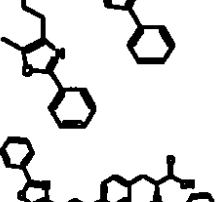
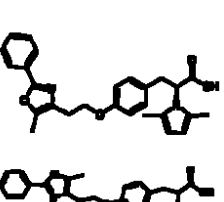
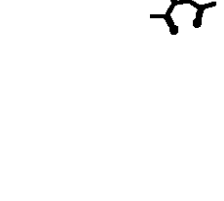
| Compuesto                                                                           | ADPDIF<br>%BRL<br>● 5 μM | Glucosa | Δ %BRL | MKNRCV1<br>CE <sub>50</sub> | MKNRCV1<br>%BRL<br>● 25 μM | ANTCV1<br>INHIB<br>● 25 μM |
|-------------------------------------------------------------------------------------|--------------------------|---------|--------|-----------------------------|----------------------------|----------------------------|
|    | 33                       | 108.6   | -30.3  | 12.9                        | 46                         |                            |
|    | 89                       | 12.4    | -5.1   | 3.6                         | 60                         | 20                         |
|   | 84                       |         |        | 0.06                        | 85                         | -57.5                      |
|  | 102                      | -84.4   | 60.8   | 2.2                         | 91                         | -20                        |
|  | 105                      | -157.2  | 113.3  | 1.7                         | 75                         | -1                         |
|  | 96                       |         |        | 1.9                         | 87 ● 5 μM                  | -15                        |
|  | 86                       | 54.8    | -40.1  | 0.01                        | 70                         | -17.5                      |
|  | 67                       | -196.0  | 109.4  | 0.03                        | 86                         | -59                        |



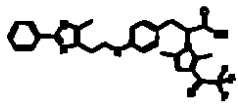
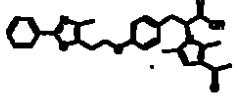
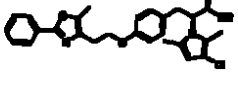
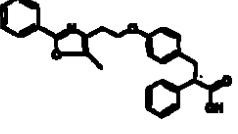
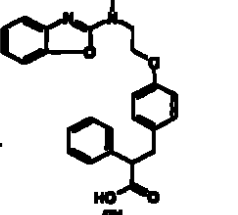
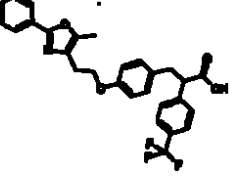
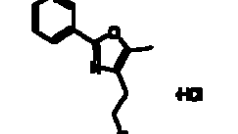
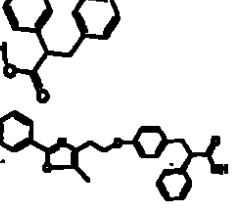
469

| Compuesto                                                                           | ADPDIFF<br>%BRL<br>● 5 μM | Glucose Δ | %BRL  | MKNRCVI<br>CE 50 | MKNRCVI<br>%BRL<br>● 25 μM<br>0.1122 | ANTCVI<br>INHIB<br>● 25 μM |
|-------------------------------------------------------------------------------------|---------------------------|-----------|-------|------------------|--------------------------------------|----------------------------|
|    |                           |           |       |                  |                                      |                            |
|    |                           |           |       |                  |                                      |                            |
|    |                           |           |       | 2000             | 48 ● 5 μM                            | -3                         |
|    | 21                        |           |       | 1.4              | 92                                   | -46                        |
|   | 29                        |           |       | 5.6              | 38                                   | 71                         |
|  |                           |           |       |                  |                                      |                            |
|  |                           |           |       |                  |                                      |                            |
|  | 92                        |           |       | 9.2              | 76                                   | -20                        |
|  | 3                         |           |       |                  | 44                                   | 3                          |
|  | 6                         |           |       | 2000             | 71                                   | -32                        |
|  |                           |           |       |                  |                                      |                            |
|  | 83                        | 182.8     | -55.3 | 2.9              | 92                                   | -31                        |
|  | 112                       |           |       | 0.4              | 80                                   | -27                        |

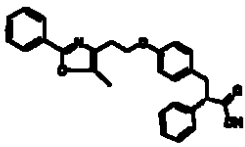
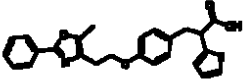
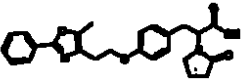
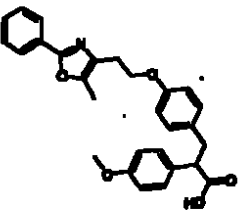
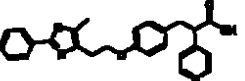
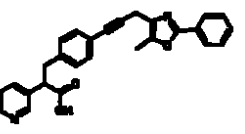
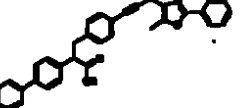
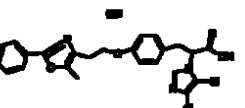
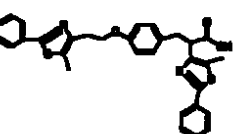
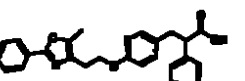
WES

| Compuesto                                                                           | ADPDIFF<br>%BRL<br>● 5 μM<br>125 | Glucose Δ | %BRL | MKNRCV1<br>CE90 | MKNRCV1<br>%BRL<br>● 25 μM<br>54 | ANTCV1<br>INHIB<br>● 25 μM<br>29 |
|-------------------------------------------------------------------------------------|----------------------------------|-----------|------|-----------------|----------------------------------|----------------------------------|
|    | 112                              |           |      | 0.9             | 54                               | 29                               |
|    | 120                              |           |      | 4.7             | 83                               | -12                              |
|  | 95                               |           |      | 23.6            | 70                               | -10                              |
|  | 125                              | -194.0    | 83.3 | 0.9             | 54                               | 29                               |
|  | 2                                |           |      |                 | 24                               | -3                               |
|  | 26                               |           |      |                 | 11                               | 80                               |
|  | 0                                |           |      |                 | 24                               | 3                                |

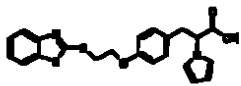
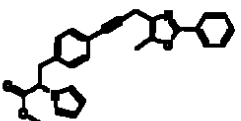
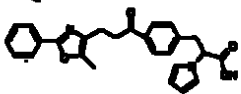
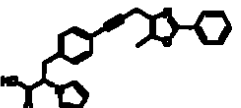
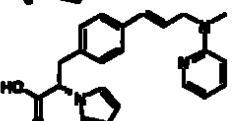
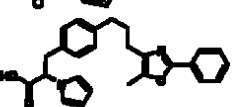
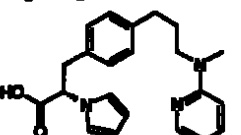
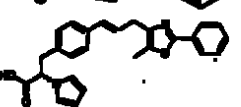
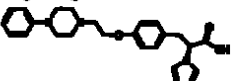
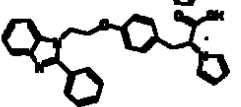
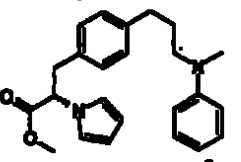
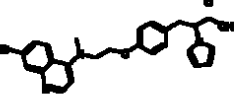
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| Compuesto                                                                           | ADPDIFF<br>%BRL<br>● 5 μM | Glucose Δ | %BRL   | MINRCV1<br>CE 50 | MINRCV1<br>%BRL<br>● 25 μM | ANTCV1<br>INHIB<br>● 25 μM |
|-------------------------------------------------------------------------------------|---------------------------|-----------|--------|------------------|----------------------------|----------------------------|
|    | 2                         |           |        | 16.0             | 28                         | 12                         |
|    | 0                         |           |        |                  | 27                         | -15                        |
|    | 28                        |           |        | 2000             | 55                         | 5                          |
|   | 94                        | 49.2      | -35.5  | 0.3              | 109                        | -48                        |
|  | 109                       | 172.0     | -52.0  | 1.0              | 91                         | -45                        |
|  | 107                       | 246.8     | -180.4 | 0.2              | 78                         | -49                        |
|  | 132                       | -72.5     | 31.1   | 0.4              | 58                         | -112                       |
|  | 95                        | -58.8     | 17.8   | 0.15             | 106                        | -104                       |

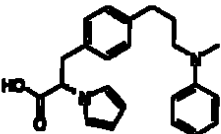
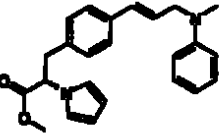
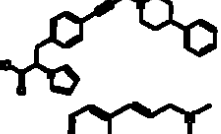
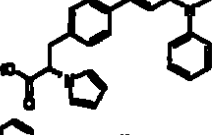
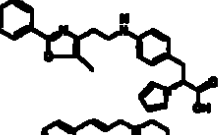
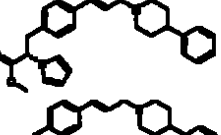
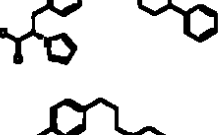
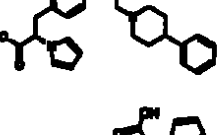
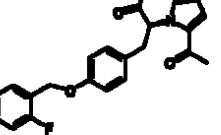
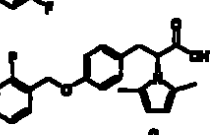
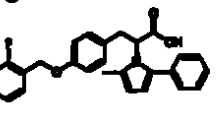
420

| Compuesto                                                                           | ADPDIFP<br>%BRL<br>● 5 μM | Glucose Δ | %BRL<br>CE 50 | MKNRCV1<br>%BRL<br>● 25 μM | MKNRCV1<br>%BRL<br>● 25 μM | ANTCV1<br>INHIB<br>● 25 μM |
|-------------------------------------------------------------------------------------|---------------------------|-----------|---------------|----------------------------|----------------------------|----------------------------|
|    | 31                        |           | 2000          | 50                         |                            | -44                        |
|    | 88                        |           |               |                            | 111                        | -127                       |
|    | 0                         |           |               |                            | 29                         | -94                        |
|   |                           |           | 2.7           | 75                         |                            | -65                        |
|  | 2                         |           |               |                            | 20                         | 55                         |
|  |                           |           | 34            | 49 ● 5 μM                  |                            | -15                        |
|  |                           |           | 2.7           | 86 ● 5 μM                  |                            | -21                        |
|  |                           |           |               | 27 ● 5 μM                  |                            | 15                         |
|  |                           |           |               | 110 ●<br>5 μM              |                            | 18                         |
|  |                           |           | 1.2           |                            |                            |                            |

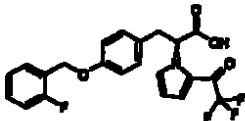
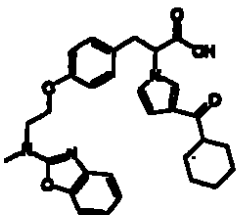
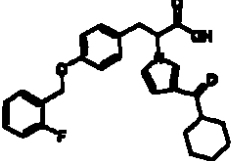
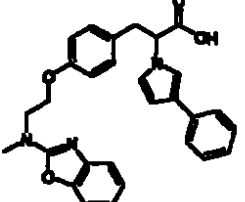
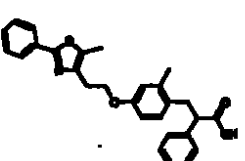
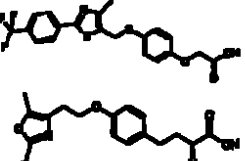
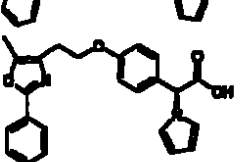
421

| Compuesto                                                                           | ADPDIFF<br>%BRL<br>● 5 μM | Glucosa Δ | %BRL  | MKNRCV1<br>CE <sub>50</sub> | MKNRCV1<br>%BRL<br>● 25 μM | ANTCV1<br>INHIB<br>● 25 μM |
|-------------------------------------------------------------------------------------|---------------------------|-----------|-------|-----------------------------|----------------------------|----------------------------|
|    | 97                        | 155.0     | -66.5 | 0.7                         | 102                        | -102                       |
|    | 90                        |           |       | 0.1                         | 123                        | -114                       |
|    | 3                         |           |       |                             |                            |                            |
|   | 100                       | 62.0      | -45.3 | 0.01                        | 94                         | -108                       |
|  | 94                        |           |       | 0.9                         | 92                         | -36                        |
|  | 62                        | -166.6    | 121.8 | 0.02                        | 69                         | -70                        |
|  | 113                       |           |       | 1.0                         | 64                         | -146                       |
|  | 76                        |           |       | 0.1                         | 94                         | -66                        |
|  | 82                        |           |       |                             | 32                         | -40                        |
|  | 19                        |           |       |                             | 39                         | -69                        |
|  | 73                        |           |       | 2000                        | 71                         | -2                         |
|  | 1                         |           |       | 2000                        | 83                         | -87                        |

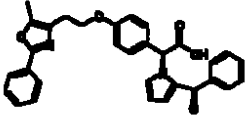
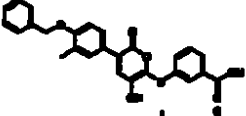
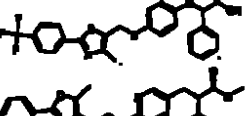
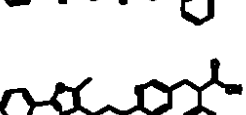
1272

| Compuesto                                                                           | ADPDIFF<br>%BRL<br>● 5 μM<br>61 | Glucose Δ | %BRL  | MEKNCV1<br>CE 10 | MEKNCV1<br>%BRL<br>● 25 μM<br>68 | ANTCV1<br>INHIB<br>● 25 μM<br>-57 |
|-------------------------------------------------------------------------------------|---------------------------------|-----------|-------|------------------|----------------------------------|-----------------------------------|
|    | 61                              | 63.0      | -27.0 | 5.4              | 68                               | -57                               |
|    | 110                             |           |       | 0.7              | 96                               | 2                                 |
|   | 112                             |           |       | 1.3              | 78                               | -42                               |
|  | 117                             |           |       | 1.7              | 79                               | -29                               |
|  | 157                             |           |       | 1.4              | 157                              | 0                                 |
|  | 32                              |           |       | 2000             | 47                               | 25                                |
|  | 183                             |           |       |                  | 40                               | 44                                |
|  | 38                              |           |       |                  | 22                               | 50                                |
|  | 3                               |           |       |                  | 25                               | -40                               |
|  | 2                               |           |       |                  | 34                               | -218                              |
|  | 2                               |           |       |                  | 30                               | -44                               |

V93

| Compuesto                                                                           | ADPDIFF<br>%BRL<br>● 5 μM<br>14 | Glucosa Δ | %BRL<br>CE 50 | MKNRCV1<br>%BRL<br>● 25 μM<br>18 | MKNRCV1<br>INHIB<br>● 25 μM<br>28 | ANTCV1<br>INHIB<br>● 25 μM<br>28 |
|-------------------------------------------------------------------------------------|---------------------------------|-----------|---------------|----------------------------------|-----------------------------------|----------------------------------|
|    | 112                             |           | 11.1          | 65                               | 4                                 |                                  |
|    | 12                              |           |               | 28                               | 1                                 |                                  |
|   | 113                             |           | 2000          | 59                               | -41                               |                                  |
|  |                                 |           | 1.0           |                                  |                                   |                                  |
|  |                                 |           |               | 70                               | -58                               |                                  |
|  |                                 |           | 1.3           | 82 ● 5 μM                        | 62                                |                                  |
|  |                                 |           | 3.6           | 57 and 47<br>● 5 μM              | 39                                |                                  |

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| Compuesto                                                                          | ADPDIFF<br>%BRL<br>● 5 μM | Glucose Δ | %BRL<br>CE 50 | MKNRCV1<br>%BRL<br>● 25 μM<br>58 and 39<br>● 5 μM | ANTCV1<br>INHIB<br>● 25 μM<br>-5 |
|------------------------------------------------------------------------------------|---------------------------|-----------|---------------|---------------------------------------------------|----------------------------------|
|   |                           |           |               |                                                   |                                  |
|   |                           |           |               | 26 ● 5 μM                                         | -29                              |
|   |                           |           |               | 40                                                | 12                               |
|   |                           |           |               |                                                   |                                  |
|  |                           |           |               | 75 ● 5 μM                                         | -58                              |



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Tabla 2  
Actividad Biológica

| Número PD          | Estructura | Indicador AD3T3-L1                        |            | In vivo                                                                 |                    |
|--------------------|------------|-------------------------------------------|------------|-------------------------------------------------------------------------|--------------------|
| No. PD/<br>Ejemplo |            | EC <sub>50</sub> (nM)                     | Max. %Rosi | Δ Glucosa @<br>20 mg/kg                                                 | %<br>Rosiglitazona |
| 0336683<br>94      |            | 9700                                      | 62.8       | -53                                                                     | 24.38              |
| 0338227<br>92      |            | 9570                                      | 59         | Not tested                                                              |                    |
| 0338228<br>91      |            | 1.06                                      | 96         | -293.07                                                                 | 128.9%             |
| 0339165<br>93      |            | 10.0<br><i>Actividad del<br/>racemato</i> | 90         | Actividad para el<br>enantiómero S<br>PD 344170; -<br>219 @ 10<br>mg/kg | 102.49%            |
| 0333941<br>53      |            | 113                                       | 50         |                                                                         | 96%                |

V.76

Haciendo referencia a la Tabla 2, se demostró que PD 0333941 reducía la glucosa en sangre en un modelo de ratón diabético Ob/Ob a 3 mg/kg. El compuesto muestra una respuesta a la dosis con un efecto máximo a 30 mg/kg.

5 Haciendo referencia de nuevo a la Tabla 2, PD 0338228 se evaluó con respecto a su actividad selectiva contra tres tipos de PPAR usando células HepG2. En estos exámenes, PD338228 demostró una  $CE_{50}$  = 71,8 nM en el ensayo HepG2-hALPHA (PPAR alfa) y una  $CE_{50}$  = 92,5 nM en el ensayo HepG2-10 mGAMMA (PPAR gamma). Fue inactivo contra PPAR beta. En el ensayo PPAR alfa, PD 3328228 a su efecto máximo sólo proporciona un 61% de la actividad máxima del agente de referencia (GW9578). Los resultados obtenidos con Rosiglitazona y PD 32634 se incluyen en la tabla mostrada a 15 continuación.

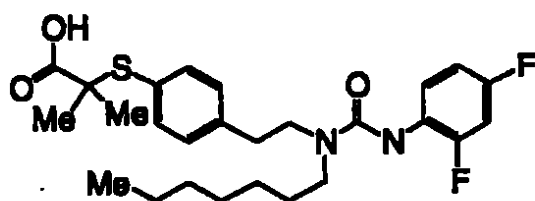
Tabla 3

| Resumen de Actividad Selectiva para 338228 con células HepG2 (2-1-2002) |              |             |           |             |          |           |              |         |           |
|-------------------------------------------------------------------------|--------------|-------------|-----------|-------------|----------|-----------|--------------|---------|-----------|
|                                                                         | HepG2-hAlpha |             |           | HepG2-hBeta |          |           | HepG2-mGamma |         |           |
|                                                                         | Veces        | Res. Máx. % | $CE_{50}$ | Veces (uM)  | % GW9578 | $CE_{50}$ | Veces (uM)   | % Rosi. | $CE_{50}$ |
| Compuesto                                                               |              |             |           |             |          |           |              |         |           |
| GW9578                                                                  | 48.8(1)      | 100.0       | 150nM     |             |          |           |              |         |           |
| GW9578                                                                  |              |             |           | 84.9(1)     | 100.0    | 2.48nM    |              |         |           |
| Rosiglitazona                                                           |              |             |           |             |          |           | 7.08(20)     | 100.0   | 289.7nM   |
| 338228-00007                                                            | 37.2(16)     | 61.3        | 71.8nM    | 4.9(20)     | 0.0      | in        | 88.7(18)     | 987.0   | 82.9nM    |

49A

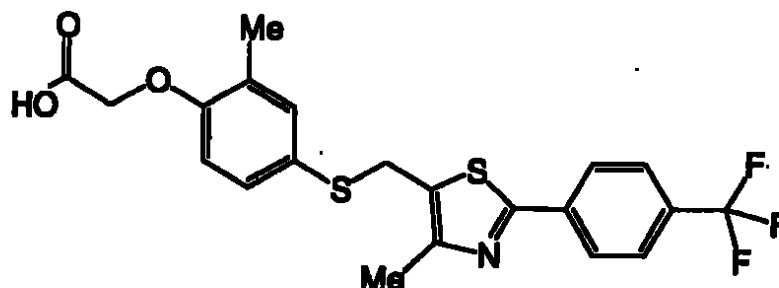
En la tabla, GW9578 se refiere a:

5



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GW501516 se refiere a:



5 PD 338228 se identificó como un potente agonista PPAR gamma completo en el ensayo del indicador AD3T3-L1. Además, este compuesto actúa como un agonista alfa/gamma doble como se demuestra por los ensayos de selectividad. Se demostró un perfil agonista parcial para PPAR alfa. Cuando se evaluó  
10 en el modelo de ratones Ob/Ob para la diabetes, PD 338228 pudo normalizar completamente los niveles de glucosa en plasma a 20 mg/kg en 14 días. Su actividad fue comparable, o incluso mejor, que la de rosiglitazona. PD 338228 es un agente potencial para el tratamiento de la diabetes de tipo  
15 II y las dislipidemias, ya que esta afección se describe, por ejemplo, en el Merck Manual (1992).

En general, los compuestos de la invención pueden inducir la diferenciación de adipocitos como se describe en el ensayo A. Los resultados del ensayo E, en particular,

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demuestran que los compuestos de la invención pueden reducir los niveles de glucosa en ratones.

Como los compuestos de la invención inducen la diferenciación de adipocitos y reducen los niveles de glucosa en sangre, pueden ser útiles en el tratamiento de trastornos asociados con la resistencia a insulina. Tales trastornos incluyen: NIDDM, angiopatía diabética, aterosclerosis, nefropatía diabética, neuropatía diabética y complicaciones diabéticas oculares tales como retinopatía, formación de cataratas y glaucoma, así como resistencia a insulina inducida por glucocorticoides, dislipidemia, síndrome de ovarios poliquísticos, obesidad, hiperglucemia, hiperlipidemia, hipercolesterolemia, hipertrigliceridemia, hiperinsulinemia e hipertensión.

Por consiguiente, la invención también incluye un procedimiento para tratar una enfermedad en un ser humano u otro mamífero en necesidad del mismo en la que se ha implicado la resistencia a insulina y se desea la reducción de los niveles de glucosa, que comprende administrar a dicho ser humano o mamífero una cantidad eficaz de un compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo. La invención también incluye un procedimiento para tratar o prevenir la resistencia a insulina en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de fórmula I o

1400

una sal farmacéuticamente aceptable del mismo. Además, los compuestos de la invención pueden usarse in vitro o in vivo como herramientas farmacológicas y bioquímicas para ayudar al descubrimiento y evaluación de otros agentes reductores 5 de glucosa y agonistas de PPAR  $\gamma$ .

Los ésteres de fórmula general VI se hidrolizan fácilmente a compuestos de la invención. Por consiguiente, la invención también incluye un procedimiento para preparar un compuesto de fórmula I por medio de la hidrólisis de un 10 compuesto de fórmula VI.

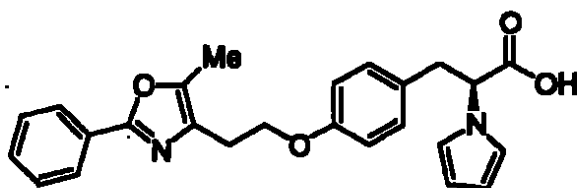
Además, puede determinarse que los ésteres de fórmula general VI actúan como profármacos para los compuestos de fórmula I. Por consiguiente, la invención también incluye un procedimiento para tratar una enfermedad en un ser 15 humano u otro mamífero en necesidad del mismo en el que se ha implicado la resistencia a la insulina y se desean reducir los niveles de glucosa, que comprende administrar a dicho ser humano o mamífero una cantidad eficaz de un compuesto de fórmula VI; o una sal farmacéuticamente 20 aceptable del mismo.

#### EJEMPLOS

##### Ejemplo 1

Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (3).

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3

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**Procedimiento General para hidrólisis de éster  
(Procedimiento General A),**

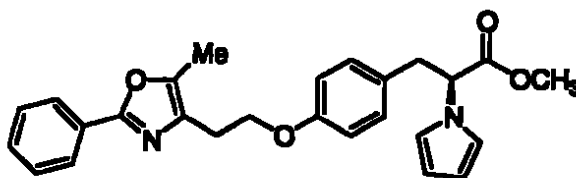
Se disolvió éster metílico del ácido (S)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)etoxi]-fenil)-2-pirrol-1-il-propiónico (400 mg, 0,930 mmol) en THF (10 ml) y H<sub>2</sub>O (10 ml). Se añadió monohidrato de LiOH (45 mg, 1,07 mmol) en una porción y la suspensión se agitó durante 1 hora. La reacción se diluyó con EtOAc (20 ml) y H<sub>2</sub>O (20 ml) y la capa orgánica se separó. Después de la acidificación de la capa acuosa a un pH de aproximadamente 2 con HCl acuoso y de la extracción con EtOAc (2 x 20 ml), las capas orgánicas se combinaron y se lavaron con H<sub>2</sub>O (10 ml) y salmuera (10 ml) y se secaron sobre MgSO<sub>4</sub>. La retirada del disolvente al vacío dio 3 en forma de un cristal blanco (320 mg, 0,769 mmol). Recristalizado en EtOAc/Hex en forma de finas agujas blancas con un rendimiento del 51%. P.F. = 155-56°C. C<sub>25</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>. Masa Calculada = 416,475; M+1 (obs) = 417,2. <sup>1</sup>H RMN (400 MHz) CDCl<sub>3</sub> δ: 7,91 (2H, m), 7,38 (3H, m), 6,90 (2H, d, J = 8,5 Hz), 6,71 (2H, d, J = 8,5 Hz), 6,69 (2H, t, J = 2,0, 2,1 Hz), 6,12 (2H, t, J = 1,9, 1,9 Hz), 4,69 (1H, dd,

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$J = 7,08, 8,03 \text{ Hz}$ ),  $4,16$  (2H, t,  $6,5, 6,5 \text{ Hz}$ ),  $3,34$  (1H, dd,  $J = 6,6, 6,6 \text{ Hz}$ ),  $3,17$  (1H, dd,  $J = 8,3, 8,3 \text{ Hz}$ ),  $2,93$  (2H, t,  $J = 6,6, 6,6 \text{ Hz}$ ),  $2,32$  (3H, s), CHN teórico = C =  $72,10$ , H =  $5,81$ , N =  $6,73$ , CHN obs.; C =  $72,09$ ; H,  $5,58$ , N  $5 = 6,63$ .

El éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (2) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-3-{4-[2-(5-metil-2-  
10 fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (2).



15

2

### Procedimiento General de Acoplamiento (Procedimiento General B)

Se disolvieron éster metílico de pirrolotirosina (1)  
20 (2,68 g, 10,9 mmol), 2-(5-metil-2-feniloxazol-4-il) etanol (2,22 g, 10,9 mmol) y trifenilfosfina (3,15 g, 12,0 mmol) en THF anhidro (100 ml) en una atmósfera de  $N_2$  a  $0^\circ C$ . Se añadió lentamente azodicarboxilato de dietilo (DEAD) (1,89 ml, 12,0 mmol) en THF (50 ml) durante 30 min y se dejó  
25 equilibrar a  $23^\circ C$  durante 18 horas. La solución se diluyó



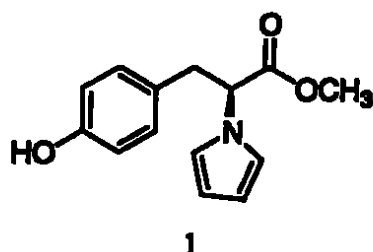
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con EtOAc (50 ml), se lavó con agua (30 ml) y salmuera (30 ml) y se secó sobre MgSO<sub>4</sub>. Después de la retirada del disolvente al vacío, la cromatografía de gel de SiO<sub>2</sub> con EtOAc al 10%/Hex, dio 2,4 g de 2 con un rendimiento del 51% en forma de un aceite transparente.

Espectroscopía de Masas de Baja Resolución (LRMS) C<sub>26</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub> PM = 430,501 calc. M+1 = 431,2 obs. <sup>1</sup>H RMN (400 MHz) CDCl<sub>3</sub> δ: 7,95 (2H, d, J = 5,8 Hz), 7,40 (3H, m), 6,85 (2H, d, J = 8,3 Hz), 6,72 (2H, d, J = 8,5 Hz), 6,66 (2H, s), 6,10 (2H, s), 4,63 (1H, dd, J = 6,83, 8,30 Hz), 4,16 (2H, t, 6,6, 6,6 Hz), 3,65 (3H, s), 3,29 (1H, dd, J = 6,3, 6,3 Hz), 3,13 (1H, dd, J = 8,8, 8,8 Hz), 2,93 (2H, t, J = 6,6, 6,6 Hz), 2,32 (3H, s).

(b) Éster metílico de pirrolotirosina (1).

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20 Se disolvieron éster metílico de S-tirosina (25,6 g, 131 mmol), 2,5-dimetoxi-tetrahidrofurano (17 ml, 223 mmol) y NaOAc (21,5 g, 262 mmol) en una mezcla 1:1 de H<sub>2</sub>O y ácido acético (150 ml:150 ml) y se agitó hasta la homogeneidad (c. 30 min.). Después, la temperatura se incrementó a 100°C durante 20 minutos en un baño de aceite, tiempo durante el

484

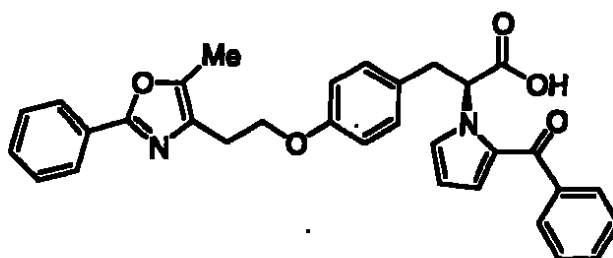
cual la solución se volvió de color pardo oscuro. Después del período de tiempo indicado, la solución se retiró del baño caliente y se dejó enfriar a 23°C. La mezcla de reacción se diluyó con H<sub>2</sub>O (100 ml) y se extrajo con EtOAc 5 (3 x 75 ml). Las capas orgánicas se combinaron y se lavaron consecutivamente con H<sub>2</sub>O (2 x 75 ml) y salmuera (50 ml) y se secaron sobre MgSO<sub>4</sub>. El disolvente se retiró al vacío y el residuo bruto se cromatografió con MeOH al 5%/CHCl<sub>3</sub>, dando 15 g (rendimiento del 35%) de cristales de color crema. <sup>1</sup>H RMN (400 MHz) δ (CDCl<sub>3</sub>) 6,83 (2H, d, 8 Hz), 6,67 (2H, d, 2 Hz), 6,65 (2H, d, 8 Hz), 6,11 (2H, d, 2 Hz), 4,65 (1H, q, 6 Hz), 4,66 (1H, s), 3,66 (3H, s), 3,31 (1H, dd, 6 Hz), 3,28 (1H, dd, 6 Hz).

Se usaron los procedimientos descritos en el Ejemplo 1 para preparar ácido (R)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico y ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico racémico.

#### Ejemplo 2

20 Ácido (S)-2-(2-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (9).

VBS



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Se realizó hidrólisis de éster del éster metílico del ácido (S)-2-(2-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (8) de una forma similar al Procedimiento General A. El tratamiento posterior con LiOH, éster metílico del ácido (S)-2-(2-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (9) (498 mg, 0,932 mmol), dio 430 mg del ácido (S)-2-(2-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (10) (0,827 mmol) con un rendimiento del 98%.  $C_{32}H_{28}N_2O_5$  Peso Molecular: 520,5752;  $M+1$  (obs) = 521,2.  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 7,93 (2H, d,  $J$  = 8,1 Hz), 7,66 (2H, d,  $J$  = 7,6 Hz), 7,48 (1H, m), 7,37 (6H, m), 7,16 (1H, s), 6,92 (2H, d,  $J$  = 8,3 Hz), 6,67 (2H, d,  $J$  = 8,3 Hz), 6,64 (1H, d,  $J$  = 3,2 Hz), 6,16 (1H, t,  $J$  = 2,9, 2,9 Hz), 5,78 (1H, s), 4,09 (2H, m), 3,52 (1H, dd,  $J$  = 6,1, 14,4 Hz), 3,21 (1H, dd,  $J$  = 9,03, 14,1 Hz), 2,91 (2H, t,  $J$  = 6,6, 6,6 Hz), 2,31 (3H, s)

El éster metílico del ácido (S)-2-(2-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-

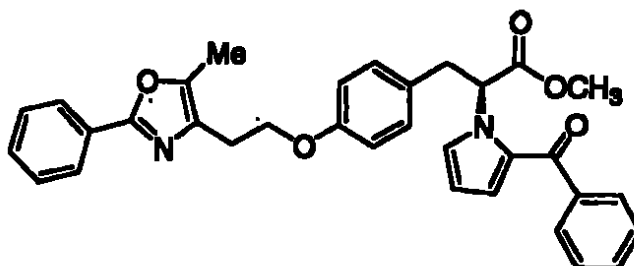
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propiónico (8) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-2-(2-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}propiónico (8)

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8

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Se acopló éster metílico del ácido (S)-2-(2-benzoil-pirrol-1-il)-3-(4-hidroxifenil)-propiónico (7) a 2-(5-metil-2-feniloxazol-4-il) etanol de una forma similar a la descrita en el Procedimiento General B. Se trató fenol 7  
15 (3,1 g, 8,88 mmol) con 1 equivalente mol de cada uno de alcohol (1,8 g, 8,88 mmol), trifenilfosfina (2,33 g, 8,88 mmol) y azodicarboxilato de dietilo (1,40 ml, 8,88 mmol), dando 2,3 g (4,31 mmol) del producto 2-sustituido con un rendimiento del 49% en forma de un aceite amarillo pálido.

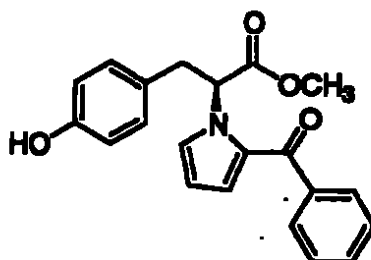
20  $C_{33}H_{30}N_2O_5$ . Peso Molecular: 534,602;  $M+1$  (obs) = 532,2.  $^1H$  RMN ( $CDCl_3$ )  $\delta$ : 7,96 (2H, dd,  $J = 1,9, 7,8$  Hz), 7,54 (2H, m), 7,40 (6H, m), 7,09 (1H, s), 6,88 (2H, d,  $J = 8,5$  Hz), 6,66 (2H, d,  $J = 8,5$  Hz), 6,56 (1H, dd,  $J = 1,5, 3,9$  Hz), 6,12 (1H, dd,  $J = 1,5, 2,7$  Hz), 6,10 (1H, s a), 4,10 (2H, m), 3,74  
25 (3H, s), 3,44 (1H, dd,  $J = 5,4, 13,9$  Hz), 3,18 (1H, dd,  $J =$

458

10,14 Hz), 2,91 (2H, t,  $J = 6,6, 6,6$  Hz), 2,32 (3H, s).

(b) Éster metílico del ácido (S)-2-(2-benzoil-pirrol-1-il)-3-(4-hidroxifenil)-propiónico (7).

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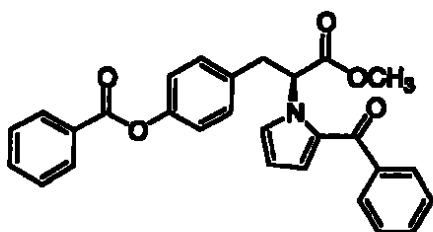
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10      **Procedimiento General C.** Se disolvió (S)-4-[2-(2-benzoil-pirrol-1-il)-2-metoxycarbonil-etil]-fenil éster del ácido benzoico (5) (300 mg, 0,661 mmol) en alcohol metílico anhidro (10 ml) y se puso en una atmósfera de  $N_2$  a  $23^\circ C$ . Después de la adición de  $K_2CO_3$  (136 mg, 0,991 mmol), la  
15 suspensión se agitó vigorosamente durante 3 horas y se controló periódicamente por TLC. Una vez completada, el metanol se retiró al vacío y el residuo se cromatografió con EtOAc al 10%/hexanos, dando el fenol libre 7 con un rendimiento del 90% (200 mg, 0,60 mmol) en forma de un  
20 polvo blanco. Éster metílico del ácido (S)-2-(2-benzoil-pirrol-1-il)-3-(4-hidroxifenil)-propiónico (7).  $C_{21}H_{19}NO_4$   
Peso Molecular.: 349,380;  $M+1$  (obs) = 350,3.  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 7,57 (2H, dd,  $J = 1,5, 7,5$  Hz), 7,46 (1H, m), 7,36 (2H, m), 7,09 (1H, s), 6,86 (2H, d,  $J = 8,5$  Hz), 6,60  
25 (2H, d,  $J = 8,5$  Hz), 6,60 (1H, s), 6,13 (1H, dd,  $J = 2,7,$

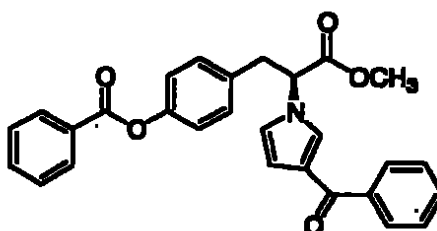
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4,1 Hz), 6,09 (1H, s), 4,62 (1H, s), 3,73 (3H, s), 3,44 (1H, dd,  $J = 5,6, 14,1$  Hz), 3,17 (1H, dd,  $J = 9,8, 14,1$  Hz).

(c) (S)-4-[2-(2-benzoil-pirrol-1-il)-2-metoxycarbonil-5 etil]-fenil éster del ácido benzoico (5) y (S)-4-[2-(3-benzoil-pirrol-1-il)-2-metoxycarbonil-etil]-fenil éster del ácido benzoico (6).



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**Procedimiento General D.** Se añadió ácido trifluorometanosulfónico (45  $\mu$ l, 0,516 mmol) a una solución agitada de 4-(2-metoxycarbonil-2-pirrol-1-il-etil)-fenil éster del ácido benzoico (4) (150 mg, 0,430 mmol) y cloruro de benzoilo (60  $\mu$ l, 0,516 mmol) en diclorometano (20 ml) a 28°C en una atmósfera de  $N_2$ . Después de la agitación durante 18 horas, el disolvente se retiró al vacío. La cromatografía en gel de  $SiO_2$  del residuo resultante con EtOAc al 10%/hexanos dio 80 mg del pirrol 2-sustituido (5) (0,177 mmol, 40%) y 37 mg del 3-sustituido (6) (0,082 mmol, rendimiento 20%).

(S)-4-[2-(2-benzoil-pirrol-1-il)-2-metoxycarbonil-

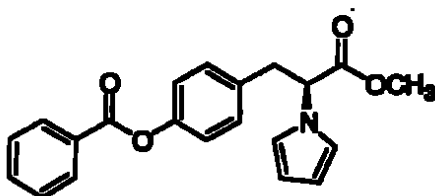
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etil]-fenil éster del ácido benzoico (5)  $C_{28}H_{23}NO_5$ : Masa (calc) 453,4860;  $M+1$  (obs) = 454,2.  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 8,13 (2H, dd,  $J = 1,2, 8,5$  Hz), 7,61 (3H, m), 7,47 (3H, m), 7,40 (2H, m), 7,07 (2H, d,  $J = 8,8$  Hz), 7,04 (1H, s), 7,00 (2H, d,  $J = 8,8$  Hz), 6,62 (1H, t,  $J = 1,7, 2,4$  Hz), 6,15 (1H, dd,  $J = 2,7, 3,9$  Hz), 6,15 (1H, s), 3,76 (3H, s), 3,55 (1H, dd,  $J = 5,6, 14,1$  Hz), 3,29 (1H, dd,  $J = 10, 14,1$  Hz).

(S)-4-[2-(3-benzoil-pirrol-1-il)-2-metoxycarbonil-  
10 etil]-fenil éster del ácido benzoico (6).  $C_{28}H_{23}NO_5$ : Masa (calc) 453,4860;  $M+1$  (obs) = 454,2.  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 8,14 (2H, d,  $J = 7,1$  Hz), 7,70 (2H, d,  $J = 7,1$  Hz), 7,60 (1H, m), 7,43 (5H, m), 7,16 (1H, t,  $J = 1,7, 1,9$  Hz), 7,09 (2H, d,  $J = 8,8$ ), 7,04 (2H, d,  $J = 8,5$  Hz), 6,67 (1H, q,  $J = 1,0, 1,9, 2,2$  Hz), 6,69 (1H, q,  $J = 1,2, 1,7, 1,7$  Hz), 4,73 (1H, dd,  $J = 5,9, 9,5$  Hz), 3,74 (3H, s), 3,43 (1H, dd,  $J = 5,8, 14,1$  Hz), 3,25 (1H, dd,  $J = 9,2, 13,9$  Hz).

(d) 4-(2-metoxycarbonil-2-pirrol-1-il-etil)-fenil éster del ácido benzoico

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**Procedimiento General E.** Se añadió trietilamina (290

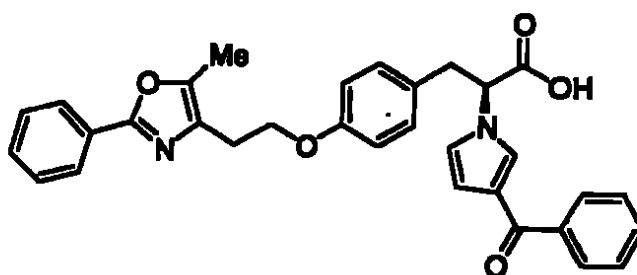
240

μl, 2,06 mmol) a una solución agitada del éster metílico de pirrolotirosina (252 mg, 1,03 mmol) en diclorometano (20 ml) en una atmósfera de N<sub>2</sub> a 23°C. Se añadió gota a gota cloruro de benzoílo (143 μl, 1,23 mmol) durante un período 5 5 minutos y la reacción se agitó durante 2 horas. El disolvente se retiró al vacío y se cromatografió en SiO<sub>2</sub> con EtOAc al 10%/hexanos, dando éster de benzoílo 4 con un rendimiento del 86% (310 mg, 0,89 mmol) en forma de una espuma blanca. C<sub>21</sub>H<sub>19</sub>NO<sub>4</sub> Masa Calculada = 349,380; M+1 (obs) 10 = 350,2 <sup>1</sup>H RMN (400 MHz, CDCl<sub>3</sub>) δ: 8,17 (2H, d, J = 6,35 Hz), 7,62 (1H, m), 7,47 (2H, m), 7,09 (2H, d, J = 8,8 Hz), 7,04 (2H, d, J = 8,6 Hz), 6,71 (2H, t, J = 2,2, 2,1 Hz), 6,16 (2H, t, J = 2,2, 2,2 Hz), 4,72 (1H, dd, J = 2,4, 2,4 Hz), 3,70 (3H, s), 3,43 (1H, dd, J = 6,3, 6,3 Hz), 3,25 (1H, dd, 15 J = 9,0, 9,0 Hz).

### Ejemplo 3

Ácido (S)-2-(3-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (12).

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25 Se realizó hidrólisis de éster de una forma similar a



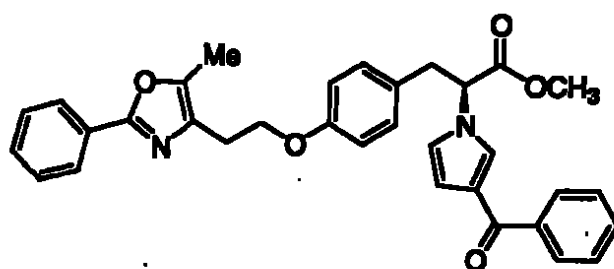
491

la del Procedimiento General A. El tratamiento posterior con LiOH, éster metílico del ácido (S)-2-(3-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (11) (400 mg, 0,749 mmol), dio 260 mg del ácido 5 (S)-2-(3-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (12). (0,500 mmol) rendimiento 67%.  $C_{32}H_{28}N_2O_5$  Peso Molecular.: 520,5752;  $M+1$  (obs) = 512,2.  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$  7,92 (2H, m), 7,62 (2H, d,  $J = 8,0$  Hz), 7,26 (6H, m), 7,06 (1H, s), 6,85 (2H, 10 d,  $J = 8,3$  Hz), 6,69 (2H, d,  $J = 7,8$  Hz), 6,68 (1H, s), 6,60 (1H, t,  $J = 1,5, 1,5$  Hz), 4,65 (1H, t,  $J = 6,8, 8,1$  Hz), 4,09 (3H, m), 3,31 (1H, dd,  $J = 6,6, 14,0$  Hz), 3,10 (1H, dd,  $J = 9,0, 14,1$  Hz), 2,95 (2H,  $J = 6,6, 6,1$  Hz), 2,31 (3H, s).

15 El éster metílico del ácido (S)-2-(3-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (11) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-2-(3-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
20 propiónico (11)

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Preparado de una forma similar a la descrita en el Procedimiento General B. Se trató éster metílico del ácido (S)-2-(3-benzoil-pirrol-1-il)-3-(4-hidroxi-fenil)-

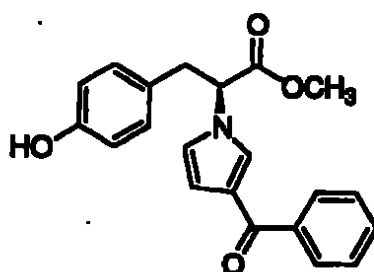
10 propiónico (8) (800 mg, 2,29 mmol) con 1 equivalente mol de cada uno de 2-(5-metil-2-feniloxazol-4-il) etanol (465 mg, 2,29 mmol), trifenilfosfina (600 mg, 2,29 mmol) y azodicarboxilato de dietilo (360  $\mu$ l, 2,29 mmol), dando 400 mg (0,749 mmol) de producto 3-sustituido (11) con un  
15 rendimiento del 32% en forma de un aceite amarillo pálido.

$C_{33}H_{30}N_2O_5$  Peso Molecular.: 534,602;  $M+1$  (obs) = 532,2  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 8,00 (2H, m), 7,67 (2H, d,  $J$  = 6,8 Hz), 7,40 (6H, m), 7,08 (1H, t,  $J$  = 1,9, 1,9 Hz), 6,84 (2H, d,  $J$  = 8,5 Hz), 6,72 (2H, d,  $J$  = 8,5 Hz), 6,71 (1H, t,  $J$  = 2,2,  
20 2,2 Hz), 6,66 (1H, t,  $J$  = 1,7 Hz), 4,65 (1H, dd,  $J$  = 5,6 Hz), 4,16 (2H, m), 3,71 (3H, s), 3,31 (1H, dd,  $J$  = 5,8, 14,1 Hz), 3,13 (1H, dd,  $J$  = 9,3, 14,0 Hz), 2,98 (2H, m), 2,01 (3H, s).

(b) Éster metílico del ácido (S)-2-(3-benzoil-pirrol-  
25 1-il)-3-(4-hidroxi-fenil)-propiónico (10).

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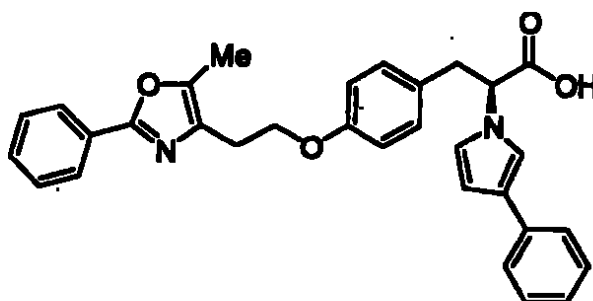
Preparado a partir de (S)-4-[2-(3-benzoil-pirrol-1-il)-2-metoxicarbonil-etil]-fenil éster del ácido benzoico (6) de acuerdo con los Procedimientos Generales C-E.

10  $C_{21}H_{19}NO_4$  Peso Molecular: 349,380;  $M+1$  (obs) = 350,3.  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 7,68 (2H, d,  $J$  = 6,8 Hz), 7,48 (1H, m), 7,40 (3H, m), 7,10 (1H, t,  $J$  = 1,7, 1,9 Hz), 6,81 (2H, d,  $J$  = 8,5 Hz), 6,73 (1H, t,  $J$  = 2,9 Hz, 2,2 Hz), 6,67 (2H, d,  $J$  = 8,5 Hz), 6,65 (1H, s), 4,66 (1H, dd,  $J$  = 5,6, 9,2 Hz), 15 3,72 (3H, s), 3,31 (1H, dd,  $J$  = 5,6, 13,9 Hz), 3,13 (1H, dd,  $J$  = 9,5, 14,1 Hz).

#### Ejemplo 4

Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-propiónico (15).

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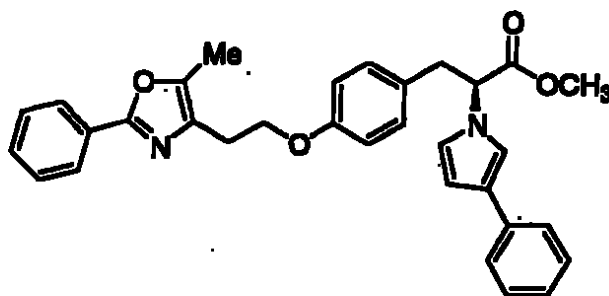
El compuesto se preparó como se describe en el Procedimiento General A. Se hidrolizó (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-5 propiónico (14) (1,6 g, 3,14 mmol), dando (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-propiónico (15) (1,2 g, 2,43 mmol) con un rendimiento del 77% en forma de cristales de color crema, que se recrystalizaron en EtOAc/Hexanos. P.f. 146°C-147°C.

10  $C_{31}H_{28}N_2O_4$  Peso Molecular: 492,565;  $M+1 = 493,2$ .  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 7,91 (2H, dd,  $J = 3,7, 7,3$  Hz), 7,44 (2H, d,  $J = 7,3$  Hz), 7,37 (3H, m), 7,27 (2H, t,  $J = 7,5, 7,8$  Hz), 7,11 (1H, t,  $J = 7,3, 7,3$  Hz), 7,01 (1H, s), 6,93 (2H, d,  $J = 8,5$  Hz), 6,71 (2H, d,  $J = 8,5$  Hz), 6,69 (1H, t,  $J = 2,4, 2,4$  Hz), 6,42 (1H, t,  $J = 2,0, 2,7$  Hz), 4,67 (1H, t,  $J = 7,1, 7,8$  Hz), 4,10 (2H, t,  $J = 6,3, 6,6$  Hz), 3,36 (1H, dd,  $J = 6,8, 14,2$  Hz), 3,18 (1H, dd,  $J = 8,0, 13,9$  Hz), 2,93 (2H, m), 2,32 (3H, s). CHN (teórico) C = 75,59; H = 5,73; N, 5,69; (Obs) C = 75,42; H, 5,80; N = 5,50.

20 El éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-propiónico (14) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-25 propiónico

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El compuesto se preparó mediante acoplamiento de Mitsunobu como se describe en el Procedimiento General B.

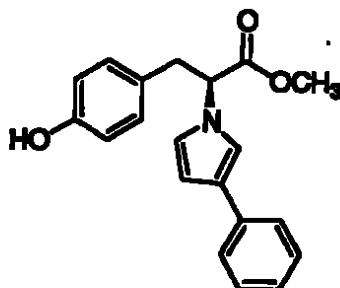
10 El éster metílico del ácido (S)-3-(4-hidroxifenil)-2-(3-fenilpirrol-1-il)-propiónico (13) (2,0 g, 6,23 mmol), dio el producto acoplado, éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-fenilpirrol-1-il)propiónico (14) (1,6 g, 3,16 mmol) con un

15 rendimiento del 51% en forma de un aceite amarillo pálido.

$C_{32}H_{30}N_2O_4$  Peso Molecular; 506,592;  $M+1$  (obs) = 507,1.  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 7,94 (2H, d,  $J$  = 8,1 Hz), 7,46 (2H, d,  $J$  = 8,1 Hz), 7,40 (3H, m), 7,29 (2H, t,  $J$  = 7,3, 7,6 Hz), 7,12 (1H, t,  $J$  = 7,3, 7,2 Hz), 7,00 (1H, s), 6,90 (2H, d,  $J$  = 8,1 Hz), 6,74 (2H, d,  $J$  = 8,1 Hz), 6,68 (1H, s), 6,42 (1H, s), 4,65 (1H, t,  $J$  = 7,8, 7,3 Hz), 4,17 (2H, t,  $J$  = 6,6, 6,8 Hz), 3,69 (3H, s), 3,33 (1H, dd,  $J$  = 6,6, 13,9 Hz), 3,19 (1H, dd,  $J$  = 9,3, 13,7 Hz), 2,92 (2H, t,  $J$  = 6,6, 7,1 Hz), 2,35 (3H, s).

25 (b) Éster metílico del ácido (S)-3-(4-hidroxifenil)-

2-(3-fenil-pirrol-1-il)propiónico (13).



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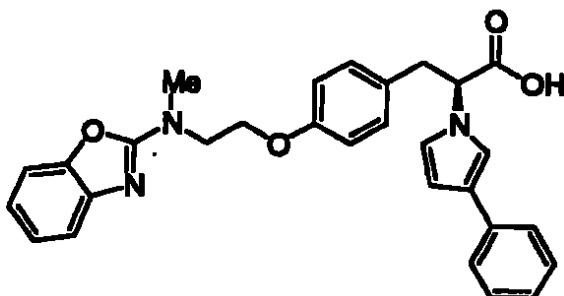
Se añadió éster metílico de tirosina (390 mg, 2,0 mmol) a una suspensión de 3-fenil-2,5-dimetoxi-tetrahidrofurano (500 mg, 2,4 mmol) y NaOAc (328 mg, 2,4 mmol) en H<sub>2</sub>O (10 ml) y HOAc (10 ml). Después se calentó a reflujo durante 1 hora, obteniéndose 562 mg (1,75 mmol) de éster metílico del ácido (S)-3-(4-hidroxi-fenil)-2-(3-fenil-pirrol-1-il)-propiónico (13) con un rendimiento del 87% en forma de un aceite amarillo pálido. C<sub>20</sub>H<sub>19</sub>NO<sub>3</sub> Peso Molecular: 321,370; M+1 (obs) = 322,1. <sup>1</sup>H RMN (400 MHz, CDCl<sub>3</sub>) δ : 7,47 (2H, d, J = 7,3 Hz), 7,30 (2H, t, J = 7,6, 7,8 Hz), 7,14 (1H, t, J = 7,3, 7,3 Hz), 7,01 (1H, s), 6,88 (2H, d, J = 8,3 Hz), 6,67 (1H, s), 6,67 (2H, d, J = 8,5 Hz), 6,43 (1H, s), 4,65 (1H, dd, J = 6,3, 8,4 Hz), 4,60 (1H, s), 3,71 (3H, s), 3,34 (1H, dd, J = 6,3, 13,9 Hz), 3,20 (1H, dd, J = 8,8, 13,9 Hz).

#### Ejemplo 5

25 Ácido (S)-3-{4-[2-(benzooxazol-2-il-metil-amino)-etoxi]-

fenil}-2-(3-fenil-pirrol-1-il)propiónico (16).

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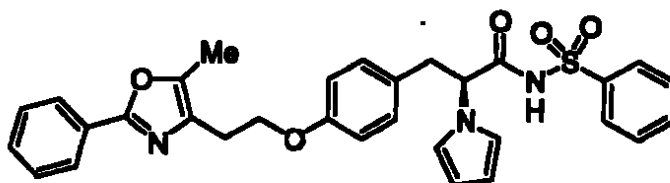
Se acopló éster metílico del ácido (S)-3-(4-hidroxifenil)-2-(3-fenil-pirrol-1-il)-propiónico (13) con 2-(benzooxazol-2-il-metil-amino)-etanol como en el Procedimiento General B (rendimiento 24%). La hidrólisis del éster como en el Procedimiento General A, dió ácido (S)-3-{4-[2-(benzooxazol-2-il-metil-amino)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-propiónico (16) con un rendimiento de 34%.  $C_{29}H_{27}N_3O_4$ . Peso Molecular: 481,543;  $M+1 = 482,2$ ;  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 7,49 (2H, d,  $J = 7,1$  Hz), 7,30 (5H, m), 7,13 (2H, dt,  $J = 1,5, 7,3$  Hz), 7,09 (1H, t,  $J = 2,0, 2,0$  Hz), 7,00 (2H, d,  $J = 8,3$  Hz), 6,77 (1H, t,  $J = 2,4, 2,7$  Hz), 6,73 (2H, d,  $J = 8,5$  Hz), 6,47 (1H, t,  $J = 2,0, 2,7$  Hz), 4,73 (1H, t,  $J = 7,6, 7,8$  Hz), 4,15 (1H, m), 4,02 (1H, m), 3,92 (1H, m), 3,80 (1H, m), 3,40 (1H, dd,  $J = 7,6, 13,9$  Hz), 3,26 (3H, s), 3,25 (1H, m).

#### Ejemplo 6

25 N-(S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-

2498

2-pirrol-1-il-propionil)-bencenosulfonamida (17).



17

Se disolvió (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (3) (275 mg, 0,661 mmol) en  $\text{CH}_2\text{Cl}_2$  (10 ml) en una atmósfera de  $\text{N}_2$  a  $23^\circ\text{C}$ , 5 después se añadió 1,1-carbonildiimidazol (128 mg, 0,793 mmol) y la solución se agitó durante 16 horas. En un matraz separado, se añadió una suspensión al 60% de hidruro sódico (26 mg, 0,661 mmol) a una solución agitada de bencenosulfonamida (124 mg, 0,793 mmol) en DMF seca (5 ml) 10 a  $-78^\circ\text{C}$  en una atmósfera de  $\text{N}_2$ . Después de 30 minutos, la solución se dejó equilibrar a  $23^\circ\text{C}$  durante 1 hora y después se transfirió gota a gota mediante una jeringa a la solución mencionada anteriormente de anhídrido mixto. Después de dos horas, la reacción se diluyó con  $\text{CH}_2\text{Cl}_2$  (50 15 ml) y se lavó con  $\text{H}_2\text{O}$  (20 ml), salmuera (20 ml) y se secó sobre  $\text{MgSO}_4$ . La cromatografía en gel de  $\text{SiO}_2$  con EtOAc al 30%/Hex dio la acilsulfonamida 17 (37 mg, 0,067 mmol) con un rendimiento del 10% en forma de un aceite transparente.  $\text{C}_{31}\text{H}_{29}\text{N}_3\text{O}_5\text{S}$ ; Peso Molecular: 555,645;  $M+1 = 556,0$ .  $^1\text{H}$  RMN (400 20 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8,01 (4H, m), 7,70 (1H, m), 7,55 (3H, m), 7,44



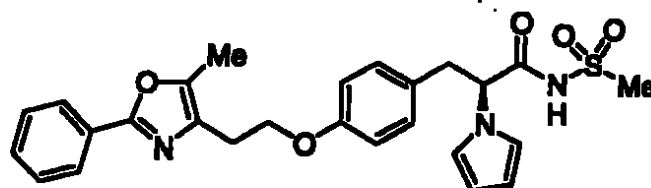
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(2H, d,  $J = 1,9$  Hz), 6,74 (2H, d,  $J = 8,5$  Hz), 6,67 (2H, d,  $J = 8,3$  Hz), 6,48 (2H, s), 6,21 (2H, s), 4,73 (1H, s), 4,55 (1H, dd,  $J = 4,4, 10,5$  Hz), 4,19 (2H, t,  $J = 6,3, 6,1$  Hz), 3,41 (1H, dd,  $J = 3,9, 14,6$  Hz), 3,02 (3H, m), 2,37 (3H, 5 s).

Ejemplo 7

N-(S)-(3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propionil)-metanosulfonamida (18).

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18

Usando el procedimiento descrito en el Ejemplo 6, el  
 15 ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
 fenil}-2-pirrol-1-il-propiónico (3) (200 mg, 0,481 mmol),  
 dio N-(S)-(3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
 fenil}-2-pirrol-1-il-propionil)-metanosulfonamida (18) (130  
 mg, 0,263) con un rendimiento del 55% en forma de un aceite  
 20 transparente, de una forma similar a la usada para obtener  
 N-(S)-(3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
 2-pirrol-1-il-propionil)-bencenosulfonamida (17).

$C_{26}H_{27}N_3O_5S$ ; Peso molecular: 493,576;  $M+1 = 494,2$ .  $^1H$  RMN (400  
 MHz,  $CDCl_3$ )  $\delta$ : 7,93 (2H, dd,  $J = 2,4, 7,8$  Hz), 7,4 (3H, m),  
 25 6,99 (1H, s), 6,85 (2H, d,  $J = 8,3$  Hz), 6,68 (2H, d,  $J =$

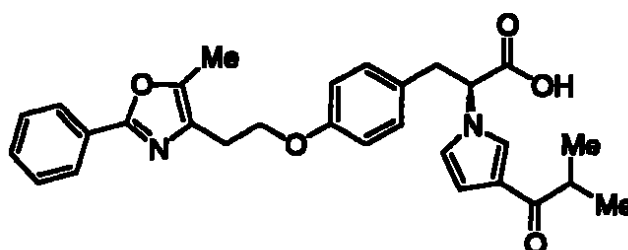
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8,5 Hz), 6,66 (2H, s), 6,03 (2H, s), 4,62 (1H, s a), 4,57 (1H, m), 4,13 (2H, t,  $J = 6,5, 6,8$  Hz), 3,35 (1H, dd,  $J = 5,1, 14,2$  Hz), 3,09 (1H, m), 3,09 (3H, s), 2,91 (2H, t,  $J = 6,6, 6,6$  Hz), 2,33 (3H, s).

### 5 Ejemplo 8

Ácido (S)-2-(3-isobutiril-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (21).

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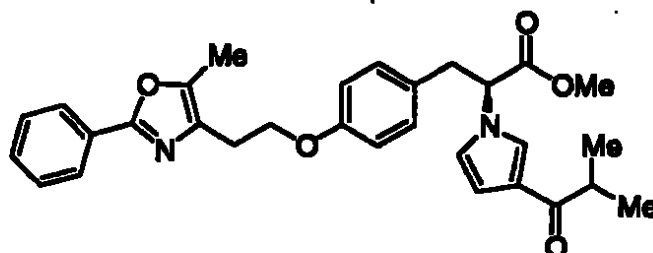


### 21

15 La hidrólisis de 107 mg del éster metílico del ácido (S)-2-(3-isobutiril-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (20) de acuerdo con el Procedimiento General A, dio el ácido (S)-2-(3-isobutiril-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (21) (23 mg, 0,047 mmol) con un rendimiento del 22% en forma de un aceite amarillo.  $C_{29}H_{30}N_2O_5$  Peso molecular para el ácido (S)-2-(3-isobutiril-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (21): 486,559;  $M-1 = 485,2$ .  $^1H$  RMN (400 25 MHz,  $CDCl_3$ )  $\delta$ : 7,96 (2H, dd,  $J = 2,2, 2,2$  Hz), 7,41 (3H, m),

7,31 (1H, t,  $J = 2,0, 2,0$  Hz), 6,92 (2H, d,  $J = 8,8$  Hz), 6,73 (2H, d,  $J = 8,8$  Hz), 6,69 (1H, d,  $J = 2,2$  Hz), 6,53 (1H, dd,  $J = 1,4, 2,9$  Hz), 4,72 (1H, dd,  $J = 7,1, 8,1$  Hz), 4,12 (2H, t,  $J = 6,6, 6,8$  Hz), 3,38 (1H, dd,  $J = 6,8; 13,9$  Hz), 3,17 (1H, dd,  $J = 8,1, 13,9$  Hz), 3,12 (1H, m), 2,99 (2H, t,  $J = 6,6, 6,6$  Hz), 2,37 (3H, s), 1,11 (6H, dd, 6,8, 8,8 Hz).

(a) El éster metílico del ácido (S)-2-(3-isobutiril-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-10 fenil}-propiónico (20) se preparó de la siguiente forma.

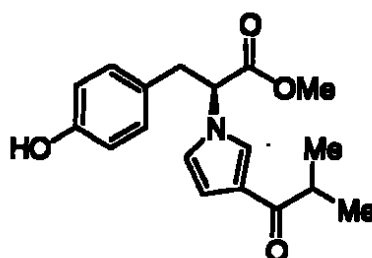


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Se acopló éster metílico del ácido (S)-2-(3-isobutiril-pirrol-1-il)-propiónico (19) (300 mg, 0,952 mmol) con 2-(5-metil-2-feniloxazol-4-il)etanol como en el Procedimiento General B, dando el éster metílico del ácido (S)-2-(3-isobutiril-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (20) (120 mg, 0,240 mmol) con un rendimiento del 25%.

(b) Éster metílico del ácido (S)-2-(3-isobutiril-pirrol-1-il)-propiónico (19)

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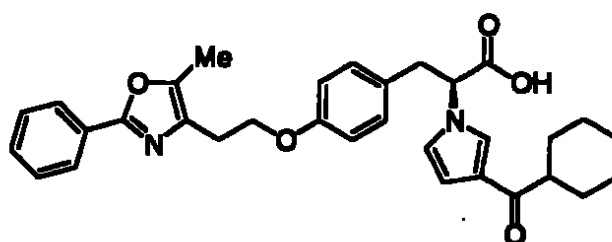
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Preparado de acuerdo con los Procedimientos Generales  
 10 C-E. El compuesto del título se obtuvo de una forma similar  
 a la usada para obtener el compuesto número 10 utilizando  
 cloruro de isobutirilo. RMN ( $\delta$ ;  $\text{CHCl}_3$ ); 7,22 (1H, s), 6,79  
 (2H, d,  $J = 8,5$  Hz), 6,69 (2H, d,  $J = 8,4$  Hz), 6,67 (1H,  
 m), 6,57 (1H, m), 4,68 (1H, m), 3,74 (3H, s), 3,34 (1H, m),  
 15 3,11 (2H, m), 1,13 (6H, t,  $J = 7,0, 7,0$  Hz), CIMS  $m/z$  316,1  
 ( $M^+$ ).

#### Ejemplo 9

Ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-{4-[2-(5-  
 metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (24).

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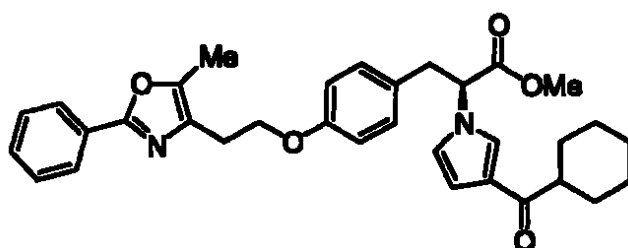
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Preparado a partir del éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (23) como en el Procedimiento General A.  $C_{32}H_{34}N_2O_5$  Peso Molecular: 526,623; 5  $M+1 = 527,2$ .  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 7,91 (2H, d,  $J = 3,7, 7,1$  Hz), 7,39 (3H, t,  $J = 3,2, 2,7$  Hz), 7,30 (1H, s), 6,89 (2H, m), 6,75 (2H, m), 6,75 (3H, m), 6,45 (1H, m), 4,68 (1H, m), 4,09 (2H, m), 3,34 (1H, m), 3,13 (1H, m), 2,95 (2H, m), 2,79 (1H, m), 2,34 (3H, s), 1,74 (5H, m), 10 1,66 (1H, m), 1,45 (2H, m), 1,26 (1H, m).

El éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (23) se preparó de la siguiente forma.

15 (a) Éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (23).

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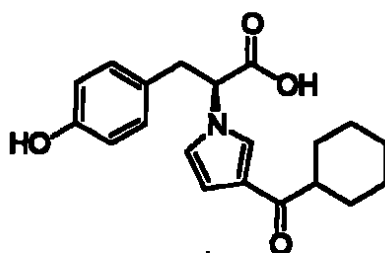
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Se acopló el éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-propiónico (22) con 2-(5-metil-2-feniloxazol-4-il)etanol de acuerdo con el 5 Procedimiento General B, dando el compuesto del título.

(b) Éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-propiónico (22)

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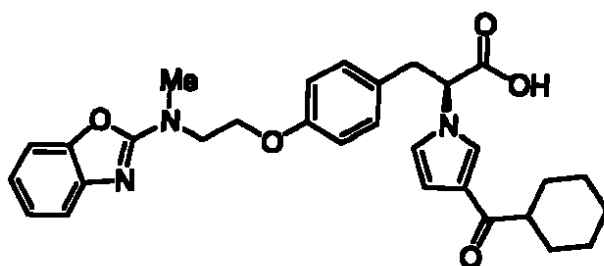
Se obtuvo el compuesto del título con un rendimiento 15 del 43% de una forma similar a la usada para la obtención del compuesto número 10, utilizando cloruro de ciclohexano carbonilo. RMN ( $\delta$ ;  $\text{CHCl}_3$ ); 6,80 (2H, d,  $J = 8,5$  Hz), 6,65 (2H, d,  $J = 8,5$  Hz), 6,63 (1H, s), 6,54 (1H, s), 4,90 (1H, s), 4,65 (1H, m), 3,71 (3H, s), 3,30 (1H, m), 3,13 (1H, m), 20 2,81 (1H, m), 1,79 (4H, m), 1,67 (1H, m), 1,45 (2H, m), 1,29 (3H, m).

#### Ejemplo 10

Ácido (S)-3-{4-[2-(benzooxazol-2-il-metil-amino)-etoxi]-fenil}-2-(3-ciclohexanocarbonil-pirrol-1-il)-propiónico

25 (26).

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La hidrólisis del éster metílico del ácido (S)-3-{4-[2-(benzooxazol-2-il-metil-amino)-etoxi]-fenil}-2-(3-ciclohexanocarbonil-pirrol-1-il)-propiónico (25) como en el

10 Procedimiento General A, dio el compuesto del título.  $C_{30}H_{33}N_3O_5$ . Peso Molecular: 515,600;  $M+1 = 516,2$ .  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 7,35 (2H, m), 7,34 (1H, s), 7,23 (1H, s), 7,15 (1H, dt =  $J = 1,0, 7,5$  Hz), 7,02 (1H, dt,  $J = 1,2, 7,8$  Hz), 6,97 (2H, d,  $J = 8,5$  Hz), 6,74 (1H, s), 6,72 (2H, d,  $J = 8,5$  Hz), 6,57 (1H, dd,  $J = 1,5, 2,9$  Hz), 4,73 (1H, t,  $J = 7,6, 7,6$  Hz), 4,07 (2H, m), 3,88 (2H, m), 3,37 (1H, dd,  $J = 7,6, 13,9$  Hz), 3,28 (3H, s), 3,18 (1H, dd,  $J = 7,6, 13,9$  Hz), 2,83 (1H, t,  $J = 8,8, 8,8$  Hz), 1,77 (4H, m), 1,66 (1H, m), 1,46 (2H, dd,  $J = 2,4, 3,9$  Hz), 1,27 (3H, m).

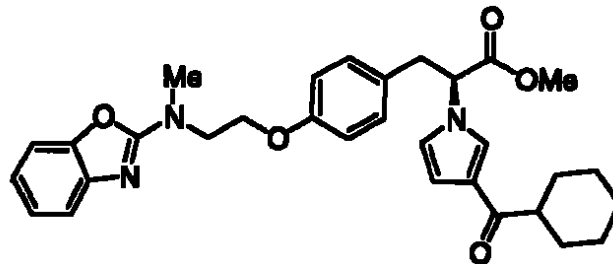
20 El éster metílico del ácido (S)-3-{4-[2-(benzooxazol-2-il-metil-amino)-etoxi]-fenil}-2-(3-ciclohexanocarbonil-pirrol-1-il)-propiónico (25) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-3-{4-[2-(benzooxazol-2-il-metil-amino)-etoxi]-fenil}-2-(3-ciclohexanocarbonil-

506

pirrol-1-il)-propiónico (25).

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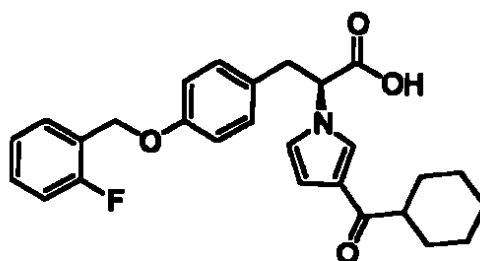


Preparado de acuerdo con el Procedimiento General B usando 2-(benzooxazol-2-il-metil-amino)-etanol como el alcohol. RMN ( $\delta$ ;  $\text{CHCl}_3$ ): 7,34 (1H, d,  $J = 7,5$  Hz), 7,25 (1H, s), 7,15 (1H, t,  $J = 7,5, 7,8$  Hz), 7,00 (1H, t,  $J = 7,5, 7,8$  Hz), 6,86 (2H, d,  $J = 8,3$  Hz), 6,73 (2H, d,  $J = 8,3$  Hz), 6,65 (1H, s), 6,55 (1H, s), 4,66 (1H, m), 4,20 (2H, t,  $J = 5,1, 5,1$  Hz), 3,92 (2H, t,  $J = 5,1, 5,1$  Hz), 3,72 (3H, s), 3,32 (1H, m), 3,32 (3H, s), 3,18 (1H, m), 2,81 (1H, m), 1,79 (4H, m), 1,65 (1H, m), 1,42 (2H, m), 1,22 (3H, m).

Ejemplo 11

Ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-[4-(2-fluorobenciloxi)-fenil]-propiónico (28).

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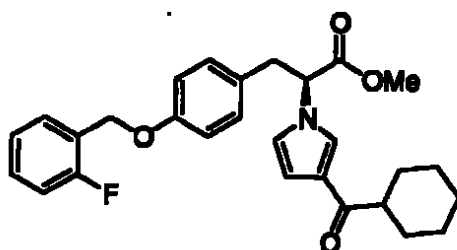
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La hidrólisis de éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-[4-(2-fluorobenciloxi)-fenil]-propiónico (27) de acuerdo con el Procedimiento General A, dio ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-[4-(2-fluorobenciloxi)-fenil]-propiónico (28) (20 mg, 0,044 mmol) con un rendimiento del 16% en forma de un aceite amarillo pálido.  $C_{27}H_{28}FNO_4$  Peso Molecular: 449,514;  $M+1 = 450,1$ .  $^1H$  RMN (400 MHz,  $CDCl_3$ )  $\delta$ : 7,46 (1H, t,  $J = 7,5, 7,5$  Hz), 7,20 (1H, m), 7,14 (1H, t,  $J = 7,3, 7,3$  Hz), 7,07 (1H, t,  $J = 9,0, 9,5$  Hz), 6,91 (2H, d,  $J = 8,5, 8,5$  Hz), 6,90 (1H, s), 6,84 (2H, d,  $J = 8,5, 8,5$  Hz), 6,66 (1H, s), 6,58 (1H, s), 5,06 (2H, s), 4,74 (1H, m), 3,40 (1H, m), 3,22 (1H, m), 2,83 (1H, t,  $d = 12,2, 12,2$  Hz), 1,80 (2H, m), 1,68 (2H, m), 1,47 (3H, m), 1,29 (3H, m).

El éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-[4-(2-fluorobenciloxi)-fenil]-propiónico (27) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-[4-(2-fluorobenciloxi)-fenil]-propiónico (27).

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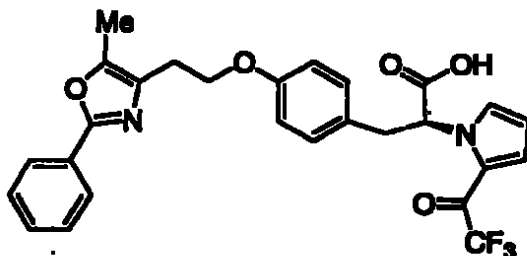
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De acuerdo con el Procedimiento General B, por acoplamiento del éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-propiónico (27) con alcohol 2-fluorobencilo. El compuesto del título se aisló con un rendimiento del 70%.

#### Ejemplo 12

Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-propiónico (33).



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De acuerdo con el Procedimiento General A. A una solución agitada de éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-propiónico (32) (2,608 g,

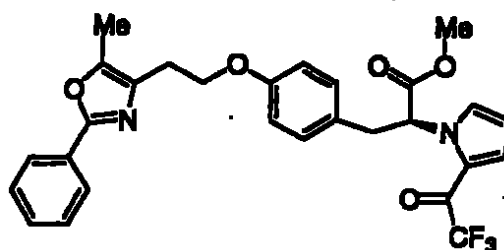
509

4,7 mmol) en 2-metoxi etanol (8 ml) y agua (2 ml) se le añadió hidróxido de litio (113 mg). La mezcla de reacción se agitó a temperatura ambiente durante 20 minutos, se vertió en agua, se acidificó con HCl acuoso, se extrajo con 5 EtOAc y se secó sobre MgSO<sub>4</sub>. El disolvente se retiró a presión reducida. El residuo restante se purificó por cromatografía sobre gel de sílice eluyendo con 1:1 de EtOAc:Hexano. La espuma blanca resultante se recrystalizó usando acetato de etilo:hexano, dando cristales blancos con 10 forma de aguja blanca. Rendimiento = 1,232 g, 51%. P.f. 187-188°C. 500 MHz <sup>1</sup>H RMN (CDCl<sub>3</sub>) δ 7,87 (m, 2H), 7,35 (m, 3H), 7,17 (m, 1H), 7,0 (s, 1H, a), 6,80 (d, 2H, J = 8 Hz), 6,66 (d, 2H, J = 8 Hz), 6,15 (m, 1H), 4,07 (t, 2H, J = 6,7 Hz), 3,41 (d, d 1H J = 14,4, 5,0) 3,11 (dd, 1H J = 14,4, 15 9,28), 2,89 (m, 2H), 2,29 (s, 3H); MS m/z 513 (M+1), 514 Análisis Calculado para C<sub>27</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> C, 63,28; H, 4,52; N, 5,47 encontrado: C, 63,19; H, 4,48; N, 5,27.

El éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-[2-(2,2,2-trifluoro- 20 acetil)-pirrol-1-il]-propiónico (32) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-propiónico (32).

166



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32

Procedimiento 32-A: A una solución agitada de éster metílico del ácido (S)-3-(4-hidroxi-fenil)-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-propiónico (31) (1,0 g, 2,93 mmol) en THF anhidro (10 ml) se le añadió trifenilfosfina (768 mg, 2,93 mmol) y 2-(5-metil-2-feniloxazol-4-il)etanol (595 mg, 2,93 mmol). Se añadió gota a gota una solución de azodicarboxilato de dietilo (DEAD) (461  $\mu$ l, 2,93 mmol) en THF anhidro (5 ml) y la mezcla de reacción se agitó a 15 temperatura ambiente durante 48 horas. El disolvente se retiró a presión reducida, dando un aceite amarillo.

Procedimiento 32-B: A una solución agitada del éster metílico del ácido (S)-3-(4-hidroxi-fenil)-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-propiónico (32) (800 mg, 2,34 mmol) en THF anhidro (10 ml) se le añadió trifenilfosfina (615 mg, 2,34 mmol) y 2-(5-metil-2-feniloxazol-4-il)etanol (476 mg, 2,34 mmol). Se añadió gota a gota una solución de azodicarboxilato de diisopropilo (DIAD) (369  $\mu$ l, 2,34 mmol) en THF anhidro (5 ml) y la 25 mezcla de reacción se agitó a temperatura ambiente durante

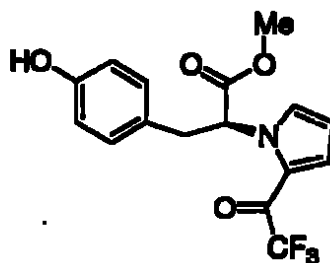
511

48 horas. El disolvente se retiró a presión reducida, dando un aceite amarillo.

Las mezclas de reacción de los Procedimientos 32-A y 32-B reunidas se combinaron y purificaron por cromatografía 5 eluyendo con 1:10 a 1:1 de EtOAc:Hexano. El compuesto del título se aisló en forma de un aceite opaco (2,608 g, rendimiento 89%). 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  7,96 (m, 2H), 7,39 (m, 3H), 7,18 (m, 1H), 7,0 (s, 1H, a), 6,79 (d, 2H  $J$  = 8,3 Hz), 6,68 (d, 2H,  $J$  = 8,3 Hz), 6,20 (m, 1H), 4,15 (t, 10 2H,  $J$  = 6,6 Hz), 3,70 (s, 3H), 3,43 (d,d 1H  $J$  = 14,4, 5,12) 3,12 (dd, 1H,  $J$  = 14,4, 9,5), 2,92 (t, 2H,  $J$  = 6,6), 2,32 (s, 3H); MS  $m/z$  526 ( $M+1$ ), 527.

(b) Éster metílico del ácido (S)-3-(4-hidroxi-fenil)-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-propiónico (31).

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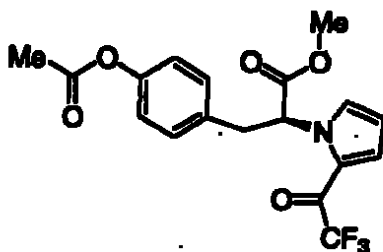
31

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A una solución agitada de éster metílico del ácido (S)-3-(4-acetoxi-fenil)-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-propiónico (30) (2,13 g, 5,57 mmol) en metanol anhidro (20 ml) se le añadió  $\text{K}_2\text{CO}_3$  (770 mg, 5,57 mmol). La 25 mezcla de reacción se agitó a temperatura ambiente durante

20 minutos y se vertió en agua, se acidificó con HCl acuoso, se extrajo con EtOAc, se secó sobre MgSO<sub>4</sub> y el disolvente se retiró a presión reducida, dando un aceite amarillo pálido. (1,826 g, rendimiento del 96%). 500 MHz <sup>1</sup>H RMN (CDCl<sub>3</sub>) δ 7.19 (m, 1H), 7.1 (s, 1H, a), 6.79 (d, 2H J = 8,6 Hz), 6.62 (d, 2H, J = 8,6 Hz), 6.22 (m, 1H), 4.67 (s, 1H), 3.72 (s, 3H), 3.44 (d, d 1H J = 14,4, 5,4), 3.12 (dd, 1H J = 14,4, 9,8), 2.01 (s, 3H); MS m/z 342 (M+1), 343.

(c) Éster metílico del ácido (S)-3-(4-acetoxi-fenil)-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-propiónico (30).



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30

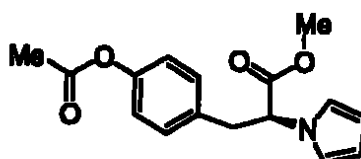
A una solución agitada de éster metílico del ácido (S)-3-(4-acetoxi-fenil)-2-[pirrol-1-il]-propiónico (29) (2,9 g, 10,1 mmol) en CH<sub>2</sub>Cl<sub>2</sub> (20 ml) se le añadió anhídrido trifluoroacético (1,71 ml, 12,1 mmol) y ácido trifluorometanosulfónico (1,07 µl, 12,1 mmol). La mezcla de reacción se volvió de color naranja. La mezcla de reacción se agitó durante 5 minutos y se vertió en una solución de NH<sub>4</sub>Cl, se extrajo con EtOAc y se secó (MgSO<sub>4</sub>). El disolvente se retiró a presión reducida. El aceite naranja resultante

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se purificó por cromatografía con 1:10 a 1:1 de EtOAc:Hexano, dando el producto deseado en forma de un aceite transparente (2,13 g, rendimiento 55%) 500 MHz,  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$ : 7,21 (m, 1H), 7,19 (s, 1H, a), 6,94 (d, 2H  $J$  = 8,6 Hz), 6,90 (d, 2H,  $J$  = 8,6 Hz), 6,23 (m, 1H), 3,72 (s, 3H), 3,51 (dd, 1H,  $J$  = 14,4, 5,4), 3,18 (dd, 1H  $J$  = 14,4, 9,5), 2,23 (s, 3H); MS  $m/z$  384 (M+1), 385.

(d) Éster metílico del ácido (S)-3-(4-acetoxi-fenil)-2-[pirrol-1-il]-propiónico (29).

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29

15 A una solución agitada del éster metílico del ácido (S)-3-(4-hidroxifeníl)-2-[pirrol-1-il]-propiónico 1 (10 g, 40 mmol) en  $\text{CH}_2\text{Cl}_2$  (100 ml) se le añadieron 2,6-lutidina (9,5 ml, 81,6 mmol) y cloruro acetilo (5,8 ml, 8,16 mmol). La mezcla de reacción se agitó a temperatura ambiente  
20 durante una noche. La mezcla de reacción se vertió en agua, se extrajo con EtOAc, se secó ( $\text{MgSO}_4$ ) y el disolvente se retiró a presión reducida. El aceite residual se purificó por cromatografía con 1:5 de EtOAc:hexano y el producto se obtuvo en forma de un aceite transparente (8,25 g, 71%).  
25 500 MHz,  $^1\text{H}$  RMN ( $\text{CDCl}_3$ ) 6,96 (d, 2H,  $J$  = 8,8 Hz), 6,91 (d,

514

2H,  $J = 8,8$  Hz), 6,67 (t, 2H,  $J = 2,0$  Hz), 6,11 (t, 2H,  $J = 2,0$  Hz), 4,68 (dd, 1H,  $J = 6,3, 8,8$ ), 3,67 (s, 3H), 3,37 (dd, 1H,  $J = 14,4, 6,3$ ), 3,25 (dd, 1H  $J = 14,4, 8,8$ ) 2,24 (s, 3H); MS  $m/z$  288 (M+1), 289.

### 5 Ejemplo 13

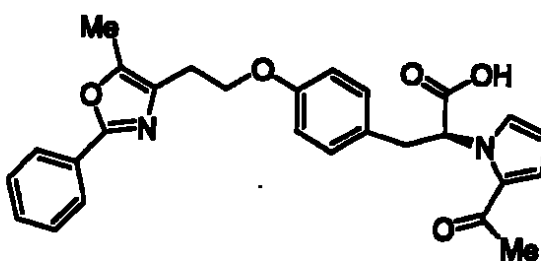
Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-4-il-propiónico (34, PD 0330732).

Este compuesto se sintetizó como se describe para el Compuesto 33 usando acetato de etil 4-piridilo como el material de partida.  $^1\text{H}$  RMN  $d_6$ -DMSO  $\delta$ : 2,30 (s, 3H), 2,85 (m, 3H), 3,02 (m, 2H), 4,11 (t, 2H), 6,80 (d, 2H), 7,06 (d, 2H), 7,44 (m, 3H), 7,65 (d, 2H), 7,84 (d, 2H), 8,63 (s, 2H), MS(M-44) (minus carboxilato): 385,1. Análisis Calculado para  $\text{C}_{26}\text{H}_{24}\text{O}_4\text{N}_2 \cdot 1,67 \text{ H}_2\text{O}$ : C, 68,05; H, 5,82; N, 15 6,11. Encontrado: C, 68,03; H, 6,00; N, 6,11.

### Ejemplo 14

Ácido (S)-2-(2-acetil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (37).

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37 .

25 Se hidrolizó el éster metílico del ácido (S)-2-(2-

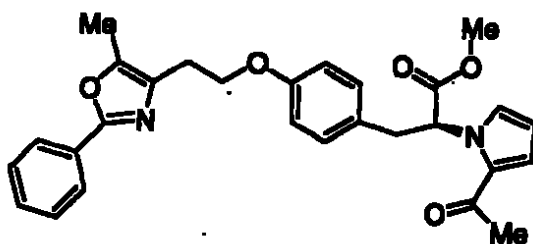


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acetil-pirrol-1-il)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-propiónico (36) (601 mg, 1,27 mmol) como se describe en el Procedimiento General A, dando el compuesto del título en forma de una espuma blanca (129 mg, 5 rendimiento 22%). P.f. 110°C-112°C. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$ : 7,91 (m, 2H), 7,37 (m, 3H), 6,95 (m, 1H), 6,87 (m, 3H, a), 6,70 (d, 2H,  $J = 8,6$  Hz), 6,09 (m, 1H), 4,12 (t, 2H,  $J = 6,8$  Hz), 3,47 (d, d 1H  $J = 14,4, 4,0$ ), 3,15 (dd, 1H  $J = 14,4, 9,0$ ), 2,90 (t, 2H,  $J = 6,8$  Hz), 2,37 (s, 3H), 2,31 10 (s, 3H); MS  $m/z$  459 (M+1), 460.

El éster metílico del ácido (S)-2-(2-acetil-pirrol-1-il)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-propiónico (36) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-2-(2-acetil-pirrol-1-il)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-propiónico (36).



36

Procedimiento 36-A: A una solución agitada del éster metílico del ácido (S)-2-(2-acetil-pirrol-1-il)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-propiónico (35) (500 mg, 1,74 mmol) en THF

anhidro (15 ml) se le añadió trifenilfosfina (685 mg, 2,61 mmol) y 2-(5-metil-2-feniloxazol-4-il)etanol (388 mg, 1,91 mmol). Se añadió gota a gota una solución de DEAD (411 µl, 2,61 mmol) en THF anhidro (5 ml) y la mezcla de reacción se 5 agitó a temperatura ambiente durante 48 horas. El disolvente se retiró a presión reducida y el residuo se obtuvo en forma de un aceite amarillo.

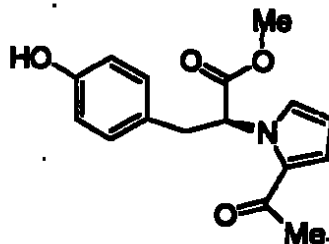
Procedimiento 36-B: A una solución agitada de éster metílico del ácido (S)-2-(2-acetil-pirrol-1-il)-3-(4-10 [hidroxi]-fenil)-propiónico (35) (500 mg, 1,74 mmol) en THF anhidro (15 ml) se le añadió trifenilfosfina (685 mg, 2,61 mmol) y 2-(5-metil-2-feniloxazol-4-il) etanol (388 mg, 1,91 mmol). Se añadió gota a gota una solución de DIAD (514 µl, 2,61 mmol) en THF anhidro (5 ml) y la mezcla de reacción se 15 agitó a temperatura ambiente durante 48 horas. El disolvente se retiró a presión reducida y el residuo se obtuvo en forma de un aceite amarillo.

Los productos brutos de las reacciones 36-A y 36-B se combinaron y se purificaron por cromatografía con 1:10 a 20 1:1 de acetato de etilo:hexano, dando el compuesto del título en forma de un aceite opaco. (601 mg, rendimiento del 73%). 500 MHz, <sup>1</sup>H RMN (CDCl<sub>3</sub>) δ 7,94 (m, 2H), 7,40 (m, 3H), 6,92 (m, 1H), 6,88 (s, 1H, a), 6,82 (m, 2H), 6,61 (m, 2H), 6,09 (m, 1H), 4,12 (t, 2H, J = 6,8 Hz), 3,69 (s, 3H), 25 3,42 (dd 1H J = 14,2, 5,37), 3,12 (dd, 1H J = 14,4, 9,76),

2,91 (t, 2H,  $J = 6,8$  Hz), 2,35 (s, 3H), 2,31 (s, 3H); MS  $m/z$  473 (M+1), 474.

(b) Éster metílico del ácido (S)-2-(2-acetil-pirrol-1-il)-3-{4-[hidroxi]-fenil}-propiónico (35).

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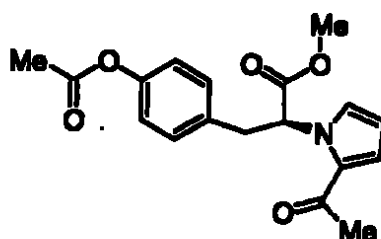
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Se desaciló el intermedio del éster metílico del ácido (S)-2-(2-acetil-pirrol-1-il)-3-{4-[acetoxi]-fenil}-propiónico intermedio (34) de acuerdo con el Procedimiento General C. El producto se purificó por cromatografía con EtOAc:Hexano 1:1, dando un aceite transparente que se solidificó tras reposo (1,756 g, rendimiento del 88%). 500 MHz,  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  6,93 (m, 1H), 6,83 (d, 2H  $J = 8,3$  Hz), 6,63 (d, 2H,  $J = 8,3$  Hz), 6,10 (m, 1H), 5,37 (s, 1H, a), 3,68 (s, 3H), 3,40 (d,d 1H  $J = 24,2, 5,6$  Hz), 3,12 (dd, 1H  $J = 14,2, 9,52$ ), 2,35 (s, 3H), MS  $m/z$  288 (M+1), 289.

(c) Éster metílico del ácido (S)-2-(2-acetil-pirrol-1-il)-3-{4-[acetoxi]-fenil}-propiónico (34).

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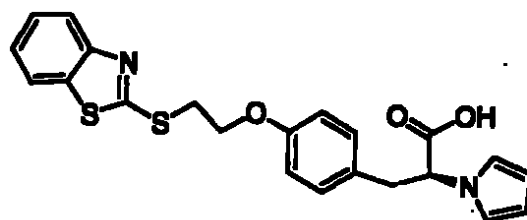
De acuerdo con los Procedimientos Generales D y E. A una solución agitada del éster metílico del ácido (S)-3-(4-acetoxi-fenil)-2-[pirrol-1-il]-propiónico (30) (4,40 g, 10 1,53 mmol) en CH<sub>2</sub>Cl<sub>2</sub> (50 ml) se le añadió cloruro de acetilo (1,31 ml, 18,4 mmol) y ácido trifluorometanosulfónico (1,63 ml, 18,4 mmol). La mezcla de reacción se volvió de color naranja. La mezcla de reacción se agitó durante 5 minutos y se vertió en una solución de NH<sub>4</sub>Cl, se extrajo con EtOAc y 15 se secó (MgSO<sub>4</sub>). El disolvente se retiró al vacío. El aceite naranja resultante se purificó por cromatografía con 1:2 de EtOAc:Hexano, dando el producto deseado en forma de un aceite transparente (2,27 g, 45%). 500 MHz, <sup>1</sup>H RMN (CDCl<sub>3</sub>) δ 6,96 (d, 2H J = 8,3 Hz), 6,92 (m, 2H), 6,89 (d, 2H, J = 8,3 20 Hz), 6,10 (m, 1H), 3,70 (s, 3H), 3,47 (d,d 1H J = 14,4, 5,62 Hz), 3,12 (dd, 1H J = 14,4, 9,52), 2,35 (s, 3H), 2,24 (s, 3H), MS, m/z 330 (M+1), 331.

#### Ejemplo 15

Ácido 3-{4-[2-(benzotiazol-2-ilsulfanil)-etoxi]-fenil}-2-25 pirrol-1-il-propiónico (39).

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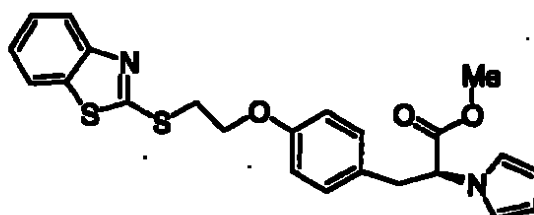
De acuerdo con el Procedimiento General A. Se  
 10 hidrolizó el éster metílico del ácido 3-{4-[2-(benzotiazol-  
 2-ilsulfanil)-etoxi]-fenil}-2-pirrol-1-il-propiónico  
 intermedio (38), dando un sólido blanco que se recristalizó  
 usando EtOAc y Hexano, dando un polvo blanco cristalino  
 (390 mg, 79%). P.f. 165°C-166°C; 500 MHz,  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$   
 15 7,85 (d, 1H,  $J = 8,05$  Hz), 7,75 (d, 8,05 Hz), 7,42 (m, 1H),  
 7,30 (m, 1H), 6,91 (d, 2H,  $J = 8,54$  Hz), 6,82 (d, 2H,  $J =$   
 8,54 Hz), 6,69 (m, 2H), 6,14 (m, 2H), 4,72 (dd, 1H,  $J =$   
 5,86, 8,79 Hz), 4,31 (t, 2H,  $J = 6,59$  Hz), 3,70 (t, 2H,  $J =$   
 6,59 Hz), 3,38 (d,d 1H  $J = 14,16, 5,86$  Hz), 3,22 (dd, 1H  $J$   
 20 = 14,16, 8,79); MS  $m/z$  404 ( $M+1$ ).

El éster metílico del ácido (S)-3-{4-[2-(benzotiazol-  
 2-ilsulfanil)-etoxi]-fenil}-2-pirrol-1-il-propiónico (38)  
 se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-3-{4-[2-(benzotiazol-  
 25 2-ilsulfanil)-etoxi]-fenil}-2-pirrol-1-il-propiónico (38).

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176



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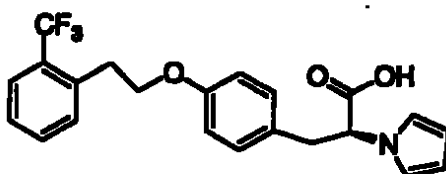
10 De acuerdo con el Procedimiento General B. A una  
solución agitada del éster metílico del ácido (S)-3-(4-  
hidroxi-fenil)-2-[pirrol-1-il]-propiónico (1) (828 mg, 3,38  
mmol) en THF anhidro (15 ml) se le añadió trifenilfosfina  
(886 mg, 3,38 mmol) y 2-(benzotiazol-2-ilsulfanil)-etanol  
15 (800 mg, 3,38 mmol). Se añadió gota a gota una solución de  
DIAD (665  $\mu$ l, 3,38 mmol) en THF anhidro (5 ml) y la mezcla  
de reacción se agitó a temperatura ambiente durante 48  
horas. El disolvente se retiró a presión reducida y el  
residuo se purificó por cromatografía con 1:10 a 1:1 de  
20 EtOAc:Hexano. El producto se obtuvo en forma de un aceite  
opaco. Rendimiento = 510 mg, 29%. 500 MHz,  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$   
7,85 (d, 1H,  $J = 8,06$  Hz), 7,75 (d, 8,06 hz), 7,40 (m, 1H),  
7,30 (m, 1H), 6,90 (d, 2H  $J = 8,8$  Hz), 6,83 (d, 2H,  $J = 8,8$   
Hz), 6,70 (m, 2H), 6,14 (m, 2H), 4,68 (dd, 1H,  $J = 6,34$ ,  
25 8,79 Hz), 4,32 (t, 2H,  $J = 6,59$  Hz), 3,71 (t, 2H,  $J = 6,59$

521

Hz), 3,693 (s, 3H), 3,33 (d,d 1H  $J = 13,9, 6,59$  Hz), 3,19 (dd, 1H  $J = 13,9, 8,79$ ); MS  $m/z$  439 (M+1).

### Ejemplo 16

Ácido (S)-2-pirrol-1-il-3-{4-[2-(2-trifluorometil-fenil)-5 etoxi]-fenil}-propiónico (41).



41

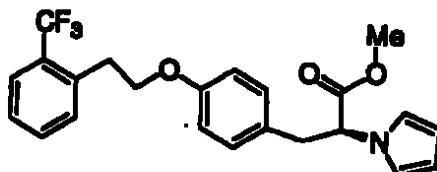
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Preparado a partir del éster metílico del ácido (S)-2-pirrol-1-il-3-{4-[2-(2-trifluorometil-fenil)-etoxi]-fenil}-propiónico (40) usando el procedimiento de hidrólisis descrito en el Procedimiento General A. El ácido (S)-2-  
 15 pirrol-1-il-3-{4-[2-(2-trifluorometil-fenil)-etoxi]-fenil}-propiónico (42) se obtuvo en forma de un aceite transparente (454 mg, rendimiento 45%)  $\delta$  7,85 (d, 1H,  $J = 8,05$  Hz), 7,45 (m, 2H), 7,33 (t, 1H,  $J = 8,05$  Hz), 6,90 (d, 1H,  $J = 8,54$ ), 6,75 (d, 2H,  $J = 8,54$ ), 6,69 (m, 2H), 6,15  
 20 (m, 2H), 4,73 (dd, 1H,  $J = 5,86, 9,3$ ), 4,12 (t, 2H,  $J = 6,84$ ), 3,37 (dd, 1H,  $J = 13,9, 5,86$ ), 3,25 (m, 5H), MS  $m/z$  425 (M+1) Análisis Calculado para  $C_{22}H_{20}F_3NO_3$  C, 65,50; H, 5,00; N, 3,47 encontrado: C, 64,92; H, 5,15; N, 3,28.

El éster metílico del ácido (S)-2-pirrol-1-il-3-{4-[2-  
 25 (2-trifluorometil-fenil)-etoxi]-fenil}-propiónico (40) se

preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-2-pirrol-1-il-3-{4-[2-(2-trifluorometil-fenil)-etoxi]-fenil}-propiónico (40).



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De acuerdo con el Procedimiento General B. Preparado a partir del éster metílico del ácido (S)-3-(4-hidroxifenil)-2-[pirrol-1-il]-propiónico intermedio (1) y 2-(2-trifluorometil-fenil)-etanol. Se obtuvo el éster metílico del ácido (S)-2-pirrol-1-il-3-{4-[2-(2-trifluorometil-fenil)-etoxi]-fenil}-propiónico (40) en forma de un aceite opaco (1,04 g, rendimiento del 61%).  $\delta$  7,64 (d, 1H,  $J$  = 7,8 Hz), 7,46 (m, 2H), 7,33 (t, 1H,  $J$  = 7,8), 6,89 (d, 1H,  $J$  = 6,59), 6,75 (d, 2H,  $J$  = 6,59), 6,69 (m, 2H), 6,14 (m, 2H), 4,68 (dd, 1H,  $J$  = 6,59, 8,78), 4,12 (t, 2H,  $J$  = 6,8), 3,69 (s, 3H), 3,33 (dd, 1H,  $J$  = 13,9; 6,59), 3,25 (t, 2H,  $J$  = 6,8), 3,16 (dd, 1H,  $J$  = 13,9, 8,78); MS  $m/z$  418 (M+1).

#### Ejemplo 17

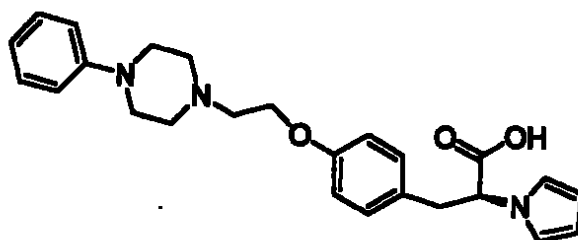
Ácido (S)-3-{4-[2-(4-fenil-piperazin-1-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (43).

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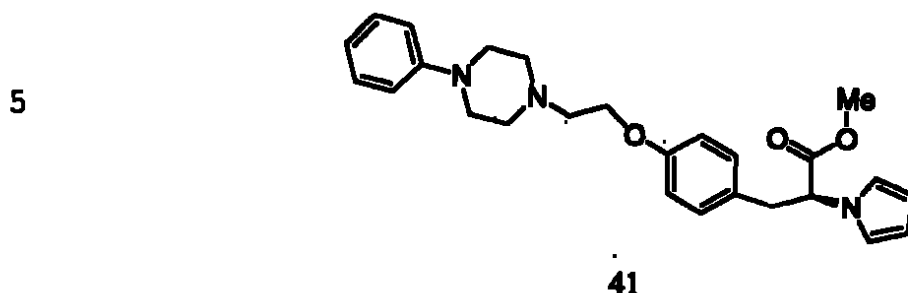
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Preparado a partir del éster metílico del ácido (S)-3-{4-[2-(4-phenylpiperazin-1-yl)-etoxi]-fenil}-2-pirrol-1-il-  
15 propiónico (42) usando el procedimiento de hidrólisis descrito en el Procedimiento General A, dando el producto deseado en forma de una espuma rosa. Rendimiento = 270 mg, 38%. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  7,28 (m, 2H), 7,09 (d, 2H,  $J$  = 9 Hz), 7,18 (m, 1H), 6,90 (m, 3H), 6,73 (m, 4H), 6,10 (m, 20 2H), 4,65 (d, d 1H,  $J$  = 5,85, 8,79 Hz), 4,125 (t, 2H,  $J$  = 5,15 Hz), 3,40 (dd, 1H  $J$  = 13,7, 8,79), 3,27-3,08 (m, 11H); MS  $m/z$  420 ( $M+1$ ), 419 ( $M-1$ ).

El éster metílico del ácido (S)-3-{4-[2-(4-phenylpiperizín-1-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (42)  
25 se preparó de la siguiente forma.

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(a) Éster metílico del ácido (S)-3-{4-[2-(4-fenil-piperizina-1-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (42).



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15 De acuerdo con el Procedimiento General B. Preparado a partir del éster metílico del ácido (S)-3-(4-hidroxifenil)-2-[pirrol-1-il]-propiónico intermedio (1) y 2-(4-fenil-piperazin-1-il)-etanol. El éster metílico del ácido (S)-3-{4-[2-(4-fenil-piperazin-1-il)-etoxi]-fenil}-2-

20 pirrol-1-il-propiónico (41) se obtuvo en forma de un aceite transparente (740 mg, rendimiento del 70%). 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  7,26 (m, 2H), 6,91 (d, 2H,  $J = 9$  Hz), 6,98-6,76 (m, 5H), 6,70 (m, 2H), 6,14 (m, 2H), 4,69 (d,d 1H,  $J = 6,95, 8,79$  Hz), 4,12 (t, 2H,  $J = 7,08$  Hz); 3,69 (s, 3H),

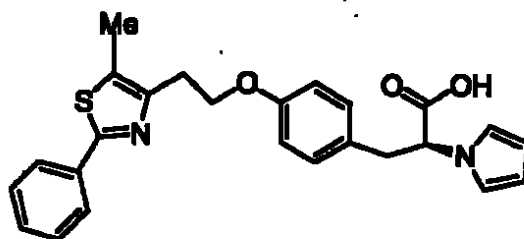
25 3,43 (dd, 1H  $J = 6,35, 13,9$ ), 3,21-3,16 (m, 5H), 2,85 (s a,

2H), 2,73 (s a, 4H); MS  $m/z$  434 (M+1).

### Ejemplo 18

Ácido (S)-3-{4-[2-(5-metil-2-fenil-tiazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (45).

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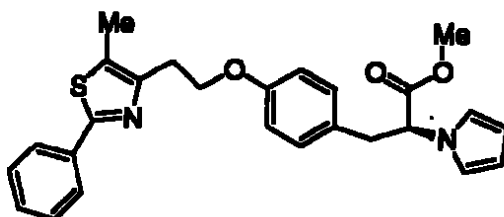
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Preparado a partir del éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-tiazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (44) usando el procedimiento de hidrólisis  
15 descrito en el Procedimiento General A. El producto se  
recristalizó a partir de acetato de etilo y hexano, dando  
el producto deseado en forma de agujas blancas. Rendimiento  
= 1,20 g, 58%. P.F. = 157-158°C.  $^1\text{H}$  RMN (500 MHz)  $\text{CDCl}_3$   $\delta$   
7,80 (2H, m), 7,34 (3H, m), 6,87 (d, 2H  $J$  = 8,5 Hz), 6,73  
20 (2H, d,  $J$  = 8,5 Hz), 6,66 (2H, m), 6,11 (2H, m), 4,68 (1H,  
dd,  $J$  = 6,35, 8,79 Hz), 4,20 (2H, t, 6,83 Hz), 3,34 (1H,  
dd,  $J$  = 6,1, 13,9 Hz), 3,17 (1H, dd,  $J$  = 8,79, 13,9 Hz),  
3,12 (2H, t,  $J$  = 6,59 Hz), 2,40 (3H, s). Análisis Calculado  
para  $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ : C 69,42; H, 5,59; N 6,48 encontrado: C,  
25 69,41; H, 5,53; N, 6,29 MS  $m/z$  433 (M+1), 431 (M-1).

El éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-tiazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (44) se preparó de la siguiente forma.

(a) Ácido (S)-3-{4-[2-(5-metil-2-fenil-tiazol-4-il)-5 etoxi]-fenil}-2-pirrol-1-il-propiónico (44).



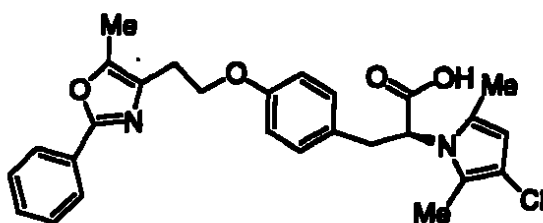
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De acuerdo con el Procedimiento General B. Preparado a partir del éster metílico del ácido (S)-3-(4-hidroxifenil)-2-[pirrol-1-il]-propiónico intermedio (1) y 2-(5-metil-2-fenil-tiazol-4-il)-etanol. El ácido (S)-3-{4-[2-(5-metil-2-fenil-tiazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (44) se obtuvo en forma de un aceite transparente. Rendimiento = 2,15 g, 59%.  $^1\text{H}$  RMN (500 MHz)  $\text{CDCl}_3$   $\delta$ : 7,82 (2H, m), 7,35 (3H, m), 6,84 (m, 2H), 6,73 (2H, m), 6,66 (2H, m), 6,10 (2H, m), 4,65 (1H, dd,  $J$  = 6,59, 8,78 Hz), 4,23 (2H, t, 6,83 Hz), 3,65 (3H, m), 3,30 (1H, dd,  $J$  = 6,59, 13,9 Hz), 3,17-3,11 (3H, m), 2,41 (3H, s), MS  $m/z$  447 (M+1).

#### Ejemplo 19

25 Ácido (S)-2-(3-cloro-2,5-dimetil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (49).

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Preparado a partir del éster metílico del ácido 2-(3-cloro-2,5-dimetil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico ` intermedio (48)

10 usando el procedimiento de hidrólisis descrito en el Procedimiento General A. El producto se purificó por cromatografía y se recrystalizó en EtOAc/hexano, dando el producto deseado en forma de un polvo blanco cristalino. Rendimiento = 158 mg, 25%.  $^1\text{H}$  RMN (500 MHz)  $\text{CDCl}_3$   $\delta$ : 7,98

15 (2H, m), 7,43 (3H, m), 6,75 (dd, 4H,  $J = 9,0$  Hz), 5,75 (1H, s), 4,70 (1H, dd,  $J = 4,64, 10,25$  Hz), 4,19 (2H, t, 6,59 Hz), 3,30 (1H, dd,  $J = 4,64, 14,16$  Hz), 3,08 (1H, dd,  $J = 14,16, 10,25$  Hz), 2,98 (2H, t, 6,59), 2,37 (3H, s), 1,99 (3H, s a), 1,88 (3H, s a) MS  $m/z$  479 (M+1) 477 (M-1).

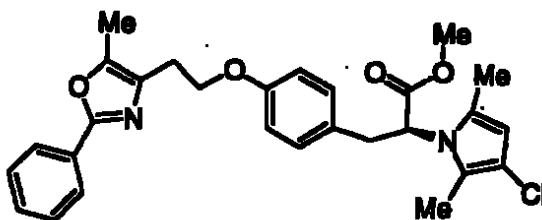
20 El éster metílico del ácido (S)-2-(3-cloro-2,5-dimetil-pirrol-1-il)-3-{4-[acetoxi]-fenil}-propiónico (48) se preparó a partir de la siguiente forma.

(a) Éster metílico del ácido (S)-2-(3-cloro-2,5-dimetil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (48).

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(48).



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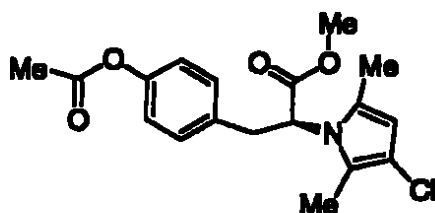
5 A una solución agitada del éster metílico del ácido (S)-2-(3-cloro-2,5-dimetil-pirrol-1-il)-3-{4-[acetoxi]-fenil}-propiónico (674 mg, 1,93 mmol) descrito en el Ejemplo 47 en metanol anhidro (10 ml) se le añadió K<sub>2</sub>CO<sub>3</sub> (266 mg, 1,93 mmol). La reacción se agitó a temperatura ambiente durante 40 minutos, se vertió en EtOAc, se lavó con agua, se secó (MgSO<sub>4</sub>) y el disolvente se retiró al vacío, dando el éster metílico del ácido 2-(3-cloro-2,5-dimetil-pirrol-1-il)-3-{4-[hidroxi]-fenil}-propiónico en forma de un aceite. Este material se usó en la reacción de acoplamiento del Procedimiento General B.

20 A una solución agitada del éster metílico del ácido (S)-2-(3-cloro-2,5-dimetil-pirrol-1-il)-3-{4-[hidroxi]-fenil}-propiónico (47) en THF (10 ml) a temperatura ambiente se le añadió trifenilfosfina (541 mg, 2,06 mmol) y 2-(5-metil-2-feniloxazol-4-il)etanol (541 mg, 2,06 mmol). Se añadió gota a gota una solución de DIAD (406 µl, 2,06 mmol) en THF anhidro (5 ml) y la mezcla de reacción se

agitó a temperatura ambiente durante 72 horas. Después, el disolvente se retiró al vacío y el residuo se purificó por cromatografía eluyendo con 1:10 de EtOAc:hexano a 1:1 de EtOAc:hexano. Esto dio el producto deseado en forma de un 5 aceite transparente. Rendimiento = 651 mg, 68%.  $^1\text{H}$  RMN (500 MHz)  $\text{CDCl}_3$ ,  $\delta$ : 7,95 (2H, m), 7,40 (3H, m), 6,76 (m, 4H), 5,75 (1H, s), 4,65 (1H, dd,  $J = 4,64, 10,25$  Hz), 4,20 (2H, t, 6,59 Hz), 3,78 (3H, s), 3,42 (1H, dd,  $J = 4,64, 14,16$  Hz), 3,06 (1H, dd,  $J = 14,16, 10,25$  Hz), 2,91 (2H, t, 6,59), 2,30 (3H, s), 1,90 (3H, s a), 1,82 (3H, s a), MS  $m/z$  493 (M+1), 492 (M-1).

(b) Éster metílico del ácido (S)-2-(3-cloro-2,5-dimetil-pirrol-1-il)-3-{4-[acetoxi]-fenil}-propiónico (47).

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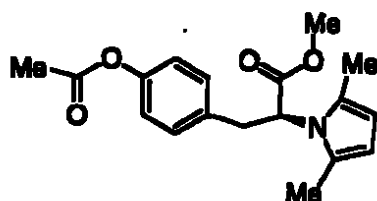
47

20 A una solución agitada del éster metílico del ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-{4-[acetoxi]-fenil}-propiónico (46) (2,45 g, 7,77 mmol) en THF (20 ml) a 0°C se le añadió N-clorosuccinamida (1,04 g, 7,77 mmol). Después de 30 minutos, el disolvente se retiró al vacío y el 25 residuo se purificó por cromatografía con 1:10 a 1:1 de

530

EtOAc:Hexano, dando un aceite amarillo. Rendimiento = 674 mg, 25%.  $^1\text{H}$  RMN (500 MHz)  $\text{CDCl}_3$   $\delta$ : 6,92-6,83 (m, 4H), 5,71 (s, 1H), 4,66 (1H, dd,  $J = 4,64, 10,01$  Hz), 3,49 (1H, dd,  $J = 4,64, 14,16$  Hz), 3,08 (1H, dd,  $J = 14,16, 10,01$  Hz), 2,235 (3H, s), 2,30 (3H, s), 1,92 (3H, s a), 1,82 (3H, s a) MS  $m/z$  350 (M+1) 348 (M-1).

(c) Éster metílico del ácido (S)-2-(2,5-dimetilpirrol-1-il)-3-{4-[acetoxi]-fenil}-propiónico (46).



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A una solución agitada de éster metílico de L-tirosina (25 g, 0,128 mol) en tolueno (300 ml) se le añadió 2,5-hexandiona (15 ml, 0,128 mol) y ácido p-toluenosulfónico (1,22 g, 6,4 mmol). La mezcla se calentó a reflujo con un purgador Dean-Stark durante 12 horas. El disolvente se retiró al vacío y el residuo se redisolvió en acetato de etilo y se filtró a través de un lecho de gel de sílice. El disolvente se retiró al vacío y el producto, un aceite amarillo, se usó en la siguiente etapa sin purificación adicional. 500 MHz,  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  6,60 (d, 2H,  $J = 6,6$  Hz), 6,47 (d, 2H,  $J = 8,5$  Hz), 5,47 (s, 2H), 4,90 (dd, 1H,

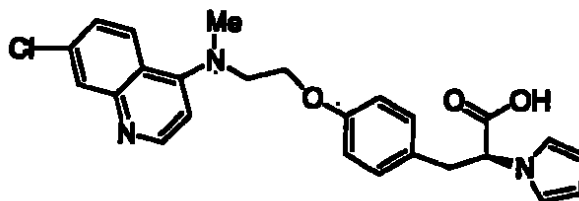


$J = 11,2, 4,3 \text{ Hz}$ ), 3,63 (s, 3H), 3,24 (dd, 1H,  $J = 13,9, 4,3 \text{ Hz}$ ), 2,92 (d, 1H,  $J = 13,9, 11,2 \text{ Hz}$ ), 1,85 (s, 6H); MS  $m/z$  274 (M+1).

Después, se disolvió el éster metílico del ácido (S)-5 2-(2,5-dimetil-pirrol-1-il)-3-(4-hidroxí-fenil)-propiónico en diclorometano (300 ml) y se añadieron cloruro de acetilo (9,1 ml, 0,128 mol) y 2,6 lutidina (14,9 ml, 0,128 mol). La mezcla de reacción se agitó durante una noche y después se vertió en acetato de etilo y se extrajo con salmuera. La 10 capa orgánica se secó sobre  $\text{MgSO}_4$  y el disolvente se retiró al vacío, dando un aceite pardo. Éste se purificó por cromatografía con acetato de etilo:hexano 1:5 a 1:1, dando un aceite transparente. Rendimiento = 22,14 g 55%.  $^1\text{H}$  RMN 500 MHz ( $\text{CDCl}_3$ )  $\delta$  6,89-6,83 (m, 4H), 5,70 (s, 2H), 4,70 (dd, 1H,  $J = 9,77, 4,88 \text{ Hz}$ ), 3,72 (s, 3H), 3,50 (dd, 1H,  $J = 13,9, 4,88 \text{ Hz}$ ), 3,11 (dd, 1H,  $J = 13,9, 9,77 \text{ Hz}$ ), 2,23 (3H, s), 1,93 (s, 6H); MS  $m/z$  316 (M+1), 314 (M-1).

#### Ejemplo 20

Ácido (S)-3-(4-{2-[(7-cloro-quinolin-4-il)-metil-amino]-20 etoxi}-fenil)-2-pirrol-1-il-propiónico (51)



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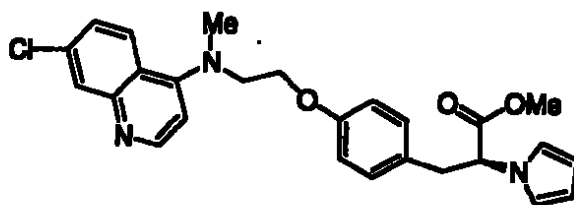
32

Se hidrolizó el éster metílico del ácido 3-(4-{2-[(7-cloro-quinolin-4-il)-metil-amino]-etoxi}-fenil)-2-pirrol-1-il-propiónico (50) usando el procedimiento descrito en el Procedimiento General A para producir ácido 3-(4-{2-[(7-cloro-quinolin-4-il)-metil-amino]-etoxi}-fenil)-2-pirrol-1-il-propiónico, 253 mg, 19%. <sup>1</sup>H RMN 500 MHz, (d<sub>6</sub> DMSO) δ 8,59 (1H, d, J = 5,13 Hz), 8,22 (1H, d, J = 9,03 Hz), 7,90 (1H, d, J = 2,13 Hz), 7,46 (1H, d, J = 9,03 Hz), 6,95 (1H, d, J = 5,13 Hz), 6,85 (1H, d, J = 8,05), 6,66-6,64 (4H, m), 5,80 (2H, s), 4,20 (1H, s a), 4,17 (2H, s a), 3,60 (2H, s a), 3,26-3,19 (1H, m), 2,96 (3H, s), 2,91-2,88 (1H, m) MS m/z 448 (M-1).

El éster metílico del ácido (S)-3-(4-{2-[(7-cloro-quinolin-4-il)-metil-amino]-etoxi}-fenil)-2-pirrol-1-il-propiónico se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-3-(4-{2-[(7-cloro-quinolin-4-il)-metil-amino]-etoxi}-fenil)-2-pirrol-1-il-propiónico (50).

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De acuerdo con el Procedimiento General B. A una 25 solución agitada del éster metílico del ácido 3-(4-hidroxi-

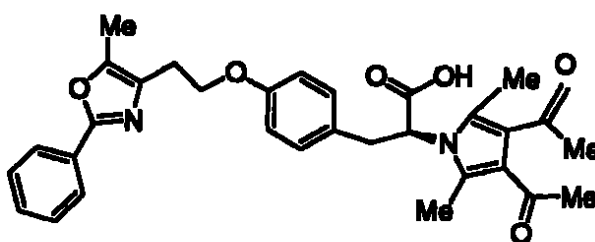
533

fenil)-2-[pirrol-1-il]-propiónico descrito en el ejemplo 1 (828 mg, 3,38 mmol) en THF anhidro (15 ml) se le añadió trifenilfosfina (886 mg, 3,38 mmol) y 2-[(7-cloro-4-quinolil)metilamino]etanol (800 mg, 3,38 mmol). Se le  
5 añadió gota a gota una solución de DIAD (665 µl, 3,38 mmol) en THF anhidro (5 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 48 horas. El disolvente se retiró al vacío y el residuo se purificó por cromatografía con 1:10 de EtOAc/Hexano a 1:1 de EtOAc/Hexano. El producto  
10 se obtuvo en forma de un aceite. Rendimiento = 1,36 g 87%. MS  $m/z$  464 (M+1), 462 (M-1).

#### Ejemplo 21

Ácido (S)-2-(3-acetil-2,5-dimetil-pirrol-1-il)-3-{4-[2-(4-metil-2-fenil-oxazol-5-il)-etoxi]-fenil}-propiónico (55).

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Preparado a partir del éster metílico del ácido (S)-2-(3-acetil-2,5-dimetil-pirrol-1-il)-3-{4-[2-(4-metil-2-fenil-oxazol-5-il)-etoxi]-fenil}-propiónico (54) descrito en el Procedimiento General A. El producto deseado se  
25 obtuvo en forma de un polvo cristalino de color crema.

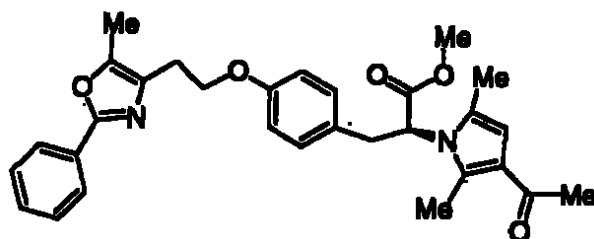
534

Rendimiento = 148 mg.

El éster metílico del ácido (S)-2-(3-acetil-2,5-dimetil-pirrol-1-il)-3-{4-[2-(4-metil-2-fenil-oxazol-5-il)-etoxi]-fenil}-propiónico (54) se preparó de la siguiente 5 forma.

(a) Éster metílico del ácido (S)-2-(3-acetil-2,5-dimetil-pirrol-1-il)-3-{4-[2-(4-metil-2-fenil-oxazol-5-il)-etoxi]-fenil}-propiónico (54).

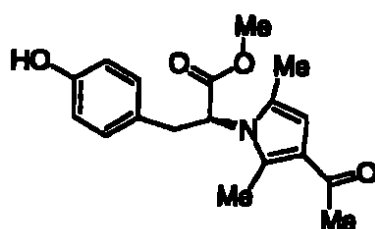
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15 Preparado a partir del éster metílico del ácido (S)-2-(3-acetil-2,5-dimetil-pirrol-1-il)-3-{4-[hidroxi]-fenil}-propiónico (53) y 2-(5-metil-2-feniloxazol-4-il)etanol usando el procedimiento descrito en el Procedimiento General B. El producto deseado se obtuvo en forma de un 20 aceite incoloro. Rendimiento = 474 mg.

(b) Éster metílico del ácido (S)-2-(3-acetil-2,5-dimetil-pirrol-1-il)-3-{4-[hidroxi]-fenil}-propiónico (53).

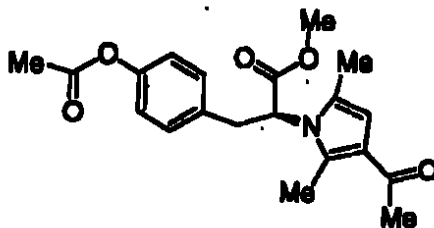


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Se desacetiló el éster metílico del ácido 2-(3-acetil-2,5-dimetil-pirrol-1-il)-3-{4-[acetoxi]-fenil}-propiónico (52) usando el procedimiento descrito en el Ejemplo 32. El 10 producto se purificó usando cromatografía con 1:1 de EtOAc:Hexano y se obtuvo el producto en forma de un aceite que solidificó tras reposo dando un sólido blanco cristalino. Rendimiento = 487 mg, 72%.

(c) Éster metílico del ácido (S)-2-(3-acetil-2,5-15 dimetil-pirrol-1-il)-3-{4-[acetoxi]-fenil}-propiónico (52).



52

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A una solución agitada del éster metílico del ácido 2-(2,5-dimetil-pirrol-1-il)-3-{4-[acetoxi]-fenil}-propiónico (2,45 g, 7,77 mmol) en  $\text{CH}_2\text{Cl}_2$ , se le añadió cloruro de 25 acetilo y ácido trifluorometanosulfónico. El disolvente se

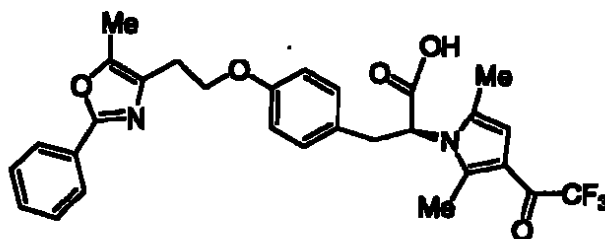
536

retiró al vacío. El residuo se purificó por cromatografía con 1:10 a 1:1 de EtOAc:Hexano dando el compuesto del título en forma de un aceite amarillo. Rendimiento = 674 mg, 25%.

5 Ejemplo 22

Ácido (S)-2-[2,5-dimetil-3-(2,2,2-trifluoro-acetil)-pirrol-1-il]-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (59).

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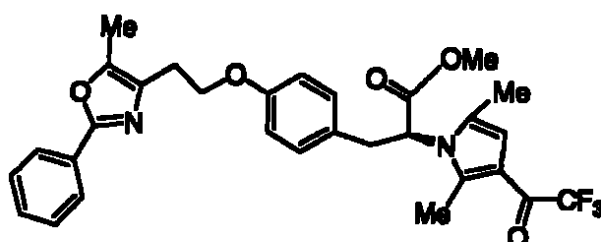
59

15 De acuerdo con el Procedimiento General A. Preparado a partir del éster (58) (1,48 g, 2,62 mmol), dando el producto deseado en forma de un polvo blanco. 0,50 g, 34%. Espectro de Masas (M+1), 541 (M-1) 539.

El éster metílico del ácido (S)-2-[2,5-dimetil-3-  
20 (2,2,2-trifluoro-acetil)-pirrol-1-il]-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (58) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-2-[2,5-dimetil-3-(2,2,2-trifluoro-acetil)-pirrol-1-il]-3-{4-[2-(5-metil-2-  
25 fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (58).

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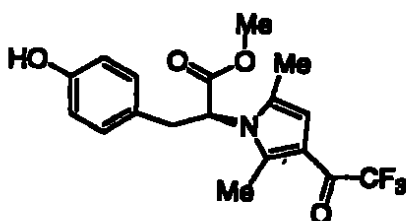


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Preparado de acuerdo con el Procedimiento General B usando el éster metílico del ácido (S)-2-[2,5-dimetil-3-(2,2,2-trifluoro-acetil)-pirrol-1-il]-3-{4-[hidroxi]-fenil}-propiónico (57) (1,08 g, 2,9 mmol) dando el producto deseado aislado por cromatografía con 1:10: 1:1 acetato de etilo: hexano en forma de una espuma blanca. Rendimiento = 1,48 g, 92% Espectro de Masas (M+1), 555 (M-1) 553.

(b) Éster metílico del ácido (S)-2-[2,5-dimetil-3-(2,2,2-trifluoro-acetil)-pirrol-1-il]-3-{4-[hidroxi]-fenil}-propiónico (57).



57

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Preparado a partir del intermedio descrito en el ejemplo. El éster metílico del ácido (S)-2-[2,5-dimetil-3-(2,2,2-trifluoro-acetil)-pirrol-1-il]-3-{4-[acetoxi]-

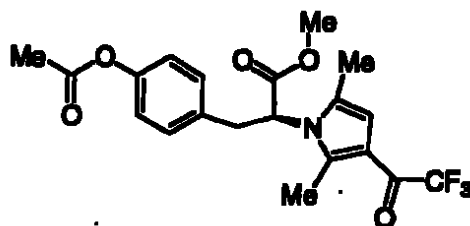
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538

fenil}-propiónico (56) se desacetiló usando el procedimiento descrito en Procedimiento General C. El producto se purificó usando cromatografía con 1:1 de EtOAc:Hexano y el producto se obtuvo en forma de un aceite 5 que solidificó tras reposo dando un sólido blanco cristalino. Rendimiento = 4,5 g, 81% (M+1) 370 (M-1) 368.

(c) Éster metílico del ácido (S)-2-[2,5-dimetil-3-(2,2,2-trifluoro-acetil)-pirrol-1-il]-3-{4-[acetoxi]-fenil}-propiónico (57).

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A una solución agitada del éster metílico del ácido 2-(2,5-dimetil-pirrol-1-il)-3-{4-[acetoxi]-fenil}-propiónico (6,0 g, 19 mmol) en CH<sub>2</sub>Cl<sub>2</sub> (50 ml) se le añadió anhidro trifluoroacético (4,0 ml, 28,5 mmol) y ácido 20 trifluorometanosulfónico (4,0 ml, 28,5 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 20 minutos. La mezcla de reacción se vertió en una solución de cloruro amónico y se extrajo con acetato de etilo. La capa orgánica se secó (MgSO<sub>4</sub>) y el disolvente se retiró al vacío. 25 El residuo se purificó por cromatografía con 1:10 a 1:1 de

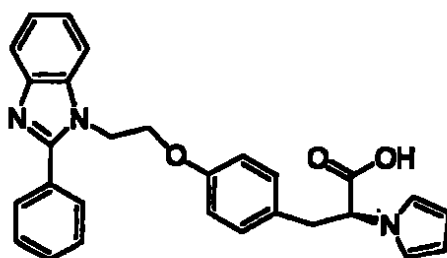


539

EtOAc:Hexano dando un aceite amarillo. Rendimiento = 6,22 g, 805 (M+1) 412 (M-1) 410.

Ejemplo 23

Ácido 3-{4-[2-(2-fenil-bencimidazol-1-il)-etoxi]-fenil}-2-  
5 pirrol-1-il-propiónico (61).



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61

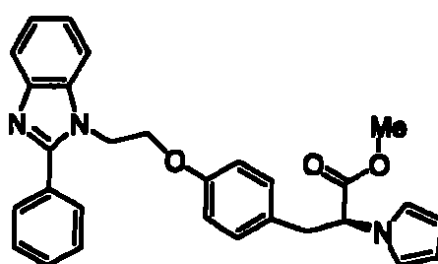
Preparado a partir del éster metílico del ácido 3-{4-[2-(2-fenil-benzimidazol-1-il)-etoxi]-fenil}-2-pirrol-1-il-  
15 propiónico (60) usando el procedimiento de hidrólisis descrito en el Procedimiento General A, dando el producto deseado en forma de una espuma blanca. Rendimiento = 697 mg, 65% P.f. 210-212°C. (M+1) 452, (M-1) 450.

El éster metílico del ácido 3-{4-[2-(2-fenil-  
20 benzimidazol-1-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (60) se preparó de la siguiente forma.

(a) Éster metílico del ácido 3-{4-[2-(2-fenil-benzimidazol-1-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (60).

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196



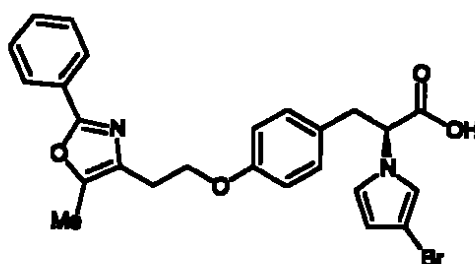
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Preparado a partir del éster metílico del ácido 3-(4-hidroxifenil)-2-[pirrol-1-il]-propiónico intermedio (1) descrito en el Ejemplo 1 y 2-(2-fenil-bencimidazol-1-il)-  
10 etanol usando el procedimiento descrito en el Procedimiento General B. El producto deseado se obtuvo en forma de una espuma blanca. 1,125 g, rendimiento del 71%. M+1 (obs) = 466

#### Ejemplo 24

15 Ácido 2-(3-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (64).



64

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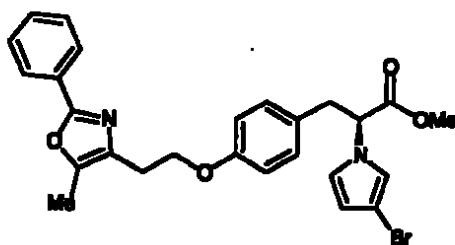
Una mezcla del éster metílico del ácido (S)-2-(3-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
25 etoxi]-fenil}-propiónico (64) (150 mg, 0,29 mmol) e

hidróxido de litio (35 mg, 1,47 mmol) en 2-metoxietanol (4 ml) y agua (1 ml) se agitó a temperatura ambiente durante 1 hora. La mezcla se vertió en agua, se acidificó con HCl acuoso 2 N, se extrajo con EtOAc y se secó sobre MgSO<sub>4</sub>. El 5 disolvente se retiró a presión reducida, produciendo el ácido propiónico deseado (125 mg, 87%) en forma de un sólido blanco. 500 MHz <sup>1</sup>H RMN (CDCl<sub>3</sub>) δ 7,96 (m, 2H), 7,43 (m, 3H), 6,92 (d, 2H, J = 8,5 Hz), 6,74 (m, 3H), 6,57 (m, 1H), 6,12 (m, 1H), 4,63 (dd, 1H, J = 8,3, 6,8 Hz), 4,16 (t, 10 2H, J = 6,6 Hz), 3,33 (dd, 1H, J = 13,9, 6,8 Hz), 3,14 (dd, 1H, J = 13,9, 8,3 Hz), 2,98 (t, 2H, J = 6,6 Hz), 2,37 (s, 3H); MS m/z 495, 497 (M+1).

El éster metílico del ácido (S)-2-(3-bromo-pirrol-1-il)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-15 propiónico (63) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-2-(3-bromo-pirrol-1-il)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-propiónico (63).

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63

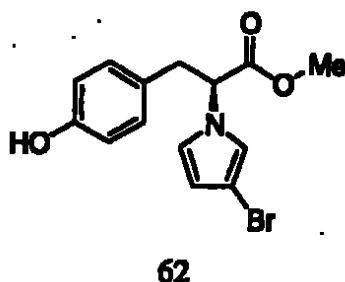
25 De acuerdo con el Procedimiento General B. A una

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solución agitada del éster metílico del ácido (S)-2-(2-bromo-pirrol-1-il)-3-(4-hidroxifenil)-propiónico (63) (1,00 g, 3,08 mmol), trifenilfosfina (809 mg, 3,08 mmol) y 2-(5-metil-2-fenil-oxazol-4-il)-etanol (626 mg, 3,08 mmol) 5 en THF (15 ml) se le añadió gota a gota una solución de azodicarboxilato de dietilo (500  $\mu$ l, 3,08 mmol) en THF (4 ml). La mezcla se agitó durante una noche y después se concentró. El residuo se cromatografió sobre gel de sílice eluyendo con EtOAc al 30%-40% en hexanos, produciendo el 10 producto acoplado (590 mg, 38%) en forma de un aceite amarillo. 500 MHz,  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  7,99 (m, 2H), 7,43 (m, 3H), 6,87 (m, 2H), 6,73 (m, 3H), 6,55 (m, 1H), 6,11 (m, 1H), 4,59 (dd, 1H,  $J = 9,0, 6,1$  Hz), 4,20 (t, 2H,  $J = 6,6$  Hz), 3,71 (s, 3H), 3,29 (dd, 1H,  $J = 13,9, 6,1$  Hz), 3,14 15 (dd, 1H,  $J = 13,9, 9,0$  Hz), 2,97 (t, 2H,  $J = 6,6$  Hz), 2,36 (s, 3H); MS  $m/z$  509, 511 ( $M+1$ ).

(b) Éster metílico del ácido (S)-2-(3-bromo-pirrol-1-il)-3-(4-hidroxifenil)-propiónico (62).

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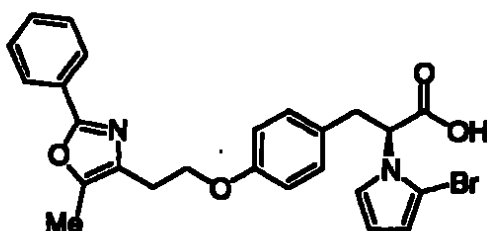
25 A una solución agitada y enfriada ( $-78^\circ\text{C}$ ) del éster

543

metílico del ácido (S)-3-(4-hidroxifenil)-2-pirrol-1-il-propiónico (1,00 g, 4,08 mmol) en THF (20 ml) se le añadió N-bromosuccinimida (724 mg, 4,08 mmol). La mezcla resultante se calentó a 0°C y se agitó durante 3 horas. El disolvente se retiró a presión reducida y el residuo se cromatografió sobre gel de sílice eluyendo con EtOAc al 17%-27% en hexanos, produciendo el producto deseado (1,08 g, 82%) en forma de un aceite pardo claro. 500 MHz <sup>1</sup>H RMN (CDCl<sub>3</sub>) δ 6,86 (d, 2H, J = 8,5 Hz), 6,71 (m, 3H), 6,55 (m, 1H), 6,11 (m, 1H), 4,59 (dd, 1H, J = 9,0, 6,3), 3,71 (s, 3H), 3,29 (dd, 1H, J = 13,9, 6,3), 3,12 (dd, 1H, J = 13,9, 9,0); MS m/z 325 (M+1).

#### Ejemplo 25

Ácido 2-(2-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (67).



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Preparado por el procedimiento descrito en el Procedimiento General A a partir del éster metílico del ácido (S)-2-(2-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (67), produciendo el

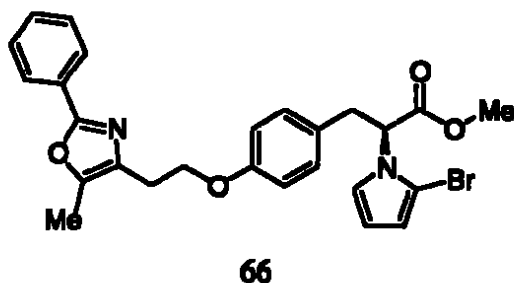
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ácido propiónico deseado (93%) en forma de un sólido blanquecino. 500 MHz,  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  7,95 (m, 2H), 7,41 (m, 3H), 6,94 (m, 2H), 6,88 (m, 1H), 6,75 (m, 2H), 6,18 (t, 1H,  $J = 3,4$  Hz), 6,10 (m, 1H), 5,10 (dd, 1H,  $J = 8,8$ , 6,1 5 Hz), 4,15 (m, 2H), 3,41 (dd, 1H,  $J = 14,2$ , 6,1 Hz), 3,18 (dd, 1H,  $J = 14,2$ , 8,8 Hz), 2,96 (m, 2H), 2,35 (s, 3H); MS  $m/z$  495, 497 ( $M+1$ ).

El éster metílico del ácido (S)-2-(2-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-10 propiónico (66) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-2-(2-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (66).

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66

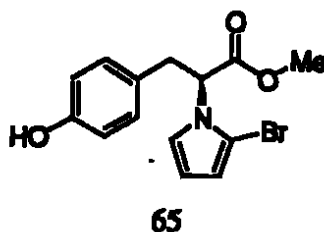
20 Preparado por el procedimiento descrito en el Procedimiento General B a partir del éster metílico del ácido (S)-2-(2-bromo-pirrol-1-il)-3-(4-hidroxifenil)-propiónico (65), produciendo una mezcla de material de partida y el producto deseado. A una solución del residuo 25 (0,61 mmol) en acetonitrilo (10 ml) se le añadió

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trietilamina (110  $\mu$ l, 0,93 mmol) y cloruro de benzoilo (130  $\mu$ l, 0,93 mmol). La mezcla se agitó a temperatura ambiente durante 30 minutos y el disolvente se retiró a presión reducida. El residuo se cromatografió sobre gel de sílice 5 eluyendo con EtOAc al 20%-30% en hexanos, produciendo el éster deseado (190 mg, total 12%) en forma de un aceite amarillo. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  7,97 (m, 2H), 7,41 (m, 3H), 6,89 (m, 3H), 6,76 (d, 2H,  $J = 8,5$  Hz), 6,17 (m, 1H), 6,09 (m, 1H), 5,05 (dd, 1H,  $J = 9,0, 6,1$  Hz), 4,19 (t, 2H, 10  $J = 6,6$  Hz), 3,71 (s, 3H), 3,35 (dd, 1H,  $J = 14,2, 6,1$  Hz), 3,15 (dd, 1H,  $J = 14,2, 9,0$  Hz), 2,95 (t, 2H,  $J = 6,6$  Hz), 2,35 (s, 3H); MS  $m/z$  509, 511 ( $M+1$ ).

(b) Éster metílico del ácido (S)-2-(2-bromo-pirrol-1-il)-3-(4-hidroxifenil)-propiónico (65).

15



20 A una solución agitada y enfriada ( $-78^\circ\text{C}$ ) del éster metílico del ácido (S)-3-(4-hidroxifenil)-2-pirrol-1-il-propiónico (1,00 g, 4,08 mmol) en THF (20 ml) se le añadió N-bromosuccinimida (724 mg, 4,08 mmol). La mezcla resultante se agitó a  $-78^\circ\text{C}$  durante 15 minutos, después se 25 calentó a  $0^\circ\text{C}$  y se agitó durante 3 horas. El disolvente se

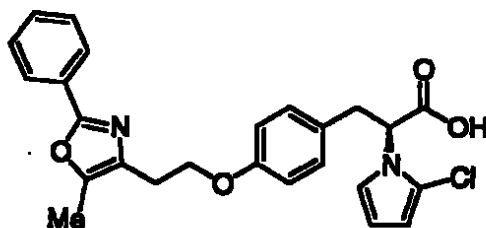
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retiró a presión reducida y el residuo se cromatografió sobre gel de sílice eluyendo con EtOAc al 17%-27% en hexanos, produciendo el pirrol deseado (1,01 g, 77%) en forma de un aceite pardo claro. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  6,89 (m, 3H), 6,69 (d, 2H,  $J = 8,5$  Hz), 6,18 (m, 1H), 6,09 (m, 1H), 5,05 (dd, 1H,  $J = 9,0, 6,3$  Hz), 3,72 (s, 3H), 3,35 (dd, 1H,  $J = 14,2, 6,3$  Hz), 3,15 (dd, 1H,  $J = 14,2, 9,0$  Hz); MS  $m/z$  324, 236 ( $M+1$ ).

#### Ejemplo 26

10 Ácido 2-(2-cloro-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (70).

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Preparado por el procedimiento descrito en el Procedimiento General A. La hidrólisis del éster metílico (70) produjo el ácido deseado (59%) en forma de un sólido blanco. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  8,03 (m, 2H), 7,44 (m, 3H), 6,93 (m, 2H), 6,75 (m, 2H), 6,13 (m, 1H), 6,00 (m, 1H),

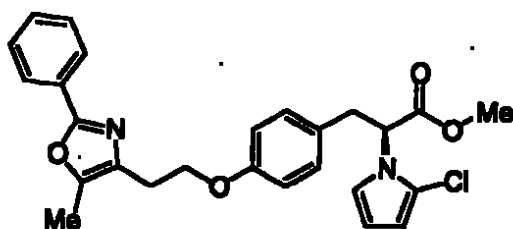


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5,08 (dd, 1H,  $J = 9,0, 6,1$  Hz), 4,20 (t, 2H,  $J = 6,4$  Hz), 3,40 (dd, 1,  $J = 14,2, 6,1$  Hz), 3,19 (d, 1H,  $J = 14,2, 9,0$  Hz), 3,00 (t, 2H,  $J = 6,4$  Hz), 2,37 (s, 3H); MS  $m/z$  451, 453 (M+1).

5 El éster metílico del ácido (S)-2-(2-cloro-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (69) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-2-(2-cloro-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
10 propiónico (69).



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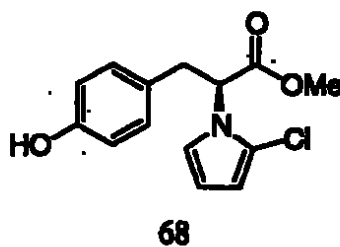
Preparado a partir del procedimiento descrito en el Procedimiento General B a partir del éster metílico del ácido (S)-2-(2-cloro-pirrol-1-il)-3-(4-hidroxifenil)-  
25 propiónico (70), produciendo el producto deseado (45%) en

548

forma de un aceite amarillo. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  7,97 (m, 2H), 7,40 (m, 3H), 6,90 (d, 2H,  $J = 8,5$  Hz), 6,75 (m, 3H), 6,12 (m, 1H), 5,98 (m, 1H), 5,02 (dd, 1H,  $J = 9,3, 6,1$  Hz), 4,19 (t, 2H,  $J = 6,7$  Hz), 3,71 (s, 3H), 3,36 (dd, 1H,  $J = 14,2, 6,1$  Hz), 3,15 (dd, 1H,  $J = 14,2, 9,3$  Hz), 2,95 (t, 2H,  $J = 6,7$  Hz), 2,35 (s, 3H); MS  $m/z$  465, 467 ( $M+1$ ).

(b) Éster metílico del ácido (S)-2-(2-cloro-pirrol-1-il)-3-(4-hidroxi-fenil)-propiónico (68).

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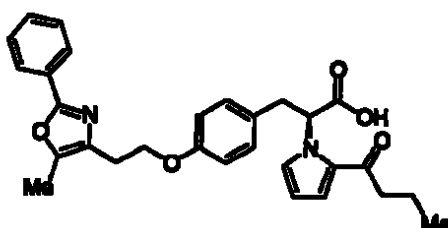


Preparado a partir del éster metílico del ácido (S)-3-15 (4-hidroxi-fenil)-2-pirrol-1-il-propiónico (1) y *N*-clorosuccinimida, produciendo el pirrol deseado (41%) en forma de un aceite amarillo. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  6,88 (d, 2H,  $J = 8,5$  Hz), 6,77 (m, 1H), 6,6 (d, 2H,  $J = 8,5$  Hz), 6,13 (m, 1H), 5,98 (m, 1H), 5,02 (dd, 1H,  $J = 9,3, 6,1$  Hz), 20 3,72 (s, 3H), 3,36 (dd, 1H,  $J = 14,2, 6,1$  Hz), 3,15 (dd, 1H,  $J = 14,2, 9,3$  Hz); MS  $m/z$  314, 316 ( $M+1$ ).

#### Ejemplo 27

Ácido (S)-2-(2-butilil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (74).

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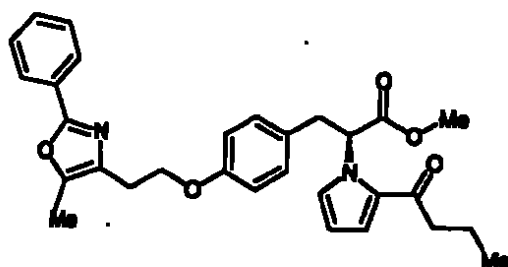
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Preparado por el procedimiento descrito en el Procedimiento General A a partir del éster metílico del ácido (S)-2-(2-butiril-pirrol-1-il)-3-{4-[2-(5-metil-2-  
10 fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (75), produciendo el ácido del título. 500 MHz,  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  7,97 (m, 2H), 7,42 (m, 3H), 6,98 (m, 1H), 6,89 (m, 3H), 6,71 (d, 2H,  $J = 8,8$  Hz), 6,12 (m, 1H), 4,16 (t, 2H,  $J = 6,6$  Hz), 3,51 (m, 1H), 3,19 (dd, 1H,  $J = 14,5, 9,4$  Hz),  
15 2,95 (t, 2H,  $J = 6,6$  Hz), 2,71 (m, 2H), 2,35 (s, 3H), 1,67 (q, 2H,  $J = 7,3$  Hz), 0,92 (t, 3H,  $J = 7,3$  Hz). MS  $m/z$  487 (M+1).

El éster metílico del ácido (S)-2-(2-butiril-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
20 propiónico (73) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-2-(2-butiril-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (73).



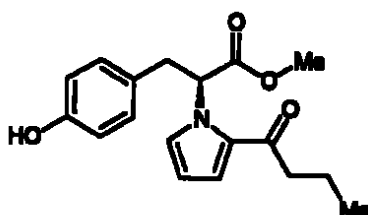
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73

Preparado por el procedimiento descrito en el Procedimiento General B a partir del éster metílico del ácido (S)-2-(2-butiril-pirrol-1-il)-3-(4-hidroxi-fenil)-  
10 propiónico (74), produciendo el producto deseado (27%) en forma de un aceite incoloro. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  7,96 (m, 2H), 7,42 (m, 3H), 6,94 (m, 1H), 6,84 (d, 2H,  $J = 8,3$  Hz), 6,08 (m, 1H), 4,16 (t, 2H,  $J = 6,6$  Hz), 3,70 (s, 3H), 3,44 (dd, 1H,  $J = 14,2, 5,4$  Hz), 3,15 (dd, 1H,  $J = 14,2, 9,8$  Hz), 2,93 (t, 2H,  $J = 6,6$  Hz), 2,66 (m, 2H), 2,34 (s, 3H), 1,64 (m, 2H), 0,90 (t, 3H,  $J = 7,3$  Hz); MS  $m/z$  501 (M+1).

Los siguientes compuestos se prepararon de acuerdo con los Procedimientos Generales C-E.

20 (b) Éster metílico del ácido (S)-2-(2-butiril-pirrol-1-il)-3-(4-hidroxi-fenil)-propiónico (72).

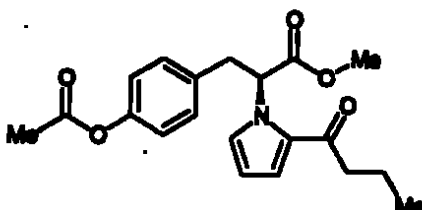


72

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A una solución agitada del éster metílico del ácido (S)-3-(4-acetoxi-fenil)-2-(2-butiril-pirrol-1-il)-propiónico (73) (790 mg, 2,21 mmol) en metanol anhidro (20 ml) se le añadió carbonato potásico (306 mg, 2,21 mmol). La mezcla se agitó a temperatura ambiente durante 30 minutos. El disolvente se retiró a presión reducida. El residuo se recogió en EtOAc, se lavó con HCl acuoso 2 N y se secó sobre  $\text{MgSO}_4$ . El disolvente se retiró a presión reducida, produciendo el fenol deseado (580 mg, 83%) en forma de un aceite incoloro. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  6,90 (m, 4H), 6,65 (d, 2H,  $J = 8,5$  Hz), 6,12 (m, 1H), 3,70 (s, 3H), 3,44 (dd, 1H,  $J = 14,3, 5,6$  Hz), 3,15 (dd, 1H,  $J = 14,3, 9,5$  Hz), 2,68 (m, 2H), 1,66 (m, 2H), 0,92 (t, 3H,  $J = 7,4$  Hz); MS 20 m/z 316 (M+1).

(c) Éster metílico del ácido (S)-3-(4-acetoxi-fenil)-2-(2-butiril-pirrol-1-il)-propiónico (71).



71

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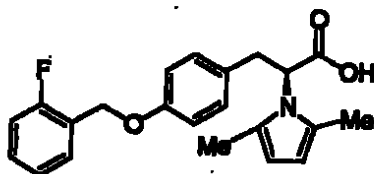
A una solución agitada del éster metílico del ácido (S)-3-(4-hidroxi-fenil)-2-pirrol-1-propiónico (1) (1,0 g, 4,04 mmol) en acetonitrilo (40 ml) se le añadió trietilamina (735  $\mu$ l, 5,26 mmol) y cloruro de acetilo (375  $\mu$ l, 5,26). Después de agitar a temperatura ambiente durante una noche, la reacción se concentró. El residuo se recogió en agua, se extrajo con EtOAc, se secó sobre  $\text{MgSO}_4$  y se concentró. Después, el material bruto se disolvió en diclorometano (15 ml). Se añadió cloruro de butirilo (505  $\mu$ l, 4,85 mmol), seguido por ácido triflico (430  $\mu$ l, 4,85 mmol). La reacción se agitó durante 10 segundos, se vertió en una solución acuosa de  $\text{NH}_4\text{Cl}$  y se extrajo con EtOAc. La capa orgánica se secó y el disolvente se retiró a presión reducida. El residuo se cromatografió sobre gel de sílice eluyendo con EtOAc al 25%-30% en hexanos produciendo el

pirrol deseado (790 mg, 55%) en forma de un aceite transparente. 500 MHz,  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  6,91 (m, 6H), 6,14 (m, 1H), 4,86 (m, 1H), 3,72 (s, 3H), 3,52 (m, 1H), 3,23 (m, 1H), 2,70 (m, 2H), 2,25 (s, 3H), 1,66 (m, 2H), 0,93 (t, 3H,  $J = 8,5$  Hz); MS  $m/z$  358 (M+1).

### Ejemplo 28

Ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-[4-(2-fluorobenciloxi)-fenil]-propiónico (76)

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76

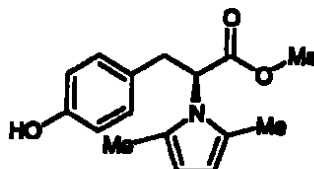
A una mezcla agitada de éster metílico del ácido (S)-  
 15 2-(2,5-dimetil-pirrol-1-il)-3-(4-hidroxifenil)-propiónico  
 (1) (500 mg, 1,82 mmol) en dimetilformamida (20 ml) se le  
 añadió hidruro sódico (218 mg, 5,46 mmol). La mezcla se  
 agitó a temperatura ambiente durante 15 minutos y se le  
 añadió bromuro de 2-fluorobencilo (440  $\mu\text{l}$ , 3,64 mmol). La  
 20 mezcla se agitó durante una noche a temperatura ambiente.  
 La reacción se diluyó con agua, se acidificó con HCl acuoso  
 2N y se extrajo con EtOAc. El disolvente se secó sobre  $\text{MgSO}_4$   
 y se concentró a presión reducida. El residuo se recogió en  
 metanol (20 ml) y se añadió hidruro de litio (437 mg, 18,2  
 25 mmol). La reacción se agitó a temperatura ambiente durante

554

3 horas. La reacción se diluyó con agua, se acidificó con HCl acuoso 2N y se extrajo con EtOAc. El disolvente se secó sobre  $\text{MgSO}_4$ , se concentró a presión reducida y se cromatografió eluyendo con un 10% a 25% de una mezcla 6:1 de EtOAc:HOAc en hexanos, produciendo el ácido propiónico deseado (300 mg, 45%). 500 MHz  $^1\text{H}$  RMN (DMSO) 7,46 (m, 1H), 7,35 (m, 1H), 7,16 (m, 2H), 6,76 (m, 4H), 5,47 (s, 2H), 5,00 (s, 2H), 4,82 (dd, 1H,  $J = 11.2, 4.4$  Hz), 3,29 (m, 1H), 2,96 (dd, 1H,  $J = 13.38, 11.2$  Hz), 2,45 (s, 6H); MS 10  $m/z$  368 (M+1).

El éster metílico de ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-(4-hidroxifenil)-propiónico (75) se preparó de la siguiente forma.

Éster metílico de ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-(4-hidroxifenil)-propiónico (75).



75

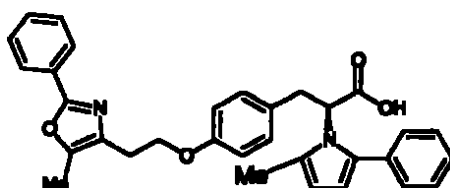
A una solución agitada de éster metílico de L-tirosina (3,90 g, 20,0 mmol) en tolueno (200 ml) se le añadió 2,5-hexandiona (2,34 ml, 20,0 mmol) y ácido p-toluenosulfónico (100 mg, 0,5 mmol). La mezcla se calentó a reflujo durante 25 96 horas, y después se concentró. El sólido insoluble se



filtró y se lavó con EtOAc. El filtrado se concentró y se cromatografió eluyendo con un 10% a 25% de una mezcla 6:1 de EtOAc:HOAc en hexanos, produciendo el pirrol deseado (3,14 g, 57%) en forma de un aceite amarillo. 500 MHz  $^1\text{H}$  RMN 5 ( $\text{CDCl}_3$ )  $\delta$  6,60 (d, 2H,  $J = 6,6$  Hz), 6,47 (d, 2H,  $J = 8,5$  Hz), 5,47 (s, 2H), 4,90 (dd, 1H,  $J = 11,2, 4,3$  Hz), 3,63 (s, 3H), 3,24 (dd, 1H,  $J = 13,9, 4,3$  Hz), 2,92 (dd, 1H,  $J = 13,9, 11,2$  Hz), 1,85 (s, 6H); MS  $m/z$  274 (M+1).

### Ejemplo 29

10 Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(2-metil-5-fenil-pirrol-1-il)-propiónico (80).



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80

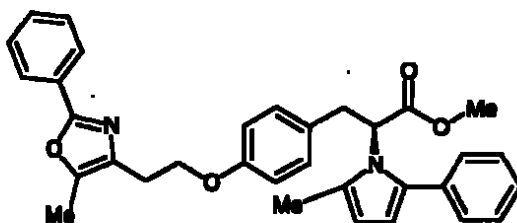
Preparado de acuerdo con el Procedimiento General A a partir del éster metílico de ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)etoxi]-fenil}-2-(2-metil-5-fenil-pirrol-1-il)-propiónico (79), que se hidrolizó, produciendo el ácido propiónico deseado (98%) en forma de un sólido pardo. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  81,3 (m, 2H), 7,46 (m, H3), 7,16 (m, H3), 6,83 (m, 2H), 6,60 (d, 2H,  $J = 9,0$  Hz), 6,55 (d, 2H,  $J = 8,8$  Hz), 5,96 (m, 1H), 5,89 (d, 1H,  $J = 3,4$  Hz), 25 4,95 (dd, 1H,  $J = 10,0, 5,1$  Hz), 4,22 (t, 2H,  $J = 6,1$  Hz),

3,25 (m, 2H), 3,07 (m, 3H), 2,86 (m, 1H), 2,40 (s, 3H), 2,33 (s, 2H); MS  $m/z$  507 (M+1).

El éster metílico de ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)etoxi]-fenil}-2-(2-metil-5-fenil-pirrol-1-il)-propiónico (79) se preparó de la siguiente forma.

(a) Éster metílico de ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)etoxi]-fenil}-2-(2-metil-5-fenil-pirrol-1-il)-propiónico (79).

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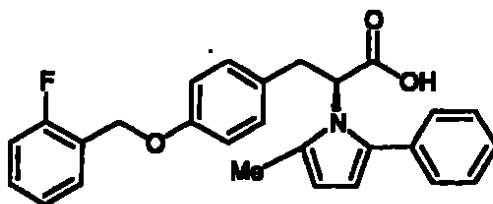
79

15 Preparado de acuerdo con el Procedimiento General B a partir de éster metílico de ácido 3-(4-hidroxifenil)-2-(2-metil-5-fenil-pirrol-1-il)-propiónico (1) y cromatografiado sobre gel de sílice eluyendo con EtOAc al 15%-50% en hexanos, produciendo el pirrol deseado (300 mg, 39%) en  
20 forma de un aceite amarillo. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  8,03 (m, 2H), 7,43 (m, 3H), 7,17 (m, 3H), 6,84 (m, 2H), 6,59 (d, 2H,  $J = 8,8$  Hz), 6,53 (d, 2H,  $J = 8,8$  Hz), 5,94 (d, 1H,  $J = 3,4$  Hz), 5,87 (d, 1H,  $J = 3,4$  Hz), 4,92 (dd, 1H,  $J = 9,9, 5,0$  Hz), 4,18 (m, 2H), 3,76 (s, 3H), 3,25 (m, 2H),  
25 2,99 (m, 3H), 2,86 (t, 1H,  $J = 6,3$  Hz), 2,37 (s, 3H), 2,25

(s, 3H); MS  $m/z$  521 (M+1).

(b) Ácido 3-[4-(2-fluoro-benciloxi)-fenil]-2-(2-metil-5-fenil-pirrol-1-il)-propiónico (78).

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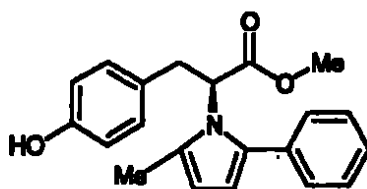


78

Preparado de acuerdo con el Procedimiento General A a  
10 partir de éster metílico de ácido 3-(4-hidroxifenil)-2-(2-metil-5-fenil-pirrol-1-il)-propiónico (77), produciendo el ácido propiónico deseado (23%) en forma de sólido amarillo.  
500 MHz  $^1\text{H}$  RMN (DMSO)  $\delta$  7,49 (t, 1H,  $J = 7,3$  Hz), 7,38 (m, 1H), 7,19 (m, 5H), 6,78 (m, 2H), 6,67 (d, 2H,  $J = 8,8$  Hz),  
15 6,53 (d, 2H,  $J = 8,5$  Hz), 5,81 (d, 2H,  $J = 3,2$  Hz), 5,70 (d, 2H,  $J = 3,4$  Hz), 5,02 (s, 2H), 4,85 (dd, 1H,  $J = 10,7$ , 4,6 Hz), 3,17 (m, 1H), 2,92 (m, 1H), 2,23 (s, 3H); MS  $m/z$  430 (M+1).

(c) Éster metílico de ácido 3-(4-hidroxifenil)-2-(2-metil-5-fenil-pirrol-1-il)-propiónico (77).

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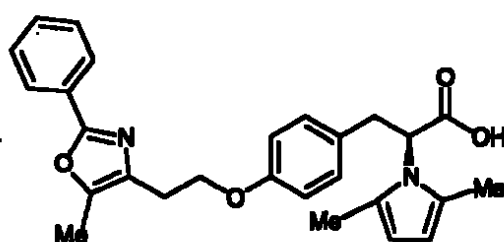
78

Preparado de acuerdo con el método descrito en el Ejemplo 27(a) a partir de 1-fenil-1,4-pentanodiona, produciendo el pirrol bruto que se utilizó en las etapas posteriores. MS  $m/z$  336 (M+1).

5 Ejemplo 30

Ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (82).

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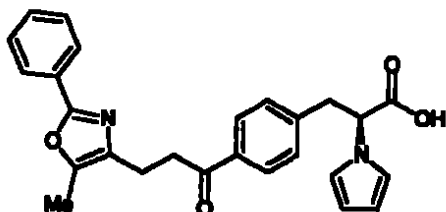
82

Preparado de acuerdo con el procedimiento descrito en el Procedimiento General A por hidrólisis in situ del éster metílico (81). El producto se cromatografió sobre gel de sílice eluyendo con EtOAc al 30%-60% en hexanos, aislándose el ácido propiónico deseado (5%) en forma de cristales rojos. 500 MHz  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  7,96 (m, 2H), 7,40 (m, 3H), 6,63 (m, 4H), 5,61 (s, 2H), 4,63 (dd, 1H,  $J = 10,0, 4,9$  Hz), 4,38 (t, 2H,  $J = 6,5$  Hz), 3,38 (dd, 1H,  $J = 13,9, 4,9$  Hz), 3,00 (dd, 1H,  $J = 13,9, 10,0$  Hz), 2,77 (m, 2H), 2,09 (s, 3H), 1,84 (s, 6H); MS  $m/z$  445 (M+1).

Ejemplo 31

25 Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propionil]-

fenil)-2-pirrol-1-il-propiónico (87).



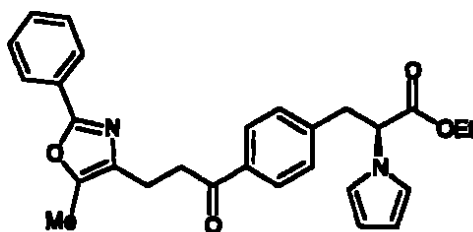
87

5  
10 De acuerdo con el Procedimiento General A. Se añadió LiOH (0,24 g, 10 mmol) en 10 ml de H<sub>2</sub>O a una solución de éster etílico de ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico (86) en 20 ml de THF/metanol (1/1) y se agitó durante 17 horas. El  
15 disolvente se retiró y el residuo se disolvió de nuevo en H<sub>2</sub>O. La mezcla se acidificó con HCl 1N y el producto se recogió por filtración. 0,36 g (rendimiento del 56%). P.f.: de 90° a 92°C, MS (M+1) 429.

El éster etílico de ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico  
20 (86) se preparó de la siguiente forma.

(a) Éster etílico de ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico (86).

560

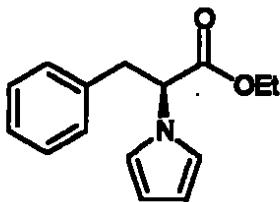


86

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Se añadió cloruro oxalilo (0,5 ml) a una solución de ácido 2-(5-metil-2-feniloxazol-4-il)acético (84) (0,7 g, 2,88 mmol) en 10 ml de  $\text{CH}_2\text{Cl}_2$  con una gota de DMF, y se agitó a temperatura ambiente durante una hora. Después se evaporó el disolvente y se volvió a disolver el residuo en  $\text{CH}_2\text{Cl}_2$  (20 ml). A esta mezcla se le añadió 3-fenil-2-pirrolopropionato de etilo (85), y después  $\text{AlCl}_3$  (0,77 g, 5,75 mmol). La mezcla se agitó durante 17 horas. Después se añadieron agua y EtOAc. La capa orgánica se lavó con salmuera y  $\text{NaHCO}_3$  acuoso saturado. El producto puro se aisló por cromatografía en columna (2/1 = hexano/EtOAc) (0,62 g, 45%). MS:  $M+1$ : 457,2.

20 (b) 3-fenil-2 pirrolopropionato de etilo (85).



85

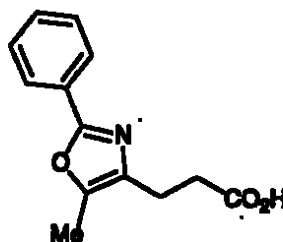
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561

A una solución de etil fenilalanina en 50 ml de  $\text{CH}_2\text{Cl}_2$  se le añadió trietilamina (3,3 ml). La mezcla se agitó a temperatura ambiente durante 20 minutos. Después se retiró el disolvente y el residuo se disolvió de nuevo en éter 5 dietílico. La sal HCl de trietilamina se retiró por filtración, y el filtrado se concentró hasta obtener un aceite. A dicho aceite se le añadieron  $\text{H}_2\text{O}$  (25 ml), ácido acético (25 ml), NaOAc (3,87 g, 47,2 mmol) y 2,5-dimetoxitetrahydrofurano (5,2 ml, 40,1 mmol). La mezcla se 10 calentó a  $100^\circ\text{C}$  durante 15 minutos y después se enfrió a temperatura ambiente y se diluyó con EtOAc/ $\text{H}_2\text{O}$ . La capa orgánica se lavó con salmuera y se secó sobre  $\text{MgSO}_4$  y el disolvente se retiró a presión reducida. La purificación del residuo por cromatografía en columna (10% 15 EtOAc/hexanos) produjo 2,54 g del producto puro (47%).

(c) Ácido 2-(5-metil-2-feniloxazol-4-il)acético (84).

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84

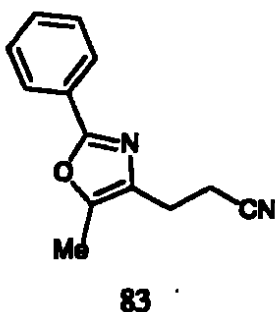
A una solución de 4-(2-cianoetil)-5-metil-2-feniloxazol (83) (1,5 g, 7,07 mmol) en etanol/ $\text{H}_2\text{O}$  a 25 temperatura ambiente se le añadió KOH (1,79 g, 31,8 mmol).

362

Después, la mezcla se calentó a reflujo durante 20 horas. El disolvente se retiró a presión reducida. El residuo se disolvió en H<sub>2</sub>O, se lavó con éter y la capa acuosa se acidificó con HCl 1N. El producto se recogió por filtración y se secó, produciendo un polvo blanco. 0,7 g (rendimiento del 44%).

(d) 4-(2-cianoetil)-5-metil-2-feniloxazol (83).

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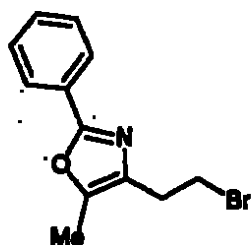
15

A una suspensión de KCN (0,65 g, 10 mmol) en 10 ml de DMSO a temperatura ambiente se le añadió 4-(2-bromoetil)-5-metil-2-feniloxazol (84-1) (1,33 g, 5 mmol). La mezcla se agitó durante 17 horas y después se diluyó con agua (100 ml), se extrajo con EtOAc, se secó y se evaporó, produciendo 1,1 g del producto que se usó en la siguiente etapa sin purificación adicional.

(e) 4-(2-bromoetil)-5-metil-2-feniloxazol (82).



219



82

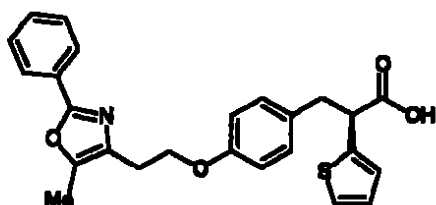
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A una solución de 2-(5-metil-2-feniloxazol-4-il)etanol (11,16 g, 54,9 mmol) en 100 ml de THF se le añadieron trifenilfosfina (18 g, 68,9 mmol) y N- bromosuccinimida (12 10 g, 68,9 mmol). La mezcla se agitó a temperatura ambiente durante 2 horas. Los análisis de TLC y MS mostraron que la reacción estaba completa. Después, la mezcla de reacción se repartió entre EtOAc y NaHCO<sub>3</sub> saturado. La capa orgánica se lavó con salmuera, se secó y se purificó por cromatografía 15 en columna (3:1 = hexanos:EtOAc). El producto se aisló en forma de polvo amarillo pálido (13,5 g, 92,5%).

#### Ejemplo 32

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-2-il-propiónico (91).

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91

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De acuerdo con el Procedimiento General A. El

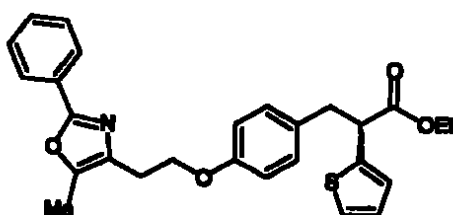
564

compuesto diana se obtuvo por hidrólisis básica (LiOH) del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-2-il-propiónico (90) en THF/H<sub>2</sub>O. P.f.: de 146°C a 147°C, MS (M+1):434, Análisis calculado para C<sub>25</sub>H<sub>23</sub>O<sub>4</sub>NS: C, 69,26; H, 5,35, N, 3,23. Encontrado: C, 68,90; H, 5,43, N, 3,06. <sup>1</sup>H RMN (DMSO-D<sub>6</sub>) δ 7,95-6,75 (m, 14H), 4,1 (t, 2H), 4,05 (t, 2H), 3,1 (m, 1H), 2,85 (m, 2H), 2,3 (s, 3H).

El éster etílico de ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-2-il-propiónico (90) se preparó de la siguiente forma.

(a) Éster etílico de ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-2-il-propiónico (90).

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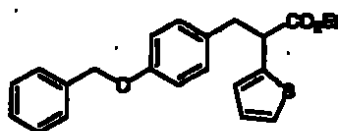


90

El grupo bencilo en 3-(p-benciloxifenil)-2-tiofenopropionato de etilo (89) se retiró con TMSI utilizando acetonitrilo como disolvente. Se siguió el Procedimiento General B para preparar el compuesto del título. A una solución a 0°C de 2-(5-metil-2-fenil-oxazol-4-il)etanol, el fenol resultante y trifenil fosfina en 10 ml de THF se le añadió DEAD (1,00 ml, 6,4 mmol). Después,

la mezcla se agitó a temperatura ambiente durante 20 horas. Se retiró el disolvente y el éster etílico del ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-tiofen-2-il-propiónico se aisló por cromatografía en columna (2,1 g, 5 84%).

(b) 3-(p-benciloxifenil)-2-tiofenopropionato de etilo (89).

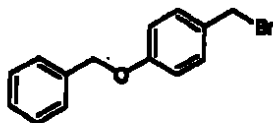


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A una solución de 2-tiofen acetato de etilo (1,5 ml, 9,99 mmol) en 50 ml de THF en nitrógeno se le añadió gota a gota a  $-40^{\circ}\text{C}$  LiHMDS (10 ml, 1,0 M en THF). Después, la 15 mezcla se agitó durante 30 minutos y se añadió el compuesto 3 en THF (50 ml). La mezcla resultante se agitó a temperatura ambiente durante 20 horas más. El disolvente se retiró y el producto se recogió por cromatografía en columna (2,9 g, 81%).

20 (c) Bromuro de p-benciloxibencilo (88).



88

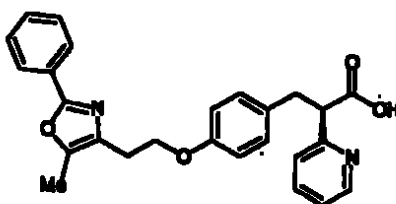
25 A una solución de 4,6 g de  $\text{PBr}_3$  en 5 ml de THF seco a -

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5°C se le añadió una solución de 0,66 ml de piridina en 1,3 ml de THF, seguido de una solución de 2 en 75 ml de THF. Después, la mezcla se agitó a temperatura ambiente durante 20 horas y los análisis de TLC y MS indicaron que la 5 reacción se había completado. La reacción se diluyó con THF (100 ml) y se filtró a través de celite, usándose el producto obtenido (12 g, 87%) en la siguiente etapa sin purificación adicional.

### Ejemplo 33

10 Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-3-il-propiónico (92).



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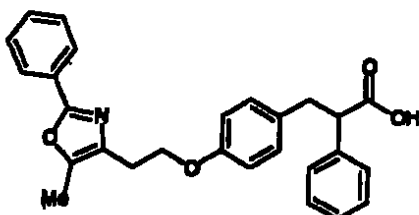
Este compuesto se sintetizó de la misma forma que en el ejemplo 32, con la excepción de que se reemplazó 2-tiofen acetato de etilo por 2-2-piridin-3-il acetato de metilo. P.f.: 74,4-75,80°C, MS (M+1):471, Análisis 25 calculado para  $C_{26}H_{24}O_4N_2$ : C, 66,32; H, 5,49, N, 5,95.

567

Encontrado: C, 66,34; H, 5,86, N, 5,81.  $^1\text{H}$  RMN(DMSO- $\text{D}_6$ ) 8,37-6,73 (m, 13H), 4,1 (t, 2H), 3,8 (t, 2H), 2,95 (m, 1H), 2,80 (m, 2H), 2,3 (s, 3H).

#### Ejemplo 34

5 Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico (93).



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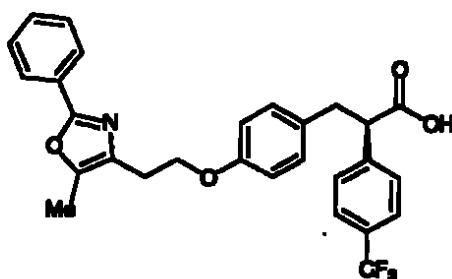
Este compuesto se sintetizó de la misma forma que el ejemplo 32, con la excepción de que se reemplazó 2-tiofen acetato de etilo por 2-fenil acetato de metilo. P.f.: de 15 177,9°C a 179,1°C, MS(M+1):417. Análisis calculado para  $\text{C}_{25}\text{H}_{24}\text{O}_4\text{N}_2$ : C, 72,10; H, 5,81, N, 6,73. Encontrado: C, 73,41; H, 6,04, N, 6,64.  $^1\text{H}$  RMN( $\text{CDCl}_3$ )  $\delta$  6,6-7,9 (m, 15H), 4,3 (t, 2H), 3,7 (m, 2H), 3,41 (m, 1H), 3,2 (m, 2H), 2,3 (s, 3H).

#### 20 Ejemplo 35

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-trifluorofenil)-propiónico (94).

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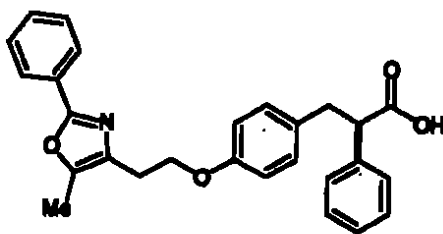
94

Este compuesto se sintetizó de la misma forma que el ejemplo 32, con la excepción de que se reemplazó 2-tiofen acetato de etilo por 2-(3-trifluorofenil) acetato de metilo. P.f.: de 118,8°C a 110°C, MS(M+1): 496,2; Análisis calculado para C<sub>29</sub>H<sub>24</sub>O<sub>4</sub>NF<sub>3</sub> HCl: C, 65,00; H, 4,79, N, 2,71. Encontrado: C, 65,17; H, 4,37, N, 2,32. <sup>1</sup>H RMN(DMSO-D<sub>6</sub>) 6,65-7,9 (m, 14H), 4,1 (t, 2H), 4,0 (m, 2H), 3,35 (m, 1H), 3,2 (m, 2H), 2,3 (s, 3H).

#### Ejemplo 36

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico (R) (95).

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A una solución de ácido 2-fenilacético (10 g, 73,4 mmol) en cloruro de oxalilo (7 ml, 80,2 mmol) y 200 ml de  $\text{CH}_2\text{Cl}_2$  se le añadieron 2 gotas de DMF, se agitó a 5 temperatura ambiente durante 2 horas, se retiró el disolvente y el residuo se disolvió de nuevo en 50 ml de THF. A esta solución se le añadió gota a gota una solución de (R)-(+)-4-bencil-2-oxazolidinona de litio (6,58 g, 37,1 mmol) en THF (50 ml). La mezcla resultante se agitó a 10 temperatura ambiente durante 17 horas. Se retiró el disolvente, el residuo se trató con  $\text{NH}_4\text{Cl}$  saturado y se extrajo en  $\text{CH}_2\text{Cl}_2$ . La capa orgánica se lavó con salmuera, y el disolvente se retiró, produciendo 10,5 g de aceite (97%).

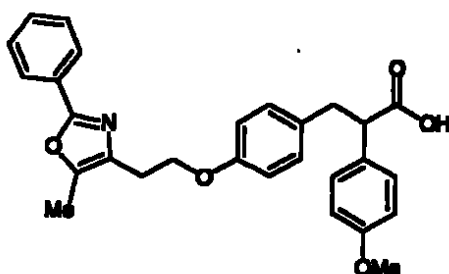
15 P.f.: de 124,1°C a 125°C, MS(M+1): 428,1; Análisis calculado para  $\text{C}_{27}\text{H}_{25}\text{O}_4\text{N}$ : C, 75,86; H, 5,89, N, 3,28. Encontrado: C, 75,84; H, 5,91, N, 3,24.  $^1\text{H}$  RMN(DMSO- $\text{D}_6$ )  $\delta$  12,5 (s a, 1H), 7,05-6,75 (m, 14H), 4,1 (t, 2H), 3,72 (t, 2H), 3,15 (m, 1H), 2,7-2,88 (m, 2H), 2,3 (s, 3H).

## 20 Ejemplo 37

Ácido 2-(4-metoxi-fenil)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (96).

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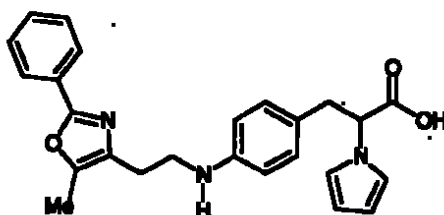
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Este compuesto se sintetizó de la misma forma que el Ejemplo 32 excepto que se reemplazó 2-tiofenoacetato de etilo por p-metoxifenilacetato de metilo. P.f. 114,7°C a 10 116,6°, MS (M+1): 458,1; Análisis Calculado para C<sub>28</sub>H<sub>27</sub>O<sub>5</sub>N: C, 73,51; H, 5,95, N, 3,06. Encontrado: C, 73,31; H, 5,76, N, 2,89. <sup>1</sup>H RMN (DMSO-D<sub>6</sub>) δ 7,85-6,70 (m, 13H), 3,65 (s, 3H), 4,1 (t, 2H), 3,1 (m, 1H), 2,85 (m, 2H), 2,7,-2,88 (m, 2H), 2,25 (s, 3H).

# 15 Ejemplo 38

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-fenil}-2-pirrol-1-il-propiónico (100)



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Se mezclaron el compuesto 99 (0,213 g, 1,06 mmol) y 97 25 (0,285 g, 1,17 mmol) en 20 ml de CH<sub>2</sub>Cl<sub>2</sub> junto con NaBH(OAc)<sub>3</sub>



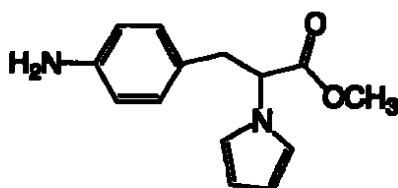
571

(0,337 mg, 1,6 mmol) y HOAc (0,7 ml) a 0°C durante 24 horas. Después, la mezcla de reacción se diluyó con CH<sub>2</sub>Cl<sub>2</sub> y se lavó con NaHCO<sub>3</sub> saturado. La capa orgánica se concentró y se purificó por cromatografía (4:1 EtOAc:hexano), produciendo el producto en forma de un sólido (0,15 g, 35%). P.f. 85,1°C a 87,4°C, MS(M+1): 416,1; Análisis Calculado para C<sub>25</sub>H<sub>25</sub>O<sub>3</sub>N<sub>3</sub>: C, 70,42; H, 5,98; N, 9,85. Encontrado: C, 70,36; H, 5,97; N, 9,65. <sup>1</sup>H RMN (DMSO-D<sub>6</sub>) δ 7,9-5,9 (m, 13H), 4,79 (t, 2H), 2,89-3,5 (m, 3H), 2,6 (t, 2H), 2,2 (s, 3H).

Se prepararon los compuestos 99 y 98 de la siguiente forma.

(a) Éster metílico del ácido 3-(4-aminofenil)-2-pirrolopropiónico (99).

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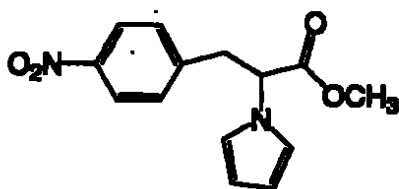
99

20 El grupo nitro en el compuesto 98 se redujo a un grupo amino con níquel Raney en MeOH, que se usó sin purificación adicional.

(b) Éster metílico del ácido 3-(4-nitrofenil)-2-pirrolopropiónico (98).

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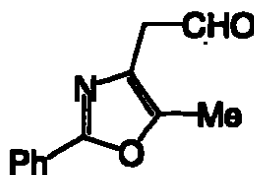
98

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Un mezcla de 4-nitrofenilalanina (2,03 g, 9,66 mmol), 2,5-dimetoxitetrahydrofurano (2,15 ml, 16,6 mmol) y acetato  
10 sódico (1,603 g, 19,5 mmol) en 10 ml de agua y 10 ml de ácido acético se calentó a 100°C durante 20 minutos. El sólido negro se repartió entre EtOAc y H<sub>2</sub>O. La capa orgánica se secó y el disolvente se retiró. Se obtuvieron 0,6 g de compuesto puro, ácido 3-(4-nitrofenil)-2-pirrolpropiónico, 15 por cromatografía en columna (MeOH al 5%/CH<sub>2</sub>Cl<sub>2</sub>). El producto se trató con TMSCHN<sub>2</sub>, produciendo el éster metílico (98).

(c) 2-(5-metil-2-fenil-oxazol-4-il)acetaldehído (97).

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97

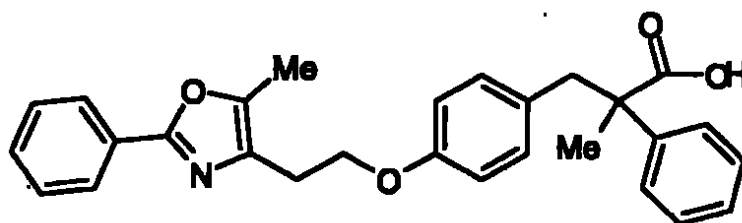
A una solución de ([1,1,1-triacetoxi-1,1-dihidro-1,2-25 benciodoxol-3(1H)-ona (reactivo de Dess-Martín) en 10 ml de

573

$\text{CH}_2\text{Cl}_2$  se le añadió 2-(5-metil-2-fenil-oxazol-4-il)etanol (0,5 g, 2,5 mmol). La mezcla se agitó a temperatura ambiente durante una hora. Los análisis de TLC y MS mostraron que la reacción se había completado y el aldehído 5 97 se aisló en forma de un aceite.

#### Ejemplo 39

Ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico (101).



101

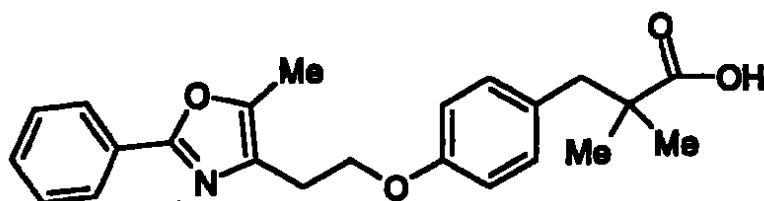
10 Este compuesto se sintetizó de la misma forma que el Ejemplo 32 excepto que se reemplazó 2-tiofenoacetato de etilo por 2,2-metilfenilacetato de metilo. P.f. de 178°C a 179°C, MS(M+1): 442,1; Análisis Calculado para  $\text{C}_{28}\text{H}_{27}\text{O}_5\text{N}_1$  1/3  $\text{H}_2\text{O}$ : C, 75,08; H, 6,18, N, 3,12. Encontrado: C, 75,21; H, 15 6,34; N, 2,77.  $^1\text{H}$  RMN ( $\text{DMSO}-\text{D}_6$ )  $\delta$  7,9-6,5 (m, 14H), 4,1 (t, 2H), 2,85 (t, 2H), 2,45 (s, 3H), 2,3 (s, 2H), 1,25 (s, 3H).

#### Ejemplo 40

Ácido 2,2-dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (102).

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230

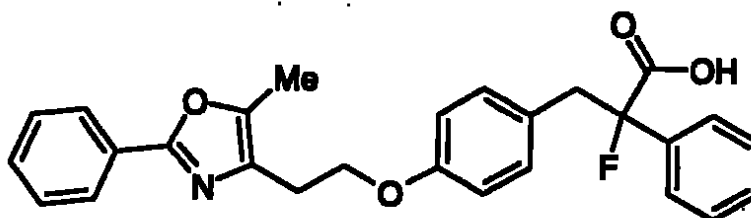


102

Este compuesto se sintetizó de la misma forma que el Ejemplo 32 excepto que se reemplazó 2-tiofenoacetato de 5 etilo por 2,2-dimetilacetato de metilo. P.f. de 133°C a 134°C. MS (M+1): 380,1: Análisis Calculado para C<sub>23</sub>H<sub>25</sub>O<sub>4</sub>N: C, 72,80; H, 6,64; N, 3,69. Encontrado: C, 72,60; H, 6,66, N, 3,50. <sup>1</sup>H RMN (DMSO-D<sub>6</sub>) δ 7,85 (m, 2H), 7,45 (m, 3H), 6,95 (d, 2H), 4,15 (t, 2H), 2,85 (t, 2H), 2,65 (s, 2H), 2,3 (s, 10 3H), 0,99 (s, 3H).

#### Ejemplo 41

Ácido 2-fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico (103).



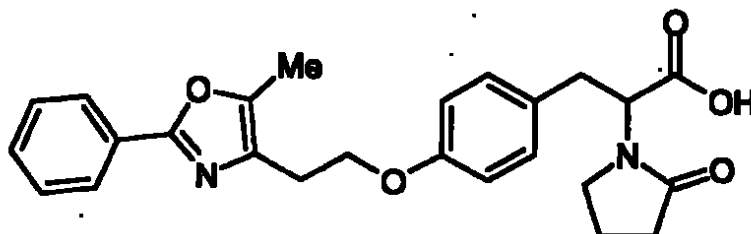
103

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Este compuesto se sintetizó de la misma forma que en el Ejemplo 32 excepto que se reemplazó 2-tiofenoacetato de etilo por 2,2-fluorofenilacetato de metilo. P.f: 163-165°C, MS(M-1): 444,0; Análisis Calculado para  $C_{27}H_{24}O_4NF$ : C, 72,80, 5 H, 5,43, N, 3,14. Encontrado: C, 72,50; H, 5,56; N, 3,06.  $^1H$  RMN (DMSO- $D_6$ )  $\delta$  7,9-6,72 (m, 14H), 4,10 (t, 2H), 3,5 (t, 2H), 2,85 (t, 2H), 2,3 (s, 3H).

#### Ejemplo 42

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
10 2-(2-oxo-pirrolidin-1-il)-propiónico (104).



104

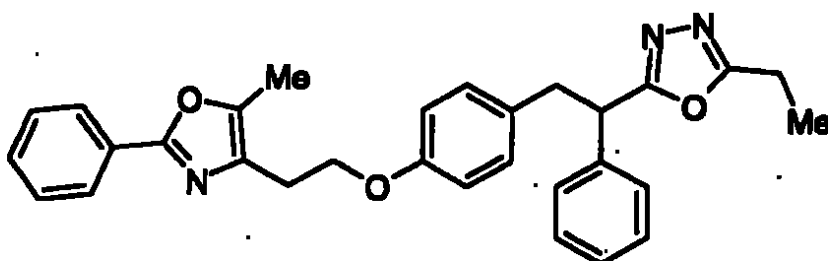
Este compuesto se sintetizó de la misma forma que el Ejemplo 32 excepto que se reemplazó 2-tiofenoacetato de etilo por 2-(2-oxo-pirrolidin-1-ilfenil)acetato de metilo. MS(M-1): 435,1; Análisis Calculado para  $C_{25}H_{26}O_5N_2 \cdot H_2O$ : C, 66,30; H, 6,19, N, 6,19. Encontrado: C, 66,26; H, 6,19; N, 6,19.  $^1H$  RMN (DMSO- $D_6$ )  $\delta$  7,88 (d, 2H), 7,4 (m, 3H), 7,05 (d, 2H), 6,75 (d, 2H), 4,60 (m, 1H), 4,1 (t, 2H), 3,1-2,75 (m,

576

4H), 2,3 (s, 3H), 2,1-1,65 (m, 6H).

Ejemplo 43

2-Etil-5-(2-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-1-fenil-etil)-1,3,4-oxadiazol (105).



105

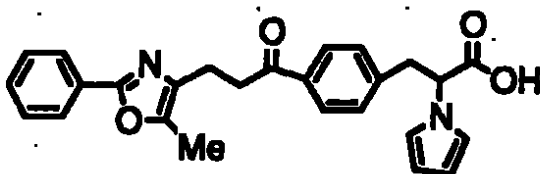
5 Al ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico (93) (0,197 g, 0,46 mmol) a 0°C en 3 ml de THF en una atmósfera de N<sub>2</sub> se le añadió 4-metilmorfolina (0,084 ml, 0,65 mmol) seguido de cloroformiato de isobutilo (0,084 ml, 0,65 mmol). La mezcla  
10 de reacción se agitó a 0°C durante 30 minutos, después se filtró en una solución a 0°C de hidrazina (0,07 ml, 2,23 mmol) en 3 ml de THF. La mezcla se agitó durante 50 minutos a 0°C. Después, se añadieron EtOAc (10 ml), agua y NH<sub>4</sub>Cl. La parte orgánica se separó y se evaporó hasta un sólido  
15 blanco. El sólido se redisolvió en 4 ml de dioxano. A la solución resultante se le añadió trietilortopropionato (0,28 ml, 1,39 mmol) y ácido metanosulfónico (0,60 ml, 0,09 mmol). La mezcla se calentó a 105°C durante 15 minutos y después se enfrió a temperatura ambiente. Se añadió EtOAc y

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después se lavó con  $\text{NaHCO}_3$  saturado y salmuera. El disolvente se evaporó y el residuo se trituro con  $\text{Et}_2\text{O}$  y hexanos. Se obtuvo un sólido blanco (105). P.f.  $110^\circ\text{C}$ , MS (M+1): 480,2; Análisis Calculado para  $\text{C}_{30}\text{H}_{29}\text{O}_3\text{N}_3 \cdot 1/2 \text{H}_2\text{O}$ : C, 73,97; H, 6,31; N, 8,40. Encontrado: C, 73,68; H, 6,14, N, 8,59.  $^1\text{H}$  RMN ( $\text{CDCl}_3$ )  $\delta$  7,95 (d, 2H), 7,45-7,2 (m, 8H), 6,95 (d, 2H), 6,67 (d, 2H), 4,35 (t, 1H), 4,15 (t, 2H), 3,5 (m, 1H), 3,2 (m, 1H), 2,95 (t, 2H), 2,75 (m, 2H), 3,25 (s, 3H), 1,3 (t, 3H).

10 Ejemplo 44

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico (107).



107

De acuerdo con el Procedimiento General A. A una solución de 8 en 20 ml de THF/Metanol (1/1) se le añadió 20 LiOH (0,24 g, 10 mmol) en 10 ml de  $\text{H}_2\text{O}$  y se agitó durante 17 horas. El disolvente se retiró y el residuo se redisolvió en  $\text{H}_2\text{O}$ , éste se acidificó con HCl 1 N y el producto se recogió por filtración, peso total de 0,36 g (56%). P.F.  $90^\circ\text{C}$  a  $92^\circ\text{C}$ , MS (M+1) 429.

25 El éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-

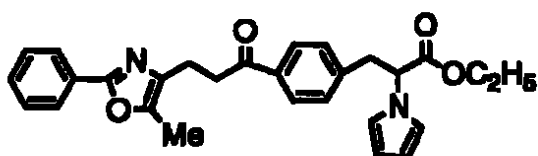
578

oxazol-4-il)-propionil]-fenil)-2-pirrol-1-il-propiónico  
(106) se preparó de la siguiente forma.

(a) Éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico

5 (106).

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106

A una solución del ácido 2-(5-metil-2-feniloxazol-4-il)acético (Véase Ejemplo 31) (0,7 g, 2,88 mmol) en 10 ml de  $\text{CH}_2\text{Cl}_2$  con una gota de DMF se le añadió cloruro de oxalilo (0,5 ml) y se agitó a temperatura ambiente durante una hora, el disolvente se evaporó y el residuo se disolvió de nuevo en  $\text{CH}_2\text{Cl}_2$  (20 ml). Después se añadió 3-fenil-2-pirrolpropionato de etilo (Véase Ejemplo 31), seguido de 20  $\text{AlCl}_3$  (0,77 g, 5,75 mmol), la mezcla se agitó durante 17 horas, se le añadió agua y EtOAc y la capa orgánica se lavó con salmuera y  $\text{NaHCO}_3$  saturado. El producto bruto se aisló por cromatografía en columna (2/1 = hexano/EtOAc), peso de 0,62 g (45%).

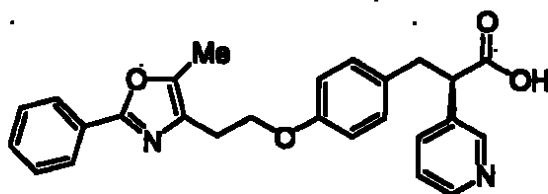
## 25 Ejemplo 45

Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-



57d

fenil}-2-piridin-3-il-propiónico (108).



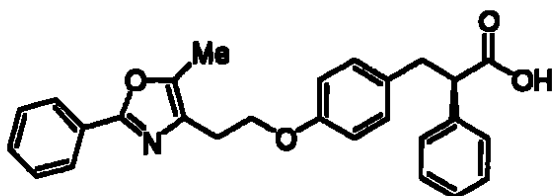
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108

Este compuesto se sintetizó de la misma forma que el Ejemplo 32 excepto que se reemplazó 2-tiofenoacetato de etilo por 2,2-piridin-3-il acetato de metilo. P.f. de 74,4°C a 75,80°C, MS (M+1): 471, Análisis Calculado para  $C_{26}H_{24}O_4N_2$ : C, 66,32; H, 5,49, N, 5,94. Encontrado: C, 66,34; H, 5,86, N, 5,81.  $^1H$  RMN (DMSO- $D_6$ )  $\delta$  8,37-6,73 (m, 13H), 4,1 (t, 2H), 3,8 (t, 2H), 2,95 (m, 1H), 2,80 (m, 2H), 2,3 (s, 3H).

15 Ejemplo 46

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico (110).



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110

Este compuesto se sintetizó de la misma forma que el Ejemplo 32 a partir del correspondiente éster metílico con la excepción de que se usó el compuesto 108 en la reacción

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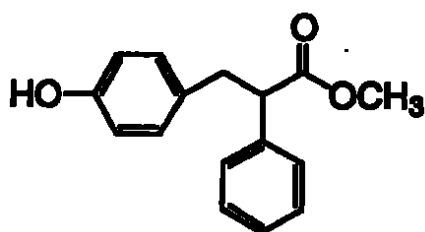
580

de acoplamiento. P.f. de 177,9°C a 179,1°C, MS (M+1): 417  
 Análisis Calculado para  $C_{25}H_{24}O_4N_2$ : C, 72,10; H, 5,81, N,  
 6,73. Encontrado: C, 73,41; H, 6,04, N, 6,64.  $^1H$  RMN ( $CDCl_3$ )  
 $\delta$  6,6-7,9 (m, 15H); 4,3 (t, 2H), 3,7 (m, 2H), 3,41 (m, 1H),  
 5 3,2 (m, 2H), 2,3 (s, 3H).

Se preparó propionato de metil-2-fenil-3-(p-  
 hidroxifenilo (109) de la siguiente forma.

(a) Propionato de metil-2-fenil-3-(p-hidroxifenilo  
 (109).

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109

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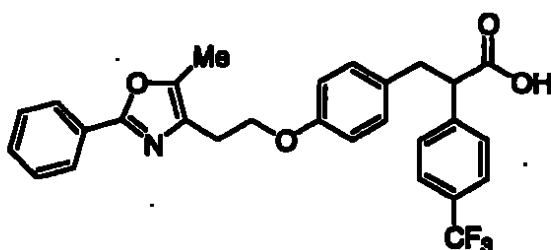
Preparado a partir del ácido 2-fenil-3-(p-  
 hidroxifenil) propiónico usando trimetilsilil azida como el  
 agente de esterificación.

Ejemplo 47

20 Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
 2-(3-trifluorofenil)-propiónico (111).

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237



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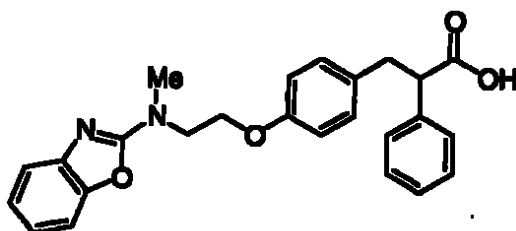
111

Este compuesto se sintetizó de la misma forma que el Ejemplo 32 con la excepción de que se reemplazó 2-tiofenoacetato de etilo por 2-(3-trifluorofenil)acetato de 10 metilo. P.f: de 118,8°C a 110°C, MS(M+1): 496,2; Análisis Calculado para  $C_{28}H_{24}O_4NF_3$  0,6 HCl: C, 65,00; H, 4,79, N, 2,71. Encontrado: C, 65,17, H, 4,37, N, 2,32.  $^1H$  RMN (DMSO- $D_6$ )  $\delta$  6,65-7,9 (m, 14H), 4,1 (t, 2H), 4,0 (m, 2H), 3,35 (m, 1H), 3,2 (m, 2H), 2,3 (s, 3H).

#### 15 Ejemplo 48

Ácido (R)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico (113).

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113

Sintetizado de la misma forma que el Ejemplo 32 con la 25 excepción de que se reemplazó 2-tiofenoacetato de etilo por

552

el compuesto 112. P.f. de 124,1°C a 125°C, MS (M+1): 428,1: Análisis Calculado para  $C_{27}H_{25}O_4N$ : C, 75,86; H, 5,89, N, 3,28. Encontrado: C, 75,84; H, 5,91, N, 3,24.  $^1H$  RMN (DMSO- $D_6$ )  $\delta$  12,5 (b, 1H), 7,06-6,75 (m, 14H), 4,1 (t, 2H), 3,72 5 (t, 2H), 3,15 (m, 1H), 2,7-2,88 (m, 2H), 2,3 (s, 3H).

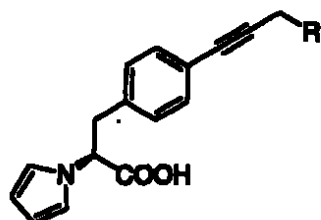
El compuesto 112 se preparó de la siguiente forma.

(a) Compuesto (112).

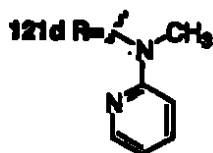
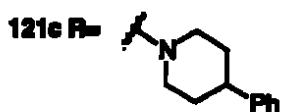
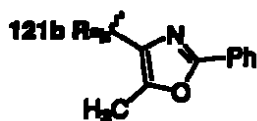
A una solución del ácido 2-fenilacético (10 g, 73,4 mmol) en cloruro de oxalilo (7 ml, 80,2 mmol) y 200 ml de  $CH_2Cl_2$  se le añadieron 2 gotas de DMF y se agitó a temperatura ambiente durante 2 horas. El disolvente se retiró y el residuo se disolvió de nuevo en 50 ml de THF. A esta solución se le añadió gota a gota una solución de (R)-15 (+)-4-bencil-2-oxazolidinona de litio (6,58 g, 37,1 mmol) en THF (50 ml). La mezcla se agitó de nuevo a temperatura ambiente durante 17 horas. El disolvente se retiró y el residuo se trató con  $NH_4Cl$  saturado y se extrajo con  $CH_2Cl_2$ . La capa de  $CH_2Cl_2$  se lavó con salmuera, se secó sobre  $MgSO_4$  20 y se concentró al vacío, dando 10,5 g, de aceite (rendimiento del 97%).

#### Ejemplo 49

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*Procedimiento General para la preparación de los análogos 121 a-d*

Ácido (S)-3-{4-[3-(metil-fenil-amino)-prop-1-inil]-fenil}-2-pirrol-1-il-propiónico (121a). Se disolvió el  
 15 éster 120a (0,82 g, 2,201 mmol) en THF:H<sub>2</sub>O (40:10 ml) y se  
 añadió LiOH·H<sub>2</sub>O (0,138 g, 3,301 mmol) y la mezcla se agitó a  
 temperatura ambiente durante 3,5 horas. El disolvente se  
 retiró y el residuo se diluyó con agua y se acidificó con  
 HCl al 10%. La mezcla se extrajo con CHCl<sub>3</sub> (3 x 50 ml). Los  
 20 extractos orgánicos reunidos se secaron sobre MgSO<sub>4</sub>, se  
 filtraron y el disolvente se retiró. La purificación por  
 cromatografía sobre gel de sílice, eluyendo con MeOH al 0-  
 2% en CHCl<sub>3</sub> que contenía ácido fórmico (0-0,1%), dio 129a  
 puro en forma de un sólido pardo claro (0,727 g, 92%): P.f.  
 25 de 55°C a 60°C; <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,29-7,25 (m, 2H),

584

7,21 (d,  $J = 8,0$  Hz, 2H), 6,92 (d,  $J = 8,0$  Hz, 2H), 6,88 (d,  $J = 8,4$  Hz, 2H), 6,83 (t,  $J = 7,4$  Hz, 1H), 6,65 (t,  $J = 2,0$  Hz, 2H), 6,13 (t,  $J = 2,0$  Hz, 2H), 4,72 (dd,  $J = 9,2$  y  $6,0$  Hz, 1H), 4,23 (s, 2H), 3,41-3,20 (m, 2H), 3,00 (s, 3H); CIMS  $m/z$  359 (M+H)<sup>+</sup>; IR 3418, 2960, 1726, 1597, 1272  $\text{cm}^{-1}$ . Análisis Calculado para  $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_2 \cdot 0,3\text{H}_2\text{O}$ : C, 75,93; H, 6,26; N, 7,74. Encontrado: C, 75,73; H, 6,19; N, 7,53.

Ácido (S)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-2-pirrol-1-il-propiónico (121b). Preparado a 10 partir del éster metílico 120b (0,337 g, 0,794 mmol) por el procedimiento general descrito para 129a. La purificación por cromatografía sobre gel de sílice, eluyendo con hexanos:acetato de etilo (2:1) seguido de hexanos:acetato de etilo (2:1) que contenía ácido fórmico al 0,2% dio el 15 ácido 128b en forma de un sólido amarillo pálido (0,231 g, 71%): p.f. 178°C a 180°C:  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,78-7,76 (m, 2H), 7,22 (m, 3H), 7,05 (d,  $J = 8,0$  Hz, 2H), 6,72 (d,  $J = 8,4$  Hz, 2H), 6,46 (t,  $J = 2,0$  Hz, 2H), 5,86 (t,  $J = 2,0$  Hz, 2H), 4,48 (dd,  $J = 9,6$  y  $5,6$  Hz, 1H), 3,50 (s, 20 2H), 3,27-2,97 (m, 2H), 2,26 (s, 3H): CIMS  $m/z$  409 (M-H)<sup>+</sup>. Análisis Calculado para  $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_3$ : C, 76,08; H, 5,40; N, 6,82. Encontrado: C, 75,77; H, 5,45; N, 6,70.

Ácido (S)-3-{4-[3-(4-fenil-piperidin-1-il)-prop-1-inil]-fenil}-2-pirrol-1-il-propiónico (121c). Preparado a 25 partir del éster 120c (0,344 g, 0,806 mmol) siguiendo el

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procedimiento general descrito para el 129a. La purificación por cromatografía, eluyendo con MeOH al 0-8% en CHCl<sub>3</sub> que contenía ácido fórmico al 0,1% dio 129c en forma de un sólido blanco (0,307 g, 92%): P.f. 201°C-203°C; 5 <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,33-21 (m, 5H), 7,17 (d, J = 7,3 Hz, 2H), 7,01 (d, J = 8,3 Hz, 2H), 6,70 (t, J = 2,2 Hz, 2H), 6,08 (t, J = 2,2 Hz, 2H), 4,68 (dd, J = 8,8 y 6,1 Hz, 1H), 3,91 (s, 2H), 3,48-3,20 (m, 4H), 2,98 (t, J = 11,5 Hz, 2H), 2,61 (t, J = 11,9 Hz, 1H), 2,52-2,13 (m, 2H), 1,96 10 (d, J = 12,7 Hz, 2H); CIMS m/z 413 (M+H)<sup>+</sup>. Análisis calculado para C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>·0,9H<sub>2</sub>O: C, 75,64; H, 7,01; N, 6,53. Encontrado: C, 75,29; H, 6,75; N, 6,44.

Ácido (S)-3-{4-[3-(metil-piridin-2-il-amino)-prop-1-inil]-fenil}-2-pirrol-1-il-propiónico (121d). Preparado a 15 partir del éster 120d (0,110 g, 0,294 mmol) por el procedimiento general descrito anteriormente. Se obtuvo el ácido 129d en forma de un sólido amarillo (0,098 g, 93%). <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 8,02 (m, 1H), 7,51-7,46 (m, 1H), 7,14 (d, J = 8,3 Hz, 2H), 6,82 (d, J = 8,0 Hz, 2H), 6,62-6,54 20 (m, 2H), 6,58 (t, J = 2,0 Hz, 2H), 6,00 (t, J = 2,2 Hz, 2H), 4,61 (dd, J = 9,4 y 5,6 Hz, 1H), 4,37 (s, 2H), 3,35-3,10 (m, 2H), 3,05 (s, 3H); CIMS m/z 360 (M+H)<sup>+</sup>. Análisis Calculado para C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>·0,5C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>: C, 71,44; H, 6,25; N, 6,25; N, 10,41. Encontrado: C, 71,14; H, 6,07; N, 10,20.

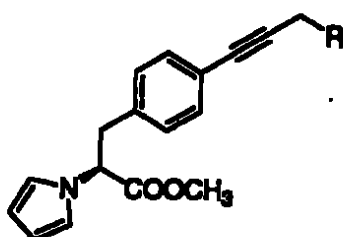
25 Los materiales de partida de éster se prepararon de la

1480

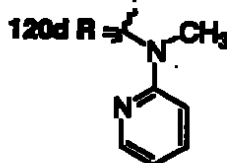
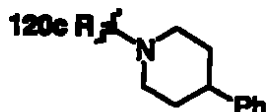
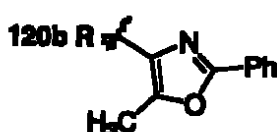
siguiente forma.

(a) (120 a-d).

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*Procedimiento General para la síntesis de ésteres 120 a-d.*

15      Éster metílico del ácido (S)-3-{4-[3-(metil-fenil-amino)-prop-1-inil]-fenil}-2-pirrol-1-il-propiónico (120a). Se disolvieron el triflato 119 (1,66 g, 4,399 mmol) y Pd(PPh<sub>3</sub>)<sub>4</sub> (0,356 g, 0,308 mmol) en DMF seca (10 ml). Se añadió una solución de N-metil-N-prop-2-inil anilina 20 (Magnus, P.; Ladlow, M.; Elliot, J.; Sook Kim, C.J. *Chem. Soc. Chem. Comm.* 1989, 518-519) (1,27 g, 8,798 mmol) en DMF (2 ml), seguido de trietilamina (1,84 ml, 13,197 mmol). Se pasó nitrógeno a través de la mezcla de reacción durante 0,5 horas. Se añadió CuI (0,167 g, 0,880 mmol) y la mezcla 25 se calentó a 45-50°C durante 6 horas en una atmósfera de



148A

nitrógeno. En este momento se incorporó más  $\text{Pd}(\text{PPh}_3)_4$  adicional (0,356 g, 0,308 mmol). Se continuó calentando durante 14 h y se añadieron más *N*-metil-*N*-prop-2-inil anilina (0,635 g, 4,399 mmol) y catalizador (0,254 g, 0,220 5 mmol). La mezcla se calentó durante otras 12 horas. En este momento, la mezcla se dejó enfriar y se diluyó con agua (150 ml) y  $\text{Et}_2\text{O}$  (100 ml). Las fases se separaron y la fase acuosa se extrajo con  $\text{Et}_2\text{O}$  (4 x 80 ml). Los extractos orgánicos reunidos se lavaron con agua y salmuera. Se 10 añadió carbono activado y la mezcla se hirvió durante 15-20 minutos. Se secó sobre  $\text{MgSO}_4$ , se filtró y el disolvente se retiró. La purificación por cromatografía ultrarrápida sobre gel de sílice, eluyendo con éter de petróleo al 60%-0% en diclorometano seguido de una segunda purificación 15 cromatográfica, eluyendo con hexanos:acetato de etilo (7:1 a 5:1), dio 11 puro en forma de un aceite espeso (1,256 g, 77%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,29-7,21 (m, 4H), 7,23 (d,  $J = 8,0$  Hz, 2H), 6,92-6,66 (m, 1H), 6,89 (d,  $J = 8,4$  Hz, 2H), 6,66 (t,  $J = 2,4$  Hz, 2H), 6,12 (t,  $J = 2,4$  Hz, 2H), 20 6,68 (dd,  $J = 9,2$  y 6,4 Hz, 1H), 4,24 (s, 2H), 3,67 (s, 3H), 3,39-3,18 (m, 2H), 3,02 (s, 3H); CIMS  $m/z$  373 ( $\text{M}+\text{H}$ ) $^+$ .

Éster metílico del ácido (*S*)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-2-pirrol-1-il-propiónico (120b). Este compuesto se preparó a partir del triflato 119 25 (1,47 g, 3,9 mmol) y 5-metil-2-fenil-4-prop-2-iniloxazol

580

125 (1,0 g, 5,070 mmol) siguiendo el procedimiento general descrito para 128a, excepto que no se añadió más catalizador adicional o 127 y la mezcla de reacción se realizó a 90°C. La purificación por cromatografía, eluyendo 5 con hexanos:acetato de etilo (5:1 a 4:1), dio 128b puro en forma de un aceite espeso (1,20, 73%).  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,99 (d,  $J = 8,4$  Hz, 1H), 7,98 (d,  $J = 7,2$  Hz, 1H), 7,45-7,39 (m, 3H), 7,29 (d,  $J = 8,0$  Hz, 2H), 6,92 (d,  $J = 8,4$  Hz, 2H), 6,68 (t,  $J = 2,0$  Hz, 2H), 6,13 (t,  $J = 2,0$  Hz, 10 2H), 4,40 (dd,  $J = 8,8$  y 6,4 Hz, 1H), 3,71 (s, 2H), 3,69 (s, 3H), 3,40-3,20 (m, 2H), 2,46 (s, 3H); CIMS  $m/z$  425 ( $\text{M}+\text{H}$ ) $^+$ .

Éster metílico del ácido (S)-3-{4-[3-(4-fenilpiperidin-1-il)-prop-1-inil]-fenil}-2-pirrol-1-il-15 propiónico (120c). Este compuesto se preparó a partir del triflato 119 (0,500 g, 1,325 mmol) y N-prop-2-inil-4-fenilpiperidina (Lambert, S. J., Kabalka, G.W.; Knapp, F.F. Jr.; Srivastava, P.C.J. *Org. Chem.* 1991, 56, 3707-3711) (0,396 g, 1,987 mmol) siguiendo el procedimiento descrito 20 para 128a con la excepción de que la reacción se realizó a 85°C. Después de 20 horas se añadieron más catalizador (5 % en moles) y N-prop-2-inil-4-fenilpiperidina (0,132 g, 0,662 mmol). La purificación por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo al 35%-45% 25 produjo 128c puro en forma de un aceite espeso (0,344 g,

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61%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,32-7,17 (m, 5H), 7,31 (d,  $J = 8,4$  Hz, 2H), 6,93 (d,  $J = 8,0$  Hz, 2H), 6,69 (t,  $J = 2,0$  Hz, 2H), 6,14 (t,  $J = 2,0$  Hz, 2H), 4,71 (dd,  $J = 9,2$  y 6,4 Hz, 1H), 3,70 (s, 3H), 3,53 (s, 2H), 3,41-3,21 (m, 2H), 5 3,08 (d a,  $J = 11,6$  Hz, 2H), 2,55-2,46 (m, 1H), 2,36 (t,  $J = 11,2$  Hz, 1H), 2,35 (t,  $J = 11,2$  Hz, 1H), 1,91-1,79 (m, 4H); CIMS  $m/z$  427 ( $\text{M}+\text{H}$ ) $^+$

Éster metílico del ácido (S)-3-{4-[3-(metil-piridin-2-il-amino)-prop-1-inil]-fenil}-2-pirrol-1-il-propiónico

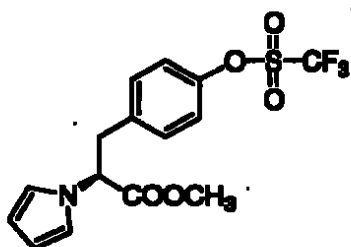
- 10 (120d). Este compuesto se preparó a partir del triflato 119 (0,526 g, 1,394 mmol) y 2-(N-metil-N-prop-2-inil)-piridina (véase 126, anterior) (0,407 g, 2,788 mmol) siguiendo el procedimiento general descrito para 128a con la excepción de que se usó piperidina como disolvente en lugar de DMF.
- 15 La purificación por cromatografía sobre gel de sílice, eluyendo con hexanos:acetato de etilo (4:1), dio 128d en forma de un aceite amarillento espeso (0,132 g, 25,3%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8,19-8,17 (m, 1H), 7,48-7,43 (m, 1H), 7,22 (d,  $J = 8,0$  Hz, 2H), 6,87 (d,  $J = 8,0$  Hz, 2H), 6,64 20 (t,  $J = 2,0$  Hz, 2H), 6,59 (d,  $J = 7,6$  Hz, 1H), 6,58 (d,  $J = 6,4$  Hz, 1H), 6,09 (t,  $J = 2,0$  Hz, 2H), 4,66 (dd,  $J = 9,0$  y 6,4 Hz, 1H), 4,54 (s, 2H), 3,65 (s, 3H), 3,36-3,16 (m, 2H), 3,09 (s, 3H); CIMS  $m/z$  374 ( $\text{M}+\text{H}$ ) $^+$ .

(b) El triflato 119, usado en la acción de 25 acoplamiento anterior, se preparó de la siguiente forma.

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Éster metílico del ácido (S)-2-pirrol-1-il-3-[(4-trifluorometanosulfonilo)fenil]-propiónico (119).

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119

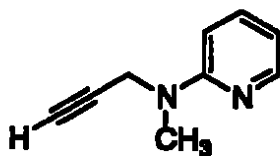
Una mezcla de fenol 1 (Véase Ejemplo 1) (6,64 g, 10 27,088 mmol) y *N*-feniltrifluorometanosulfonimida (10,47 g, 27,9 mmol) en CH<sub>2</sub>Cl<sub>2</sub> (70 ml) se enfrió a 0°C en una atmósfera de nitrógeno. Se añadió lentamente trietilamina (4,15 ml, 29,8 mmol). La mezcla se agitó a 0°C durante 1 hora. Después, se dejó que la temperatura alcanzará 15 lentamente la temperatura ambiente y se agitó a esta temperatura durante 2,5 horas. La mezcla se diluyó con Et<sub>2</sub>O (70 ml) y se lavó con agua, NaOH 1 N y salmuera. La fase orgánica se secó sobre MgSO<sub>4</sub>, se filtró y el disolvente se retiró. La purificación por cromatografía ultrarrápida 20 sobre gel de sílice, eluyendo con hexanos:acetato de etilo (5:1), produjo 127 en forma de un aceite espeso (9,55 g, 93%) que solidificó después del enfriamiento y trituración, dando un sólido blanco:  $[\alpha]^{25}_D -93,6^\circ$  ( $c = 5$ , CHCl<sub>3</sub>); <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7,13 (d,  $J = 8,8$  Hz, 2H), 7,02 (d,  $J = 25$  8,8 Hz, 2H), 6,66 (t,  $J = 2,1$  2H), 6,14 (t,  $J = 2,1$  Hz,

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2H), 4,69 (dd,  $J = 9,3$  y  $5,9$  Hz, 1H), 3,72 (s, 3H), 3,43-3,25 (m, 2H); IR 1731, 1426, 1203, 1136  $\text{cm}^{-1}$ ; CIMS  $m/z$  378 (M+H)<sup>+</sup>. Análisis Calculado para  $\text{C}_{15}\text{H}_{14}\text{F}_3\text{NO}_5\text{S}$ : C, 47,75; H, 3,74; N, 3,71. Encontrado: C, 47,83; H, 3,64; N, 3,54.

5 (c) Los alquinos que se usaron en la reacción de acoplamiento anterior se prepararon de la siguiente forma.

2-(*N*-metil-*N*-prop-2-ynil)piridina (118).

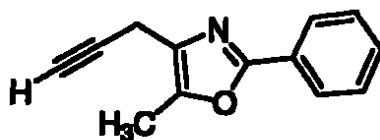


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10 Se suspendió hidruro sódico (0,467 g, 11,673 mmol) en DMF (10 ml) en una atmósfera de nitrógeno y se agitó en un  
15 baño de hielo. Se añadió 2-(metilamino)piridina (1 ml, 9,728 mmol) y la mezcla se agitó a 0°C durante 45 minutos. Después, se incorporó una solución al 80% de bromuro de propargilo en tolueno (1,19 ml, 10,7 mmol). Se dejó que la  
mezcla alcanzará la temperatura ambiente y se agitó durante  
20 una noche. La mezcla se diluyó con agua y se extrajo con  $\text{Et}_2\text{O}$ . Los extractos orgánicos reunidos se lavaron con agua y salmuera, se secaron sobre  $\text{MgSO}_4$ , se filtraron y el disolvente se retiró. La purificación por cromatografía sobre gel de sílice, eluyendo con hexanos:acetato de etilo  
25 (8:1), produjo 126a en forma de un aceite (0,867 g, 61%):  $^1\text{H}$

RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8,17 (dd,  $J = 4,6$  y  $1,7$  Hz, 1H), 7,46 (dt,  $J = 8,5$  y  $2,0$  Hz, 1H), 6,58 (m, 2H), 4,35 (d,  $J = 2,4$  Hz, 2H), 3,04 (s, 3H), 2,11 (t,  $J = 2,4$  Hz, 1H); CIMS  $m/z$  147 ( $\text{M}+\text{H}$ )<sup>+</sup>.

5 5-Metil-2-fenil-4-prop-2-iniloxazol (117).



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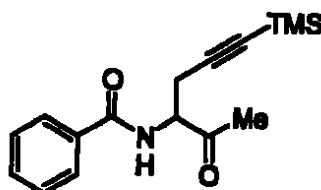
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De acuerdo con el procedimiento de Hulin (Hulin, B.; Newton, L.S.; Lewis, D.M.; Genereux, P.E.; Gibbs, M.; Clark, D.A. *J. Med. Chem.* **1996**, 39, 3897-3907). Se disolvió alquino 7 (3,01 g, 10,472 mmol) en MeOH (150 ml) y se trató con KOH al 10% (10 ml). La mezcla se agitó a temperatura ambiente durante 4,5 horas. En este momento, los disolventes se retiraron y el residuo se diluyó con agua y se acidificó a pH ~ 2 con HCl 6 M. El sólido precipitado se separó por filtración al vacío y se secó. El filtrado se extrajo con acetato de etilo (3 x 40 ml) y los extractos orgánicos reunidos se secaron con  $\text{MgSO}_4$ , se filtraron y el disolvente se retiró. El sólido obtenido a partir de las etapas previas (2,19 g) se trató con TFA (16 ml) y TFAA (8 ml) a 35-40°C durante una noche, como se ha descrito previamente por Hulin y colaboradores, dando el oxazol 125

después de purificación por cromatografía ultrarrápida sobre gel de sílice, eluyendo con hexanos:acetato de etilo (10:1 a 9:1). Se obtuvo el oxazol 125 en forma de un sólido blanquecino (1,89 g, 94%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,96-7,99 (m, 2H), 7,37-7,44 (m, 3H), 3,50 (d,  $J = 2,8$  Hz, 2H), 2,41 (s, 3H), 2,12 (t,  $J = 2,8$  Hz, 1H); CIMS  $m/z$  198 ( $\text{M}+\text{H}$ ) $^+$ .

*N*-[(1-acetil-4-(trimetilsilil)but-3-ynil)benzamida (116).

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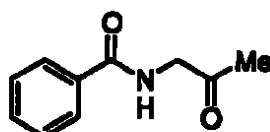
116

Se disolvió la amida 123 (2,55 g, 14,4 mmol) en THF 15 (150 ml) y se enfrió a  $-78^\circ\text{C}$  en una atmósfera de nitrógeno. Se añadió una solución de LHMDS 1,0 M en THF (14,4 ml, 14,4 mmol) y la mezcla se agitó durante 0,5 horas. Se añadió una solución de 3-bromo-1-(trimetilsilil)-1-propina (2,6 ml, 18,7 mmol) en THF (15 ml). La mezcla se dejó calentar a 20 temperatura ambiente y se agitó durante una noche. La mezcla se diluyó con agua y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (3 x 50 ml) y los extractos orgánicos reunidos se secaron sobre  $\text{MgSO}_4$ , se filtraron y el disolvente se retiró. La purificación por 25 cromatografía ultrarrápida sobre gel de sílice, eluyendo

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con hexanos:acetato de etilo (3:1), dio la amida 124 en forma de un sólido blanco (3,01 g, 73%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,68 (d,  $J = 7,2$  Hz, 2H), 7,40 (t,  $J = 7,2$  Hz, 1H), 7,32 (t,  $J = 7,2$  Hz, 2H), 7,02 (bd,  $J = 6,4$  Hz, 1H), 4,71 (q,  $J = 5,2$  Hz, 1H), 2,78 (d,  $J = 5,6$  Hz, 2H), 2,20 (s, 3H), 0,01 (s, 9H); CIMS  $m/z$  288 ( $\text{M}+\text{H}$ ) $^+$ ; IR 3396, 2961, 2174, 1722, 1644, 1481, 1250  $\text{cm}^{-1}$ . Análisis calculado para  $\text{C}_{16}\text{H}_{21}\text{NO}_2\text{Si}$ : C, 66,86; H, 7,36; N, 4,87. Encontrado: C, 67,15; H, 7,49; N, 4,72.

10 Benzamidoacetona (115).



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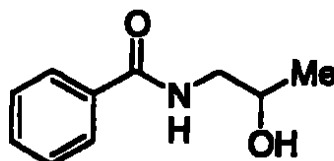
De acuerdo con el procedimiento de Ellinger (Ellinger, L.P.; Goldberg, A.A. J. Chem. Soc. 1949, 263). Se disolvió la *N*-(2-hidroxipropil)-benzamida (123) (3,0 g, 16,7 mmol) en  $\text{CH}_2\text{Cl}_2$  (60 ml) y PDC (9,42 g, 25,0 mmol). La mezcla se agitó a temperatura ambiente durante 24 y se añadió más PDC (9,42 g, 25,0 mmol). Se continuó agitando durante 24 horas. La mezcla se diluyó con acetato de etilo y se filtró a través de una capa de celite. Después, el residuo se pasó a través de columna de gel de sílice a temperatura ambiente, eluyendo con acetato de etilo. El disolvente se retiró y el



residuo se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con hexanos:acetato de etilo (1:1) que contenía MeOH (del 0 al 4%). La purificación produjo la amida 122 en forma de un sólido blanco (2,21 g, 75%);  $^1\text{H}$  RMN 5 ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,76 (dd,  $J = 7,0$  y  $1,5$  Hz, 2H), 7,48-7,36 (m, 3H), 6,69 (s a, 1H), 4,30 (d,  $J = 4,6$  Hz, 2H), 2,21 (s, 3H); CIMS  $m/z$  178 ( $\text{M}+\text{H}$ ) $^+$ .

*N*-(2-hidroxipropil)benzamida (114).

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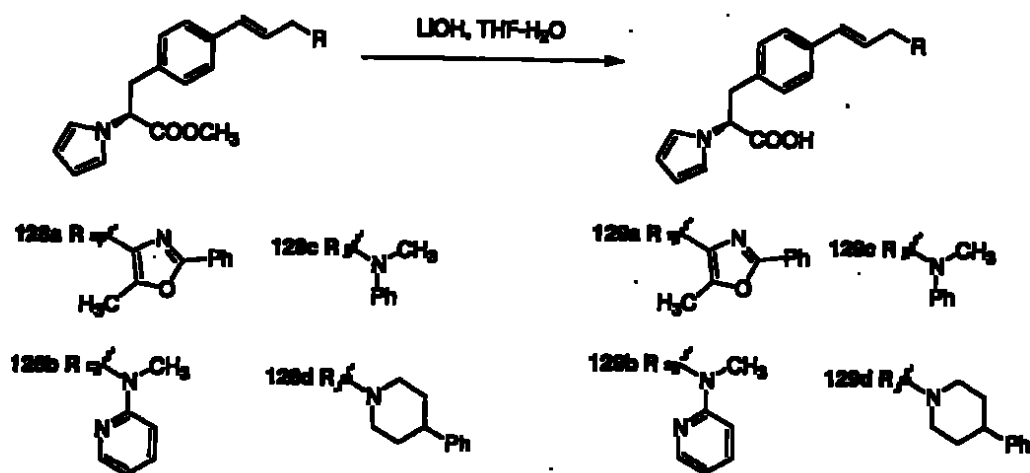


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De acuerdo con el procedimiento de Arai (Arai, K; 15 Tamura, s.; Masumizu, T.; Kawai, K.-I.; NakaJima, S.; Ueda, A. *Can. J. Chem.* 1990, 68, 903-907). Se enfrió a  $-78^\circ\text{C}$  una solución de DL-1-amino-2-propanol (3,4 ml, 43,2 mmol) y trietilamina (16,4 ml, 117,9 mmol) en  $\text{CH}_2\text{Cl}_2$  (60 ml) en una atmósfera de nitrógeno. Se añadió gota a gota cloruro de 20 benzoílo (4,6 ml, 39,3 mmol). La mezcla se dejó calentar lentamente y se agitó a temperatura ambiente durante una noche. Después, se diluyó con  $\text{CH}_2\text{Cl}_2$  (100 ml) y se lavó con HCl al 5% frío y salmuera. Las fases se separaron y la fase acuosa se extrajo con  $\text{CH}_2\text{Cl}_2$  (2 x 50 ml). Los extractos 25 orgánicos reunidos se secaron sobre  $\text{MgSO}_4$ , se filtraron y el

disolvente se retiró. El residuo se secó al vacío, dando la amida **5** en forma de un sólido amarillo pálido (6,21 g, 88%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,75 (d,  $J$  = 6,8 Hz, 2H), 7,49–7,39 (m, 3H), 6,57 (s a, 1H), 4,00 (m, 1H), 3,67–3,61 5 (m, 1H), 3,31–3,24 (m, 1H), 1,22 (d,  $J$  = 6,3 Hz, 3H).

#### Ejemplo 50



*Procedimiento general para la preparación de los análogos 129 a-d.*

- 10 Ácido (S)-3-{4-[(E)-3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil}-2-pirrol-1-il-propiónico (**129a**). Preparado a partir del éster **128a** (0,140 g, 0,328 mmol) siguiendo el procedimiento general. La purificación por cromatografía sobre gel de sílice, eluyendo con hexanos:acetato de etilo 15 (2:1) que contenía ácido fórmico (0-0,2%), dio el ácido **138a** en forma de un sólido blanco (0,085 g, 63%): P.f.

132°C-133°C;  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,95-7,92 (m, 2H), 7,41-7,39 (m, 3H), 7,19 (d,  $J = 8,0$  Hz, 2H), 6,90 (d,  $J = 8,4$  Hz, 2H), 6,65 (t,  $J = 2,0$  Hz, 2H), 6,37 (d,  $J = 15,6$  Hz, 1H), 6,25 (dt,  $J = 16,0$  y 6,4 Hz, 1H), 6,13 (t,  $J = 2,0$  Hz, 2H), 4,57 (dd,  $J = 8,8$  y 6,0 Hz, 1H), 3,39 (d,  $J = 6,8$  Hz, 2H), 3,38-3,15 (m, 2H), 2,33 (s, 3H); CIMS  $m/z$  413 ( $\text{M}+\text{H}$ ) $^+$ . Análisis calculado para  $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_3 \cdot 0,1\text{H}_2\text{O}$ : C, 75,38; H, 5,89; N, 6,76. Encontrado: C, 75,58; H, 6,21; N, 6,37.

Ácido (S)-3-{4-[(E)-3-(metil-piridin-2-il-amino)-10 propenil]-fenil}-2-pirrol-1-il-propiónico (129b). Preparado a partir del éster 128b (0,481 g, 1,281 mmol) siguiendo el procedimiento general descrito anteriormente. La purificación por cromatografía sobre gel de sílice, eluyendo con MeOH al 0-15% en  $\text{CHCl}_3$  seguido de THF, dio 138b 15 puro (0,123 g, 26%): P.f. 155°C-165°C;  $^1\text{H}$  RMN ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  7,98 (dd,  $J = 5,2$  y 1,0 Hz, 1H), 7,52-7,47 (m, 1H), 7,13 (d,  $J = 8,4$  Hz, 2H), 6,91 (d,  $J = 8,4$  Hz, 2H), 6,66 (t,  $J = 2,0$  Hz, 2H), 6,56 (dd,  $J = 6,4$  y 5,2 Hz, 1H), 6,38 (d,  $J = 15,6$  Hz, 1H), 6,14 (dt,  $J = 16,0$  y 5,6 Hz, 1H), 20 5,92 (t,  $J = 2,0$  Hz, 2H), 4,58 (dd,  $J = 9,6$  y 5,6 Hz, 1H), 4,22 (dd,  $J = 5,6$  y 1,2 Hz, 2H), 3,34-3,08 (m, 2H), 3,02 (s, 3H); CIMS  $m/z$  362 ( $\text{M}+\text{H}$ ) $^+$ .

Ácido (S)-3-{4-[(E)-3-(metil-fenil-amino)-propenil]-fenil}-2-pirrol-1-il-propiónico (129c). Se disolvió el 25 éster 128c (0,877 g, 2,342 mmol) en THF:H<sub>2</sub>O (40:10 ml) y se

añadió LiOH·H<sub>2</sub>O (0,147 g, 3,513 mmol) y la mezcla se agitó a temperatura ambiente durante 3,5 horas. El disolvente se retiró y el residuo se diluyó con agua y se acidificó con HCl al 10%. La mezcla se extrajo con CHCl<sub>3</sub> (3 x 50 ml). Los 5 extractos orgánicos reunidos se secaron sobre MgSO<sub>4</sub>, se filtraron y el disolvente se retiró. La purificación por cromatografía sobre gel de sílice, eluyendo con MeOH al 0-3% en CHCl<sub>3</sub> que contenía ácido fórmico al 0,1%, dio 138c puro en forma de un sólido pardusco (0,280 g, 33%): p.f. 10 85°C-90°C; <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ **E-isómero**: 7,26-7,18 (m, 3H), 6,92 (d, J = 8,4 Hz, 2H), 6,81-6,69 (m, 4H), 6,68 (t, J = 2 Hz, 2H), 6,44 (d, J = 15,6 Hz, 1H), 6,14 (t, J = 2,0 Hz, 2H), 4,73 (dd, J = 9,2 y 6,0 Hz, 1H), 4,03 (dd, J = 5,6 y 1,2 Hz, 2H), 3,48-3,24 (m, 2H), 2,97 (s, 3H); CIMS 15 m/z 361 (M+H)<sup>+</sup>. Análisis calculado para C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>·0,9H<sub>2</sub>O: C, 74,41; H, 6,84; N, 7,55. Encontrado: C, 74,03; H, 6,62; N, 7,36.

Ácido (S)-3-{4-[(E)-3-(4-fenil-piperidin-1-il)-propenil]-fenil}-2-pirrol-1-il-propiónico (129d). Preparado 20 a partir del éster 128d (1,772 g, 4,135 mmol) siguiendo el procedimiento general. La purificación por cromatografía sobre gel de sílice, eluyendo con MeOH al 0-12% en CHCl<sub>3</sub> que contenía ácido fórmico (0%-0,1%), dio el ácido 138d en forma de una espuma amarilla pálida (1,38 g, 80%): P.f. 25 126°C-130°C; <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,30-7,18 (m, 5H),

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7,17 (d,  $J = 7,1$  Hz, 2H), 6,95 (d,  $J = 8,1$  Hz, 2H), 6,57 (d,  $J = 16,0$  Hz, 1H), 6,55 (t,  $J = 2,0$  Hz, 2H), 6,26 (dt,  $J = 15,6$  y  $7,3$  Hz, 1H), 6,02 (t,  $J = 2,0$  Hz, 2H), 4,56 (dd,  $J = 8,8$  y  $6,1$  Hz, 1H), 3,69-3,49 (m, 4H), 3,42-3,12 (m, 2H), 5 2,70-2,62 (m, 3H), 2,33-2,26 (m, 2H), 1,91 (m, 2H); CIMS  $m/z$  415 (M+H)<sup>+</sup>. Análisis calculado para  $C_{27}H_{30}N_2O_2 \cdot 1,0 CH_2O_2$ . C, 73,02; H, 7,00; N, 6,08. Encontrado: C, 72,85; H, 7,05; N, 6,06.

Los materiales de partida de éster se prepararon de la siguiente forma.

Ésteres 128 a-b.

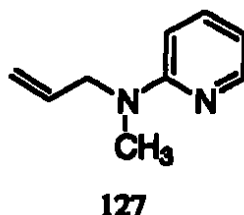
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Éster metílico del ácido (S)-3-{4-[(E)-3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil}-2-pirrol-1-il-propiónico (128a). Una mezcla del triflato 119 (Ejemplo 49) 5 (1,5 g 3,975 mmol), 5-metil-2-fenil-4-prop-2-eniloxazol 135 (1,19 g, 5,962 mmol), Pd(OAc)<sub>2</sub> (0,045 g, 0,199 mmol), PPh<sub>3</sub> (0,114 g, 0,437 mmol) y trietilamina (1,10 ml, 7,95 mmol) se disolvió en DMF (15 ml). Se pasó nitrógeno a través de la mezcla durante 20-25 minutos. La mezcla de reacción se 10 calentó a 90°C en una atmósfera de nitrógeno durante 44 horas. La mezcla se dejó enfriar y se filtró a través de una capa de celite, lavándose con éter etílico. Se añadió agua y las fases se separaron. La fase acuosa se extrajo con éter etílico (4 x 60 ml). Los extractos orgánicos 15 reunidos se lavaron con agua y salmuera, se secaron sobre MgSO<sub>4</sub>, se filtraron y el disolvente se retiró. La purificación por cromatografía sobre gel de sílice, eluyendo con acetato de etilo al 20%-25% en hexanos, produjo 137a en forma de un aceite espeso (0,668, 39%): <sup>1</sup>H 20 RMN (CDCl<sub>3</sub>, 400 MHz) δ 8,00-7,97 (m, 2H), 7,44-7,39 (m, 3H), 7,22 (d, J = 8,0 Hz, 2H), 6,91 (d, J = 8,0 Hz, 2H), 6,69 (t, J = 2,0 Hz, 2H), 6,42 (d, J = 14,8 Hz, 1H), 6,32 (dt, J = 15,6 y 6,4 Hz, 1H), 6,13 (t, J = 2,0 Hz, 2H), 4,71 (dd, J = 8,8 y 6,4 Hz, 1H), 3,68 (s, 3H), 3,42 (d, J = 6,4 Hz, 25 2H), 3,39-3,18 (m, 2H), 2,34 (s, 3H); CIMS m/z 427 (M+H)<sup>+</sup>.

Éster metílico del ácido (S)-3-{4-[(E)-3-(metilpiridin-2-il-amino)-propenil]-fenil}-2-pirrol-1-il-propiónico (128b). Este compuesto se preparó a partir del triflato 119 (1,0 g, 5,30 mmol) y 2-(N-metil-N-prop-2-enil)-piridina 136 (0,785 g, 5,300 mmol) siguiendo el procedimiento general descrito para 137a. Después de 16 horas, se añadió más Pd(OAc)<sub>2</sub> (5 % en moles). La reacción se completó después de 24 horas. La purificación por cromatografía, eluyendo con acetato de etilo al 20%-25% en 10 hexanos, dio 137b en forma de un aceite espeso (0,600, 60%): <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 8,18-8,16 (m, 1H), 7,47-7,42 (m, 1H), 7,21 (d, J = 8,4 Hz, 2H), 6,92 (d, J = 8,0 Hz, 2H), 6,69 (t, J = 2,0 Hz, 2H), 6,67-6,51 (m, 2H), 6,42 (d, J = 15,6 Hz, 1H), 6,18 (dt, J = 16,0 y 5,6 Hz, 1H), 6,13 (t, J = 2,0 Hz, 2H), 4,71 (dd, J = 8,6 y 6,0 Hz, 1H), 4,30 (dd, J = 5,6 y 1,2 Hz, 2H), 3,66 (s, 3H), 3,39-3,19 (m, 2H), 3,05 (s, 3H); CIMS m/z 376 (M+H)<sup>+</sup>.

2-(N-metil-N-prop-2-enil)-piridina (127).

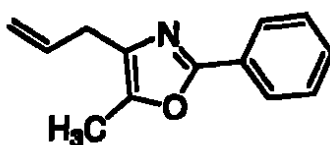
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Se suspendió hidruro sódico (0,82 g, 20,4 mmol) en DMF 25 (10 ml) en una atmósfera de nitrógeno y se agitó en un baño

de hielo. Se añadió 2-(metilamino)piridina (1,5 ml, 14,6 mmol). El baño de hielo se retiró y la mezcla se agitó a temperatura ambiente durante 0,5 horas. La mezcla se enfrió de nuevo en un baño de hielo y se añadió bromuro de alilo 5 (1,9 ml, 21,9 mmol). Se dejó que la mezcla alcanzara la temperatura ambiente y se agitó durante una noche. La mezcla se diluyó con agua y se extrajo con Et<sub>2</sub>O. Los extractos orgánicos reunidos se lavaron con agua y salmuera, se secaron sobre MgSO<sub>4</sub>, se filtraron y el 10 disolvente se retiró. La purificación por cromatografía ultrarrápida sobre gel de sílice, eluyendo con hexanos:acetato de etilo (20:1), produjo 127 en forma de un aceite (1,74 g, 80%): <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 8,15 (m, 1H), 7,42 (m, 1H), 6,53 (dd, *J* = 6,8 y 4,8 Hz, 1H), 6,48 15 (d, *J* = 8,4 Hz, 1H), 5,89-5,79 (m, 1H), 5,14 (m, 1H), 4,14 (d, *J* = 5,1 Hz, 2H), 3,03 (s, 3H); CIMS *m/z* 149 (M+H)<sup>+</sup>.

5-Metil-2-fenil-4-prop-2-eniloxazol (126).



126

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Se disolvió la amida 125 (2,00 g, 9,205 mmol) en TFA (16 ml) y se añadió TFA (8 ml). La mezcla se calentó a 25 35°C-40°C durante 16 horas. La mezcla se dejó enfriar y los

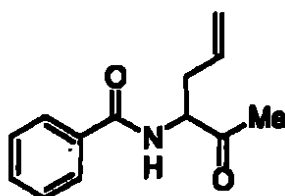


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disolventes se retiraron a presión reducida. El residuo se diluyó con  $\text{NaHCO}_3$  saturado (50 ml) y se añadió  $\text{NaHCO}_3$  sólido para neutralizar la mezcla. Después, se extrajo con acetato de etilo (3 x 60 ml). Los extractos orgánicos reunidos se lavaron con salmuera, se secaron sobre  $\text{MgSO}_4$ , se filtraron y el disolvente se retiró. La purificación por cromatografía ultrarrápida sobre gel de sílice, eluyendo con hexanos:acetato de etilo (15:1) dio 135 (1,751 g, 95,5%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,98 (d,  $J = 7,8$  Hz, 2H), 7,43–7,35 (m, 3H), 6,03–5,93 (m, 1H), 5,13 (dq,  $J = 16,9$  y 1,7 Hz, 1H), 5,09 (dq,  $J = 10,0$  y 1,5 Hz, 1H), 3,29 (d,  $J = 6,3$  Hz, 2H), 2,32 (s, 3H); CIMS  $m/z$  200 ( $\text{M}+\text{H}$ ) $^+$ ; IR 3070, 2924, 1638, 1450  $\text{cm}^{-1}$ .

N-(1-acetilbut-3-enil)benzamida (125).

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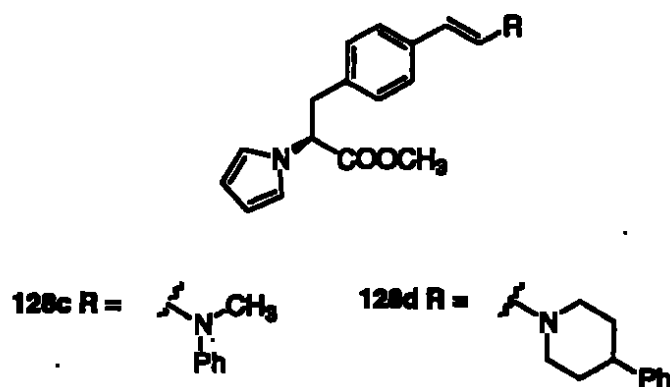
125

20 Se disolvió benzamidoacetona (Véase el Ejemplo 49) (2,098 g, 11,839 mmol) en THF (120 ml) y se enfrió a  $-78^\circ\text{C}$  en una atmósfera de nitrógeno. Se añadió una solución de LHMDS 1,0 M en THF (11,9 ml, 11,9 mmol) y la mezcla se agitó durante 40 minutos. Se añadió una solución de bromuro 25 de alilo (1,33 ml, 15,39 mmol) en THF (10 ml). La mezcla se

col

dejó calentar a temperatura ambiente y se agitó durante una noche. La mezcla se diluyó con salmuera y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (3 x 50 ml) y los extractos orgánicos reunidos se secaron sobre  $\text{MgSO}_4$ , se filtraron y el disolvente se retiró. La purificación por cromatografía ultrarrápida sobre gel de sílice, eluyendo con hexanos:acetato de etilo (2:1 a 1:1), dio la amida 9 (2,019 g, 78,5%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,79 (d,  $J = 7,1$  Hz, 2H), 7,51-7,41 (m, 3H), 6,95 (d a,  $J = 5,4$  Hz, 1H), 5,74-5,64 (m, 1H), 5,17-5,12 (m, 2H), 4,88 (dt,  $J = 6,8$  y 5,4 Hz, 1H), 2,85-2,78 (m, 1H), 2,61-2,54 (m, 1H), 2,28 (s, 3H); CIMS  $m/z$  218 ( $\text{M}+\text{H}$ ) $^+$ ; IR 3263, 3081, 1719, 1632, 1556  $\text{cm}^{-1}$ . Análisis calculado para  $\text{C}_{13}\text{H}_{15}\text{NO}_2$ : C, 71,87; H, 6,96; N, 6,45. Encontrado: C, 71,91; H, 7,03; N, 15 6,52.

(a-2) Los ésteres 128c-d se prepararon de la siguiente forma.



605

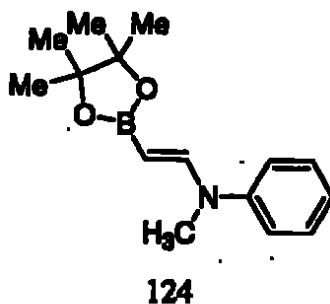
Éster metílico del ácido (S)-3-{4-[(E)-3-(metil-fenil-amino)-propenil]-fenil}-2-pirrol-1-il-propiónico (128c). Se agitaron el triflato 127 (0,98 g, 2,592 mmol), éster de boronato 124 (0,850 g, 3,111 mmol) y  $K_2CO_3$  (0,716 g, 5,184 mmol) en tolueno seco (25 ml). Se pasó nitrógeno a través de la mezcla durante 0,5 horas. Se añadió  $Pd(PPh_3)_4$  (0,149 g, 0,129 mmol) y la mezcla de reacción se calentó a 85°C-90°C durante 24 horas. La mezcla se dejó enfriar, se diluyó con acetato de etilo (70 ml) y se lavó con  $NaHCO_3$  saturado, 10 agua y salmuera. Los extractos orgánicos se secaron sobre  $MgSO_4$ , se filtraron y el disolvente se retiró. La purificación por cromatografía ultrarrápida sobre gel de sílice, eluyendo con éter de petróleo al 50-0% en diclorometano seguido de una segunda purificación 15 cromatográfica eluyendo con hexanos:acetato de etilo (8:1 a 5:1), dio el éster 137c en forma de una mezcla 94:6 de isómeros E:Z (0,819 g, 84%): **Isómero E**:  $^1H$  RMN ( $CDCl_3$ , 400 MHz)  $\delta$  7,23-7,20 (m, 2H), 7,21 (d,  $J = 8,0$  Hz, 2H), 6,92 (d,  $J = 8,0$  Hz, 2H), 6,77-6,70 (m, 3H), 6,69 (t,  $J = 2,0$  20 Hz, 2H), 6,44 (d,  $J = 16,0$  Hz, 1H), 6,19 (dt,  $J = 15,6$  y 5,6 Hz, 1H), 6,13 (t,  $J = 2,0$  Hz, 2H), 4,71 (dd,  $J = 9,2$  y 6,4 Hz, 1H), 4,05 (dd,  $J = 5,6$  y 1,2 Hz, 2H), 3,69 (s, 3H), 3,40 -3,19 (m, 2H), 2,95 (s, 3H); CIMS  $m/z$  375 ( $M+H$ ) $^+$ .

Éster metílico del ácido (S)-3-{4-[(E)-3-(4-fenil-25 piperidin-1-il)-propenil]-fenil}-2-pirrol-1-il-propiónico

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(128d). Este compuesto se preparó a partir del triflato 127 (2,0 g, 5,296 mmol) y el éster de boronato 124 (2,6 g, 7,944 mmol) siguiendo el procedimiento descrito para 128c. La purificación por cromatografía ultrarrápida, eluyendo 5 con acetato de etilo al 33-45% en hexanos que contenía Et<sub>3</sub>N al 1%, dio 128d (isómero E, 1,801 g, 79%) y una mezcla E:Z (0,217 g, 9,9%) en forma de aceites. **isómero E**: <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,50-7,15 (m, 7H), 6,95 (d, J = 8,4 Hz, 2H), 6,69 (t, J = 2,0 Hz, 2H), 6,45 (d, J = 16,0 Hz, 1H), 10 6,27 (dt, J = 15,6 y 6,8 Hz, 1H), 6,13 (t, J = 2,0 Hz, 2H), 4,71 (dd, J = 8,8 y 6,4 Hz, 1H), 3,68 (s, 3H), 3,40-3,19 (m, 2H), 3,16 (d, J = 6,8 Hz, 2H), 3,08 (d, J = 11,6 Hz, 2H), 2,51-2,46 (m, 1H), 2,07 (t, J = 11,2 Hz, 1H), 2,06 (t, J = 11,2 Hz, 1H), 1,84-1,77 (m, 4H); CIMS m/z 429 (M+H)<sup>+</sup>.

15 Metil-fenil[2-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-vinil]-amina (124).



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Una mezcla de N-metil-N-prop-2-en-1-yl anilina (1,0 ml, 6,873 mmol) y pinacolborano (1,2 ml, 8,247 mmol) en CH<sub>2</sub>Cl<sub>2</sub> 25 (5 ml) se le añadió a Cp<sub>2</sub>ZrHCl (0,088 g, 0,343 mmol) a 0°C.

607

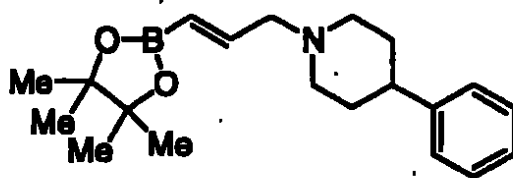
La mezcla se dejó calentar a temperatura ambiente y se agitó durante 8 días en una atmósfera de nitrógeno. En ese momento, la mezcla se diluyó con Et<sub>2</sub>O (50 ml) y se lavó con agua (30 ml). Las fases se separaron y la fase acuosa se 5 extrajo con Et<sub>2</sub>O (2 x 30 ml). Los extractos orgánicos reunidos se secaron sobre MgSO<sub>4</sub>, se filtraron y el disolvente se retiró. La purificación por cromatografía sobre gel de sílice, eluyendo con hexanos:acetato de etilo (20:1 a 10:1), produjo 124 en forma de un sólido 10 blanquecino (0,99 g, 53%): <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,21-7,17 (m, 2H), 6,69-6,64 (m, 3H), 6,60 (dt, J = 18,0 y 4,4 Hz, 1H), 5,55 (dt, J = 18,0 y 1,6 Hz, 1H), 3,99 (dd, J = 4,4 y 1,6 Hz, 2H), 2,94 (s, 3H), 1,25 (s, 12H); CIMS m/z 274 (M+H)<sup>+</sup>.

15      Éster metílico del ácido (S)-3-{4-[(E)-3-(metil-fenil-amino)-propenil]-fenil}-2-pirrol-1-il-propiónico (123). Este compuesto se preparó a partir del triflato 119 (2,0 g, 5,296 mmol) y el éster de boronato 124 (2,6 g, 7,944 mmol) siguiendo el procedimiento descrito para 137c. La 20 purificación por cromatografía ultrarrápida, eluyendo con acetato de etilo al 33-45% en hexanos conteniendo con Et<sub>3</sub>N al 1%, dio 123 (isómero E, 1,801 g, 79%) y una mezcla de E:Z en forma de aceites (0,217 g, 9,9%). **isómero E**: <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,50-7,15 (m, 7H), 6,95 (d, J = 8,4 Hz, 25 2H), 6,69 (t, J = 2,0 Hz, 2H), 6,45 (d, J = 16,0 Hz, 1H),

6,27 (dt,  $J = 15,6$  y  $6,8$  Hz, 1H), 6,13 (t,  $J = 2,0$  Hz, 2H), 4,71 (dd,  $J = 8,8$  y  $6,4$  Hz, 1H), 3,68 (s, 3H), 3,40-3,19 (m, 2H), 3,16 (d,  $J = 6,8$  Hz, 2H), 3,08 (d,  $J = 11,6$  Hz, 2H), 2,51-2,46 (m, 1H), 2,07 (t,  $J = 11,2$  Hz, 1H), 2,06 (t,  $J = 11,2$  Hz, 1H), 1,84-1,77 (m, 4H); CIMS  $m/z$  429 (M+H)<sup>+</sup>.

4-Fenil-1-[2-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-vinil]-piperidina (130).

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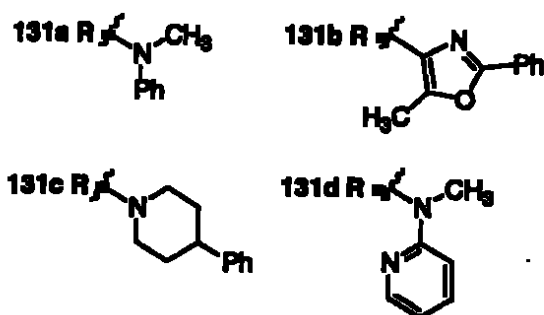
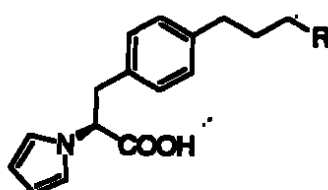
Se añadió una mezcla de *N*-prop-2-enil-4-fenilpiperidina (1,5 g, 7,526 mmol) y pinacolborano (1,64 ml, 11,289 mmol) en CH<sub>2</sub>Cl<sub>2</sub> (8 ml) a Cp<sub>2</sub>ZrHCl (0,194 g, 0,753 mmol) a 0°C. La mezcla se dejó calentar a temperatura ambiente y se agitó durante 48 horas en una atmósfera de nitrógeno. En ese momento, la mezcla se diluyó con Et<sub>2</sub>O (50 ml) y se añadió cuidadosamente agua (30 ml). Las fases se separaron y los extractos orgánicos se secaron sobre MgSO<sub>4</sub>, se filtraron y el disolvente se retiró, dando el 18 en forma de un sólido (2,46 g, 100%): <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ

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7,29-7,18 (m, 5H), 6,68 (dt,  $J = 17,6$  y  $6,0$  Hz, 1H), 5,62 (dt,  $J = 18,0$  y  $1,6$  Hz, 1H), 3,11 (dd,  $J = 6,4$  y  $1,6$  Hz, 2H), 3,04 (d,  $J = 12,0$  Hz, 2H), 2,51-2,44 (m, 1H), 2,10-2,03 (m, 2H), 1,84-1,79 (m, 4H), 1,26 (s, 12H); CIMS  $m/z$  5 328 (M+H)<sup>+</sup>.

Ejemplo 51

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*Procedimiento general para la preparación de los análogos*

*131 a-d*

25      Ácido    (S)-3-{4-[3-(metil-fenil-amino)-propil]-fenil}-

2-pirrol-1-il-propiónico (131a). Se disolvió el éster 130a (0,223 g, 0,592 mmol) en THF:H<sub>2</sub>O (10:4 ml) y se añadió LiOH·H<sub>2</sub>O (0,037 g, 0,888 mmol) y la mezcla se agitó a temperatura ambiente durante 3,5 horas. El disolvente se retiró y el residuo se diluyó con agua y se acidificó con HCl al 10%. La mezcla se extrajo con CHCl<sub>3</sub> (3 x 50 ml). Los extractos orgánicos reunidos se secaron sobre MgSO<sub>4</sub>, se filtraron y el disolvente se retiró. La purificación por cromatografía sobre gel de sílice, eluyendo con MeOH 0-5% en CHCl<sub>3</sub> contando con ácido fórmico (0-0,1%), dio 140a puro en forma de un sólido pardo pálido (0,190 g, 88%): <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,33 (m, 2H), 7,12-7,06 (m, 3H), 6,95 (d, J = 8,3 Hz, 2H), 6,91 (d, J = 8,3 Hz, 2H), 6,69 (t, J = 2,0 Hz, 2H), 6,10 (t, J = 2,0 Hz, 2H), 4,73 (dd, J = 9,1 y 6,3 Hz, 1H), 3,42-3,18 (m, 4H), 2,52 (t, J = 7,3 Hz, 2H), 1,88-1,81 (m, 2H). Análisis calculado para C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>·0,1 H<sub>2</sub>O: C, 75,84; H, 7,25; N, 7,69. Encontrado. C, 75,73; H, 7,40; N, 7,50.

Ácido (S)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propiónico (131b). Preparado a partir del éster 130b (0,243 g, 0,567 mmol) siguiendo el procedimiento general. La purificación por cromatografía ultrarrápida, eluyendo con 33-50% de acetato de etilo en hexanos que contenía ácido fórmico (0-0,2%), dio 140b puro en forma de un sólido amarillo claro (0,206 g, 88%): p.f.



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167°C-168°C;  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,94 (m, 2H), 7,40 (m, 3H), 7,04 (d,  $J = 7,8$  Hz, 2H), 6,93 (d,  $J = 7,8$  Hz, 2H), 6,71 (s a, 2H), 6,14 (s a, 2H), 4,72 (m, 1H), 3,39-3,16 (m, 2H), 2,58 (t,  $J = 7,3$  Hz, 2H), 2,47 (t,  $J = 7,3$  Hz, 2H), 2,26 (s, 3H), 1,92 (qn,  $J = 7,3$  Hz, 2H); CIMS  $m/z$  415 (M+H) $^+$ .

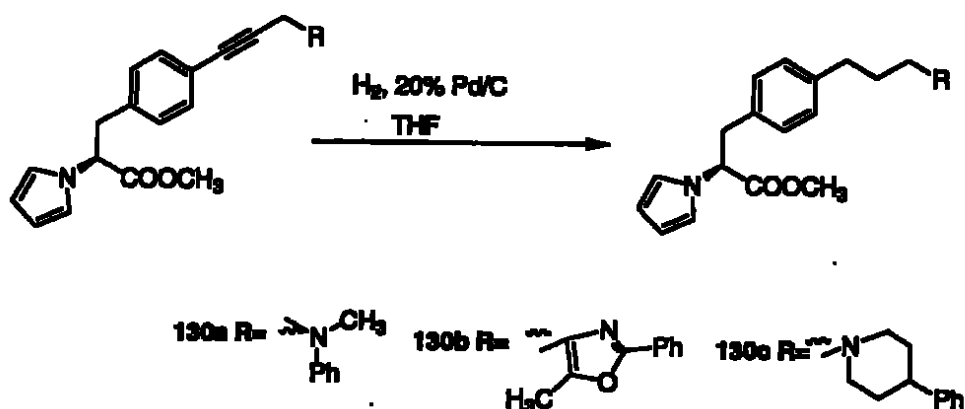
Ácido (S)-3-{4-[3-(4-fenil-piperidin-1-il)-propil]-fenil}-2-pirrol-1-il-propiónico (131c). Preparado a partir del éster 131c (0,248 g, 0,576 mmol) por el procedimiento 10 general descrito anteriormente. La purificación por cromatografía sobre gel de sílice, eluyendo con MeOH al 0-9% en  $\text{CHCl}_3$  que contenía ácido fórmico (0-0,1%), dio 139c puro en forma de una espuma blanca (0,137 g, 57%): p.f. 95°C-100°C;  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,29-7,16 (m, 3H), 15 7,14 (d,  $J = 8,3$  Hz, 2H), 6,98 (d,  $J = 8,3$  Hz, 2H), 6,95 (d,  $J = 8,0$  Hz, 2H), 6,67 (t,  $J = 2,0$  Hz, 2H), 6,04 (t,  $J = 2,0$  Hz, 2H), 4,64 (t,  $J = 7,5$  Hz, 1H), 3,50 (m, 1H), 3,45 (m, 1H), 3,41-3,09 (m, 2H), 2,82-2,78 (m, 2H), 2,57-2,33 (m, 4H), 2,21 (m, 2H), 2,03-1,99 (m, 2H), 1,84 (m, 2H); 20 CIMS  $m/z$  417 (M+H) $^+$ . Análisis calculado para  $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_2 \cdot 1,0\text{H}_2\text{O}$ : C, 74,62; H, 7,89; N, 6,45. Encontrado: C, 74,23; H, 7,63; N, 6,25.

Ácido (S)-3-{4-[3-(metil-piridin-2-il-amino)-propil]-fenil}-2-pirrol-1-il-propiónico (131d). Preparado a partir 25 del éster 131d (0,378 g, 1,001 mmol) por el procedimiento

general. La purificación por cromatografía ultrarrápida, eluyendo con MeOH al 0-15% en  $\text{CHCl}_3$ , dio 142d en forma de un sólido blanco (0,280 g, 77%): p.f.  $66^\circ\text{C}$ - $68^\circ\text{C}$ ;  $^1\text{H}$  RMN ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  7,90-7,85 (m, 1H), 7,82 (d,  $J = 6,0$  Hz, 1H), 7,01 (t,  $J = 8,0$  Hz, 3H), 6,94 (d,  $J = 8,0$  Hz, 2H), 6,87 (t,  $J = 6,8$  Hz, 1H), 6,66 (t,  $J = 2,0$  Hz, 2H), 5,96 (t,  $J = 2,0$  Hz, 2H), 4,80 (dd,  $J = 10,0$  y  $5,6$  Hz, 1H), 3,55 (t,  $J = 7,6$  Hz, 2H), 3,37-3,15 (m, 2H), 3,12 (s, 3H), 2,62 (t,  $J = 7,6$  Hz, 2H), 1,94 (qn,  $J = 7,2$  Hz, 2H); CIMS  $m/z$  364 ( $\text{M}+\text{H}$ ) $^+$ .

10 Análisis calculado para  $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_2 \cdot 0,3\text{CHCl}_3$ : C, 67,08; N, 6,39; N, 10,52. Encontrado: C, 67,30; H, 6,39, N, 10,21.

(a) Los ésteres 130a-c se prepararon de la siguiente forma.



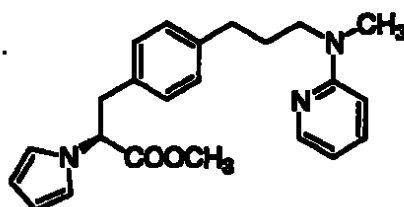
Éster metílico del ácido (S)-3-{4-[3-(metil-fenil-amino)-propil]-fenil}-2-pirrol-1-il-propiónico (130a). Se disolvió el alquino 120a (0,648 g, 1,739 mmol) en MeOH (50 ml) y se añadió Pd al 20%/C (0,050 g). La mezcla se 5 hidrogenó a temperatura ambiente durante 18 horas. La mezcla se filtró a través de celite y el disolvente se retiró. La purificación por cromatografía ultrarrápida, eluyendo con hexanos:acetato de etilo (6:1), dio 130a en forma de un aceite (0,439 g, 67%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  10 7,20 (t,  $J = 8,0$  Hz, 2H), 7,05 (d,  $J = 7,6$  Hz, 2H), 6,92 (d,  $J = 8,0$  Hz, 2H), 6,71 (t,  $J = 2,0$  Hz, 2H), 6,65 (t,  $J = 7,8$  Hz, 3H), 6,14 (t,  $J = 2,0$  Hz, 2H), 4,73 (dd,  $J = 8,8$  y 6,4 Hz, 1H), 3,69 (s, 3H), 3,41-3,20 (m, 2H), 3,30 (t,  $J = 7,4$  Hz, 2H), 2,90 (s, 3H), 2,59 (t,  $J = 7,6$  Hz, 2H), 1,86 15 (qn,  $J = 7,6$  Hz, 2H), CIMS  $m/z$  377 ( $\text{M}+\text{H}$ ) $^+$ .

Éster metílico del ácido (S)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propiónico (130 b). Este compuesto se preparó a partir del alquino 120b (0,249 g, 0,586 mmol) siguiendo el procedimiento general 20 descrito para 130a con la excepción de que la reacción se realizó en THF. El producto bruto se usó para transformaciones posteriores. Se obtuvo el éster 130b en forma de un aceite (0,243, 96,8%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,91 (dd,  $J = 8,0$  y 1,6 Hz, 2H), 7,37-7,32 (m, 3H), 6,99 25 (d,  $J = 8,4$  Hz, 2H), 6,85 (d,  $J = 8,0$  Hz, 2H), 6,64 (t,  $J =$

2,0 Hz, 2H), 6,07 (t,  $J = 2,0$  Hz, 2H), 4,65 (dd,  $J = 8,8$  y 6,8 Hz, 1H), 3,62 (s, 3H), 3,33-3,11 (m, 2H), 2,54 (t,  $J = 7,6$  Hz, 2H), 2,41 (t,  $J = 7,6$  Hz, 2H), 2,19 (s, 3H), 1,89 (qn,  $J = 7,6$  Hz, 2H); CIMS  $m/z$  429 (M+H)<sup>+</sup>.

5      Éster metílico del ácido (S)-3-{4-[3-(4-fenil-piperidin-1-il)-propil]-fenil}-2-pirrol-1-il-propiónico (130c). Este compuesto se preparó a partir del alquino 120c (0,408 g, 0,956 mmol) siguiendo el procedimiento descrito para 130a. La reacción se realizó en THF. La purificación  
10 se realizó por cromatografía, eluyendo con acetato de etilo al 33-45% que contenía Et<sub>3</sub>N al 1,0%, dando 130c en forma de un aceite (0,262 g, 64%): <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7,24-7,10 (m, 5H), 7,00 (d,  $J = 8,0$  Hz, 2H), 6,85 (d,  $J = 8,0$  Hz, 2H), 6,65 (t,  $J = 2,0$  Hz, 2H), 6,08 (t,  $J = 2,0$  Hz, 2H), 4,66 (dd,  $J = 8,8$  y 6,4 Hz, 1H), 3,62 (s, 3H), 3,34-3,12 (m, 2H), 2,98 (d,  $J = 11,6$  Hz, 2H), 2,52 (t,  $J = 7,6$  Hz, 2H), 2,42 (m, 1H), 2,31 (t,  $J = 7,6$  Hz, 2H), 1,99-1,93 (m, 2H), 1,80-1,72 (m, 6H); CIMS  $m/z$  431 (M+H)<sup>+</sup>.

20      Éster metílico del ácido (S)-3-{4-[3-(metil-piridin-2-il-amino)-propil]-fenil}-2-pirrol-1-il-propiónico (130d).

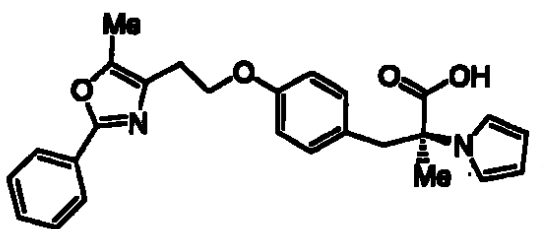


130d

Se disolvió el alqueno 128b (0,430 g, 1,145 mmol) en THF (16 ml). Se añadió Pd/C (0,050 g) y la mezcla se hidrogenó a temperatura ambiente durante 24 horas. Se añadió más catalizador (0,050 g) y la reacción se continuó durante 24 horas más. El catalizador se filtró y el disolvente se retiró, dando el éster 130d en forma de un aceite espeso (0,378 g, 87%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8,08-8,06 (m, 1H), 7,36-7,31 (m, 1H), 6,99 (d,  $J = 8,0$  Hz, 2H), 6,85 (d,  $J = 8,0$  Hz, 2H), 6,64 (t,  $J = 2,0$  Hz, 2H), 6,43 (dd,  $J = 6,4$  y  $5,4$  Hz, 1H), 6,33 (d,  $J = 8,8$  Hz), 6,07 (t,  $J = 2,0$  Hz, 2H), 6,65 (dd,  $J = 8,8$  y  $6,8$  Hz, 1H), 3,62 (s, 3H), 3,45 (t,  $J = 7,4$  Hz, 2H), 3,33-3,12 (m, 2H), 2,94 (s, 3H), 2,53 (t,  $J = 7,6$  Hz, 2H), 1,81 (qn,  $J = 7,6$  Hz, 2H); CIMS  $m/z$  378 ( $\text{M}+\text{H}$ ) $^+$ .

### Ejemplo 52

Éster metílico del ácido (S)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (134).



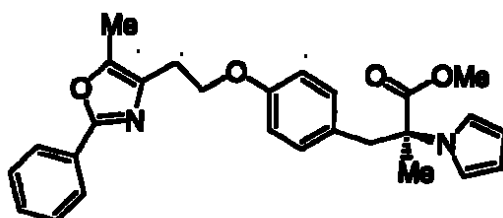
134

A una solución agitada del éster metílico del ácido (S)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (3,33 g, 7,5 mmol) en 2-metoxietanol (20 ml) y agua (5 ml) se le añadió hidróxido 5 de litio (180 mg, 7,5 mmol). La mezcla de reacción se agitó a temperatura ambiente durante una noche. La mezcla de reacción se vertió en agua y se acidificó con ácido clorhídrico diluido. La reacción se extrajo con acetato de etilo y la capa orgánica se secó (MgSO<sub>4</sub>) y se purificó por 10 cromatografía. La recristalización en acetato de etilo y hexanos dio el producto en forma de cristales blancos. Rendimiento = 1,3 g 40% P.f. 149,5°C-150,5°C. 500 MHz <sup>1</sup>H RMN (CDCl<sub>3</sub>) δ 7,94 (m, 2H), 7,41 (m, 3H), 6,76 (m, 2H), 6,70 (d, J = 9 Hz), 6,65 (d, J = 9 Hz), 6,18 (m, 2H), 4,15 (t, 2H, J = 6,8 Hz), 3,36 (d, 1H, J = 13,9), 3,29 (d, 1H, J = 13,9), 15 2,96 (t, 2H J = 6,8 Hz), 2,36 (s, 3H), 1,62 (s, 3H); MS m/z 431 (M+1), 429 (M-1). Análisis calculado para C<sub>26</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub> C, 72,54; H, 6,09; N, 6,51. Encontrado: C, 72,17; H, 6,15; N, 6,50.

20 El éster metílico del ácido (S)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-25 propiónico (133).

273

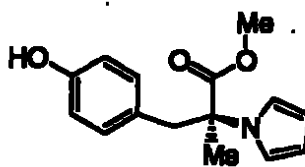


133

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A una solución agitada del éster metílico del ácido (S)-3-(4-hidroxifenil)-2-metil-2-pirrol-1-il-propiónico descrito en el ejemplo 1 (2,44 g, 9,4 mmol) en THF anhidro 10 (25 ml) se le añadió trifenilfosfina (2,47 g, 9,4 mmol) y 2-(5-metil-2-feniloxazol-4-il)etanol (1,911 g, 9,4 mmol). Se añadió gota a gota una solución de DIAD (1,85 ml, 9,4 mmol) en THF anhidro (10 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 48 horas. Después, el 15 disolvente se retiró a presión reducida, dando un aceite amarillo. La mezcla de reacción se purificó por cromatografía, eluyendo con 1:10 a 1:1 de EtOAc:Hexano dando el éster deseado en forma de un aceite opaco (3,33 g, 80%). MS  $m/z$  445 ( $M+1$ ).

20 (b) Éster metílico del ácido (S)-3-(4-hidroxifenil)-2-metil-2-pirrol-1-il-propiónico (132).



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A una solución agitada y enfriada (0°C) de metanol (20 ml) se le añadió gota a gota cloruro de tionilo (2,06 ml, 28,2 mmol) y la reacción se agitó durante 5 minutos. Se 5 añadió  $\alpha$ -metil-L-tirosina (5 g, 25,6 mmol) y la mezcla de reacción se calentó a temperatura ambiente. Después, la reacción se calentó a reflujo durante 6 horas y se enfrió a temperatura ambiente. El disolvente se retiró al vacío. El éster metílico bruto se disolvió en agua (50 ml) ácido 10 acético (50 ml) y acetato sódico (3,36 g, 40,9 mmol) y se añadió 2,5 dimetoxitetrahydrofurano (5,29 ml, 40,9 mmol). La mezcla de reacción se calentó a 90°C durante 15 minutos, se vertió en agua (200 ml) y se extrajo con acetato de etilo (3 x 100 ml). La capa orgánica se secó sobre MgSO<sub>4</sub> y 15 el disolvente se retiró a presión reducida. El residuo se purificó por cromatografía (usando acetato de etilo:hexanos 1:10 a 1:1), dando el pirrol deseado (5,38 g, 81%) en forma de un aceite transparente. 500 MHz, <sup>1</sup>H RMN (CDCl<sub>3</sub>)  $\delta$  6,71 (m, 2H), 6,63 (d, 2H,  $J$  = 8,4 Hz), 6,57 (d, 2H,  $J$  = 8,4 20 Hz), 6,17 (m, 2H), 3,34 (s, 3H), 3,36 (d, 1H,  $J$  = 13,9), 3,25 (d, 1H,  $J$  = 13,9), 1,6 (s, 3H); MS  $m/z$  258 (M-1).

### Ejemplo 53

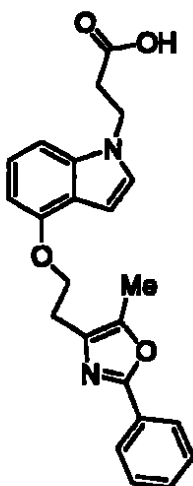
Ácido 3-{5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-propiónico (140).



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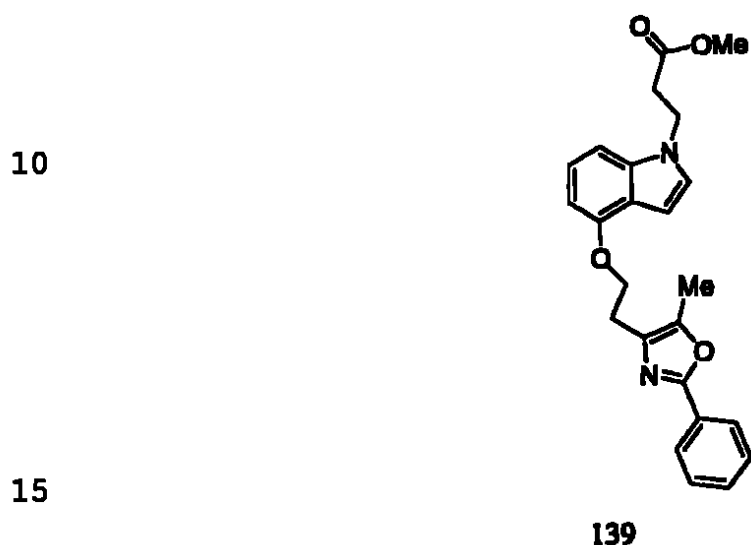
140

Una mezcla del éster metílico del ácido 4-{5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-propiónico  
 15 (136, 0,81 g, 2,00 mmol) y LiOH (240 mg, 10,0 mmol) en DME  
 (16 ml) y agua (4 ml) se agitó a temperatura ambiente  
 durante una noche. La reacción se diluyó con agua, se  
 acidificó con HCl 2 N, se extrajo con acetato de etilo, se  
 secó sobre MgSO<sub>4</sub>, y se concentró bajo presión reducida. El  
 20 sólido se recrystalizó en EtOAc/hexanos produciendo el  
 ácido propiónico deseado (560 mg, 72%). 400 MHz <sup>1</sup>H RMN  
 (DMSO-d<sub>6</sub>) δ 7,86 (m, 2H), 7,43 (m, 3H), 7,31 (d, 1H, J = 8,8  
 Hz), 7,23 (d, 1H, J = 2,9 Hz), 7,01 (d, 1H, J = 2,4 Hz),  
 6,71 (dd, 1H, J = 8,8, 2,4 Hz), 6,24 (d, 1H, J = 2,9 Hz),  
 25 4,28 (t, 2H, J = 6,8 Hz), 4,14 (t, 2H, J = 6,6 Hz), 2,88

(t, 2H,  $J = 6,6$  Hz), 2,65 (t, 2H,  $J = 6,8$  Hz), 2,32 (s, 3H). MS  $m/z$  391 (M+1).

El éster metílico del ácido 4-[S-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il]-propiónico se preparó de la siguiente forma.

(a) éster metílico del ácido 4-{5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-propiónico (139)



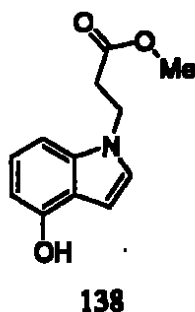
Una mezcla del éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-propiónico  
20 (0,88 g, 2,18 mmol) y LiOH (260 mg, 10,9 mmol) en 2-metoxietanol (16 ml) y agua (4 ml) se agitó a temperatura ambiente durante una noche. La reacción se diluyó con agua, se acidificó con HCl 2 N, se extrajo con acetato de etilo, se secó sobre  $MgSO_4$ , y se concentró a presión reducida. El  
25 sólido se recristalizó en EtOAc/hexanos, produciendo el

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ácido propiónico deseado (400 mg, 47%). 400 MHz  $^1\text{H}$  RMN (DMSO- $d_6$ )  $\delta$  7,86 (m, 2H), 7,43 (m, 3H), 7,16 (d, 1H,  $J = 3,2$  Hz), 6,99 (m, 2H), 6,50 (d, 1H,  $J = 7,3$  Hz), 6,30 (d, 1H,  $J = 2,7$  Hz), 4,29 (t, 2H,  $J = 6,8$  Hz), 4,24 (t, 2H,  $J = 6,4$  5 Hz), 2,94 (t, 2H,  $J = 6,4$  Hz), 2,65 (t, 2H,  $J = 6,8$  Hz), 2,35 (s, 3H). MS  $m/z$  391 (M+1).

(b) Éster metílico del ácido 3-(4-hidroxi-indol-1-il)-propiónico (138)

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15 Una mezcla de éster metílico del ácido 3-(4-hidroxi-indol-1-il)-propiónico (0,56 g, 2,55 mmol), carbonato de cesio (1,66 g, 5,11 mmol) y 2-(5-metil-2-fenil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (1,63 g, 4,57 mmol) en DMF (25 ml) se calentó a 50°C durante una noche.

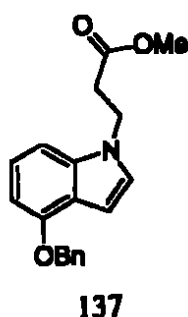
20 La reacción se diluyó con agua, se acidificó con HCl 2N, se extrajo con acetato de etilo, se secó sobre  $\text{MgSO}_4$  y se concentró a presión reducida. El aceite bruto se cromatografió, eluyendo con EtOAc al 20%-25% (con HOAc al 20%) en hexanos, produciendo el ácido propiónico deseado

25 (0,88 g, 85%). 400 MHz,  $^1\text{H}$  RMN (DMSO- $d_6$ )  $\delta$  7,86 (m, 2H),

7,44 (m, 3H), 7,14 (d, 1H,  $J = 3,2$  Hz), 6,99 (m, 2H), 6,50 (dd, 1H,  $J = 7,1, 1,0$  Hz), 6,30 (d,  $J = 3,2$  Hz), 4,33 (t, 2H,  $J = 6,8$  Hz), 4,24 (t, 2H,  $J = 6,4$  Hz), 3,49 (s, 3H), 2,94 (t, 2H,  $J = 6,4$  Hz), 2,74 (t, 2H,  $J = 6,8$  Hz), 2,35 (s, 3H). MS  $m/z$  405 (M+1).

(c) Éster metílico del ácido 3-(4-benciloxi-indol-1-il)-propiónico (137).

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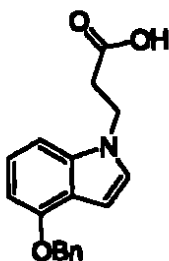


Una mezcla de éster metílico del ácido 3-(4-benciloxi-15 indol-1-il)-propiónico (1,52 g, 4,91 mmol) y Pd al 20%/C (160 mg) en metanol (25 ml) y THF (25 ml) se agitó en una atmósfera de  $H_2$  durante 3 días. La reacción se filtró y se concentró, produciendo el producto bruto desprotegido. MS  $m/z$  220 (M+1).

20 (d) Ácido 3-(4-benciloxi-indol-1-il)-propiónico (136).

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136

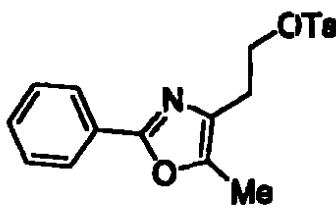
5

10 Una solución de 4-benciloxiindol (1,61 g, 7,21 mmol) e  
hidróxido potásico (2,02 g, 36,1 mmol) en DMSO (12 ml) se  
agitó a temperatura ambiente durante 1,5 horas. Se añadió  
3-bromopropionato de etilo (1,11 ml, 8,65 mmol) y la mezcla  
se agitó durante una noche. La reacción se diluyó con agua,  
15 se acidificó con HCl 2 N, se extrajo con acetato de etilo,  
se secó sobre MgSO<sub>4</sub> y se concentró a presión reducida. El  
aceite bruto se cromatografió, eluyendo con EtOAc al 25%-  
30% (con HOAc al 20%) en hexanos, produciendo el ácido  
propiónico deseado (1,65 g, 77%), 400 MHz, <sup>1</sup>H RMN (DMSO-d<sub>6</sub>)  
20 δ 7,44 (m, 2H), 7,35 (m, 2H), 7,27 (m, 1H), 7,18 (d, 1H, J  
= 3,2 Hz), 7,04 (d, 1H, J = 8,3 Hz), 6,97 (m, 1H), 6,55 (d,  
1H, J = 7,3 Hz), 6,39 (m, 1H), 5,16 (s, 2H), 4,30 (t, 2H, J  
= 6,8 Hz), 2,67 (t, 2H, J = 6,8 Hz). MS m/z 296 (M+1).

(e) 2-(5-Metil-2-fenil-oxazol-4-il)-etil éster del  
25 ácido tolueno-4-sulfónico (135)

624

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135

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10 Una solución de 2-(5-metil-2-fenil-oxazol-4-il)-etanol  
(2 g, 9,84 mmol), cloruro de *p*-toluenosulfonilo (2,25 g,  
11,8 mmol) y DMAP (10 mg) en diclorometano (40 ml) se  
enfrió a 0°C. Se añadió gota a gota trietilamina (2,75 ml,  
19,7 mmol). La reacción se agitó a 0°C durante 3 horas, y  
15 después se calentó a temperatura ambiente durante una  
noche. La solución se enfrió a 0°C, se diluyó con agua (25  
ml) y se neutralizó con HCl 1 N. La mezcla se extrajo con  
diclorometano, se lavó con NaHCO<sub>3</sub> saturado y salmuera, se  
secó con MgSO<sub>4</sub>, y se concentró, produciendo un sólido en un  
20 rendimiento casi cuantitativo. 400 MHz <sup>1</sup>H RMN (DMSO-*d*<sub>6</sub>) δ  
6,83 (m, 2H), 6,66 (m, 4H), 6,11 (m, 2H), 4,65 (dd, 1H, *J* =  
8,8, 6,6 Hz), 3,66 (s, 3H), 3,30 (dd, 1H, *J* = 13,9, 6,6  
Hz), 3,15 (dd, 1H, *J* = 13,9, 8,8 Hz). MS *m/z* 246 (*M*+1).

#### Ejemplo 53a

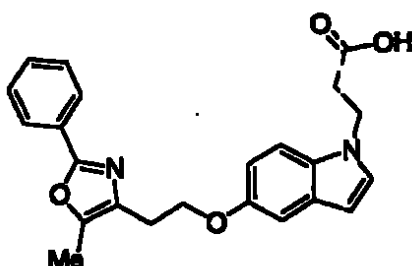
25 Ácido 4-{5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-

26  
625

281

indol-1-il)-propiónico (140a).

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140a

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Preparado como en el Ejemplo 53 a partir del correspondiente ácido 3-(5-benciloxi-indol-1-il)-propiónico. De esta manera, una mezcla de éster metílico del ácido 3-{5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il)-propiónico (0,81 g, 2,00 mmol) y LiOH (240 mg, 10,0 mmol) en 2-metoxietanol (16 ml) y agua (4 ml) se agitó a temperatura ambiente durante una noche. La reacción se diluyó con agua, se acidificó con HCl 2 N, se extrajo con acetato de etilo, se secó sobre MgSO<sub>4</sub> y se concentró a presión reducida. El sólido se recrystalizó en EtOAc/hexanos, produciendo el ácido propiónico deseado (560 mg, 72%). 400 MHz, <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ 7,86 (m, 2H), 7,43 (m, 3H), 7,31 (d, 1H, J = 8,8 Hz), 7,23 (d, 1H, J = 2,9 Hz), 7,01 (d, 1H, J = 2,4 Hz), 6,71 (dd, 1H, J = 8,8, 2,4 Hz),

6,24 (d, 1H,  $J = 2,9$  Hz), 4,28 (t, 2H,  $J = 6,8$  Hz), 4,14 (t, 2H,  $J = 6,6$  Hz), 2,88 (t, 2H,  $J = 6,6$  Hz), 2,65 (t, 2H,  $J = 6,8$  Hz), 2,32 (s, 3H). MS  $m/z$  391 (M+1).

Ácido 4-{5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-5 indol-1-il-propiónico (139a). Una mezcla de éster metílico del ácido 3-(5-hidroxi-indol-1-il)-propiónico (1,14 g, 5,20 mmol), carbonato de cesio (3,39 g, 10,4 mmol) y 2-(5-metil-2-fenil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (3,27 g, 9,14 mmol) en DMF (50 ml) se calentó a 10 50°C durante una noche. La reacción se diluyó con agua, se acidificó con HCl 2 N, se extrajo con acetato de etilo, se secó sobre  $MgSO_4$  y se concentró a presión reducida. El aceite bruto se cromatografió, eluyendo con EtOAc al 25%-30% (con HOAc al 20%) en hexanos, produciendo el ácido 15 propiónico deseado (0,81 g, 39%). 400 MHz,  $^1H$  RMN ( $DMSO-d_6$ )  $\delta$  7,86 (m, 2H), 7,44 (m, 3H), 7,31 (d, 1H, 9,0 Hz), 7,21 (d, 1H, 2,9 Hz), 7,01 (d, 1H, 2,2 Hz), 6,71 (dd, 1H, 9,0, 2,2 Hz), 6,24 (m, 1H), 4,32 (t, 2H,  $J = 6,8$  Hz), 4,14 (t, 2H,  $J = 6,8$  Hz), 3,50 (s, 3H), 2,88 (t, 2H,  $J = 6,8$  Hz), 20 2,75 (t, 2H,  $J = 6,8$  Hz), 2,32 (s, 3H). MS  $m/z$  405 (M+1).

Éster metílico del ácido 3-(5-hidroxi-indol-1-il)-propiónico (138a). Una mezcla de éster metílico del ácido 3-(5-benciloxi-indol-1-il)-propiónico (2,38 g, 7,69 mmol) y Pd al 20%/C (145 mg) en metanol (25 ml) y THF (25 ml) se 25 agito en atmósfera de  $H_2$  durante 18 horas. La reacción se



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filtró y se concentró, produciendo el producto desprotegido con un rendimiento casi cuantitativo. 400 MHz  $^1\text{H}$  RMN (DMSO- $d_6$ )  $\delta$  7,19 (d, 1H,  $J = 8,8$  Hz), 7,15 (d, 1H,  $J = 2,6$  Hz), 6,78 (1H, d,  $J = 2,6$  Hz), 6,58 (dd, 1H,  $J = 8,8, 2,4$  Hz), 5 6,15 (d, 1H,  $J = 2,4$  Hz), 4,28 (t, 2H,  $J = 6,8$  Hz), 3,51 (s, 3H), 2,74 (t, 2H,  $J = 6,8$  Hz). MS  $m/z$  220 (M+1).

Éster metílico del ácido 3-(5-benciloxi-indol-1-il)-propiónico (137a). A una solución del ácido 3-(5-benciloxi-indol-1-il)-propiónico (2,27 g, 8,87 mmol) en tolueno (72 10 ml) y metanol (18 ml) se le añadió TMS-diazometano (6,65 ml, 13,3 mmol, 2,0 M en hexanos). La reacción se agitó a temperatura ambiente durante 30 minutos, se inactivó con ácido acético y se concentró. Se obtuvo el éster deseado en forma de un aceite pardo con un rendimiento casi 15 cuantitativo. 400 MHz,  $^1\text{H}$  RMN (DMSO- $d_6$ )  $\delta$  7,41 (m, 2H), 7,33 (m, 3H), 7,25 (m, 2H), 7,06 (d, 1H,  $J = 2,4$  Hz), 6,80 (dd, 1H,  $J = 9,0, 2,4$  Hz), 6,25 (d, 1H,  $J = 2,4$  Hz), 5,03 (s, 2H), 4,33 (t, 2H,  $J = 6,7$  Hz), 3,50 (s, 3H), 2,75 (t, 2H,  $J = 6,7$  Hz). MS  $m/z$  310 (M+1).

20 Ácido 3-(5-benciloxi-indol-1-il)-propiónico (136a). Una solución de 5-benciloxiindol (4 g, 17,9 mmol) e hidróxido potásico (5,03 g, 89,6 mmol) en DMSO (30 ml) se agitó a temperatura ambiente durante 1,5 horas. Se añadió 3-bromopropionato de etilo (2,75 ml, 21,5 mmol) y la mezcla 25 se agitó durante 3 horas. La reacción se diluyó con agua,

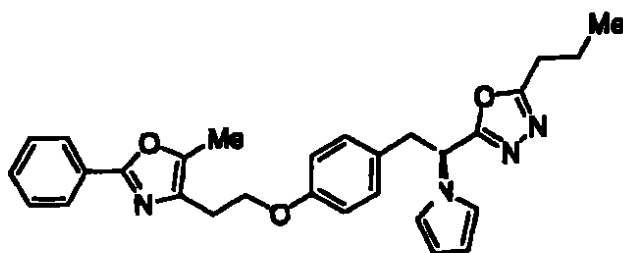
628

se acidificó con HCl 2 N, se extrajo con acetato de etilo, se secó sobre MgSO<sub>4</sub>, y se concentró a presión reducida. El aceite bruto se cromatografió, eluyendo con EtOAc al 25%-30% (con HOAc al 20%) en hexanos, produciendo el ácido 5 propiónico deseado (2,56 g, 49%). 400 MHz, <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ 7,40 (m, 2H), 7,33 (m, 3H), 7,25 (m, 2H), 7,06 (d, 1H, J = 2,4 Hz), 6,80 (dd, 1H, J = 8,8, 2,4 Hz), 6,24 (dd, 1H, J = 2,9, 0,7 Hz), 5,03 (s, 2H), 4,29 (t, 2H, J = 6,7 Hz), 2,66 (t, 2H, J = 6,7 Hz). MS m/z 324 (M+1).

10 Ejemplo 54

(S)-2-(2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol (147).

15



147

Se disolvió hidrazida del ácido (S)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-pirrol-1-il-propiónico (147, 2,95 g, 6,85 mmol) en dioxano (20 ml) y ortobutirato de trimetilo (3,29 ml, 20,5 mmol) y se añadió ácido metano sulfónico (100 µl, 1,37 mmol). La mezcla de reacción se calentó a 105°C durante 15 minutos, después se vertió en 25 agua y se extrajo con acetato de etilo (2 x 100 ml). La

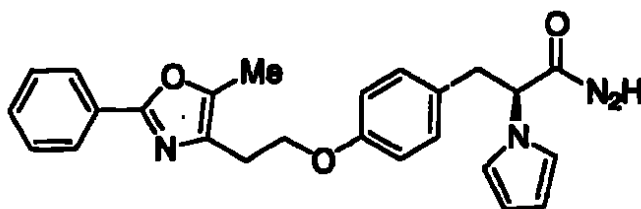
69d

capa orgánica se lavó con bicarbonato sódico y salmuera y se secó sobre  $\text{MgSO}_4$ . El disolvente se retiró al vacío y el aceite residual se purificó por cromatografía usando de 1:10 a 1:1 de acetato de etilo:hexano. Se aisló (S)-2-(2-5 {4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol en forma de un aceite transparente. Rendimiento = 0,80 g, 24%.  $^1\text{H}$  RMN (400 MHz)  $\delta$  ( $\text{CDCl}_3$ ) 7,97 (2H, m), 7,41 (3H, m), 6,88 (2H, dd,  $J = 2,2$ , 5,85) 6,74 (2H, dd,  $J = 1,95$ , 6,59 Hz), 6,69 (2H, t,  $J =$  2,2 Hz), 6,13 (2H, t,  $J = 2,2$  Hz), 5,33 (1H, dd,  $J = 6,83$ , 8,78 Hz), 4,18 (2H, t,  $J = 6,83$ ), 3,52 (1H, dd,  $J = 6,59$ , 14,16 Hz), 3,45 (1H, dd,  $J = 8,78$ , 14,16 Hz), 2,95 (2H, t,  $J = 6,59$  Hz), 2,77 (2H, m), 2,35 (3H, s), 1,76 (2H, sex,  $J = 7,32$ ), 0,97 (3H, t,  $J = 7,32$ ). MS  $m/z$  483 (M+1).

15 La hidrazida del ácido (S)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-pirrol-1-il-propiónico (146) se preparó de la siguiente forma.

(a) Hidrazida del ácido (S)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-pirrol-1-il-propiónico (146).

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146

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630

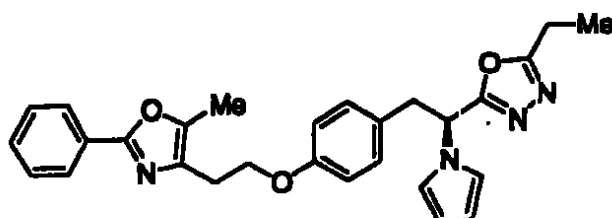
Se disolvió ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico preparado como se describe en el Ejemplo 1 (5 g, 12 mmol) en THF (60 ml) y se añadió 4-metil morfolina (1,70 ml, 15,5 mmol) seguida de 5 cloroformiato de isobutilo (2,22 ml, 17,2 mmol). La suspensión resultante se agitó durante 30 minutos a 10°C y después se filtró y se introdujo en una solución enfriada (0°C) de hidrazina (1,88 ml, 60 mmol) en THF (40 ml). Después de agitar durante 45 minutos, la mezcla se vertió 10 en acetato de etilo y se lavó con agua, seguido de una solución saturada de cloruro amónico y después salmuera. La capa orgánica se separó y se secó sobre MgSO<sub>4</sub>. La eliminación del disolvente a presión reducida, proporcionó la monoacil hidrazida deseada en forma de un aceite 15 transparente usado sin purificación adicional. <sup>1</sup>H RMN (400 MHz) δ (CDCl<sub>3</sub>) 7,96 (2H, m), 7,40 (3H, m), 6,88 (2H, d, J = 8,78), 6,73 (2H, dd, J = 1,95, 6,59 Hz), 6,62 (2H, t, J = 2,2 Hz), 6,16 (2H, t, J = 2,2 Hz), 5,59 (1H, dd, J = 4,63, 10,49 Hz), 4,16 (2H, t J = 6,59), 3,57 (1H, dd, J = 4,63, 20 6,59, 14,4 Hz), 3,15 (1H, dd, J = 14,40, 10,49 Hz), 2,93 (2H, t, J = 6,59 Hz), 2,33 (3H, s) MS m/z 431 (M+1).

#### Ejemplo 55

(S)-2-Etil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol (148).

631

287



148

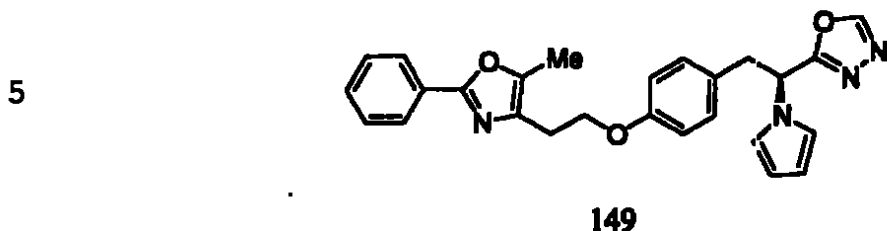
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Se disolvió hidrazida del ácido (S)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-pirrol-1-il-propiónico (146, 2,98 g, 6,72 mmol) en dioxano (20 ml) y se añadieron 10 propionato de trietilo (4,06 ml, 20,2 mmol) y ácido metano sulfónico (98 µl, 1,34 mmol). La mezcla de reacción se calentó a 105°C durante 15 minutos, después se vertió en agua y se extrajo con acetato de etilo (2 x 100 ml). La capa orgánica se lavó con bicarbonato sódico y salmuera y 15 se secó sobre MgSO<sub>4</sub>. El disolvente se retiró al vacío y el aceite residual se purificó por cromatografía usando de 1:10 a 1:1 de acetato de etilo:hexano. El 2-etil 5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol se aisló en forma de un aceite 20 transparente. Rendimiento = 0,82 g, 26%. Parte del aceite se disolvió en éter etílico y se evaporó lentamente, dando cristales transparentes. Rendimiento = 58 mg, p.f. 96,5-98°C, C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub> requerido C, 71,78; H, 6,02, N, 11,96; encontrado C, 71,68, H, 6,15, N, 11,89. 73431x34 pm= 25 468,54.

632

Ejemplo 56

(S)-2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol (149).



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Se disolvió hidrazida del ácido (S)-3-(4-[2-(5-metil-  
15 2-fenil-oxazol-4-il)-etoxi]-fenil)-2-pirrol-1-il-propiónico  
(146, 1,22 g, 2,85 mmol) en dioxano (20 ml) y ortoformiato  
de trimetilo (1,42 ml, 8,65 mmol) y se añadió ácido metano  
sulfónico (42 µl, 0,57 mmol). La mezcla de reacción se  
calentó a 105°C durante 15 minutos, después se vertió en  
20 agua y se extrajo con acetato de etilo (2 x 100 ml). La  
capa orgánica se lavó con bicarbonato sódico y salmuera y  
se secó sobre MgSO<sub>4</sub>. El disolvente se retiró al vacío y el  
aceite residual se purificó por cromatografía usando de  
1:10 a 1:1 de acetato de etilo:hexano. El (S)-2-{4-[2-(5-  
25 metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-

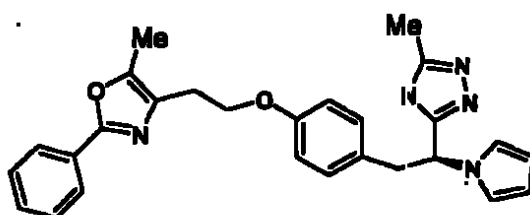
633

etil)-1,3,4-oxadiazol se aisló en forma de un aceite espeso transparente. Rendimiento = 401 mg, 32%  $^1\text{H}$  RMN (400 MHz)  $\delta$  ( $\text{CDCl}_3$ ) 8,34 (1H, s), 7,96 (2H, m), 7,41 (3H, m), 6,88 (2H, d,  $J = 8,79$ ), 6,73 (2H, m), 6,62 (2H, t,  $J = 2,2$  Hz), 6,16 (2H, t,  $J = 2,2$  Hz), 5,42 (1H, dd,  $J = 6,83, 8,78$  Hz), 4,18 (2H, t,  $J = 6,59$ ), 3,57 (1H, dd,  $J = 6,6, 13,9$  Hz), 3,15 (1H, dd,  $J = 8,54, 13,9$  Hz), 2,95 (2H, t,  $J = 6,59$  Hz), 2,35 (3H, s), MS  $m/z$  431 (M+1).

Ejemplo 57

10 (S)-3-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol (151).

15



151

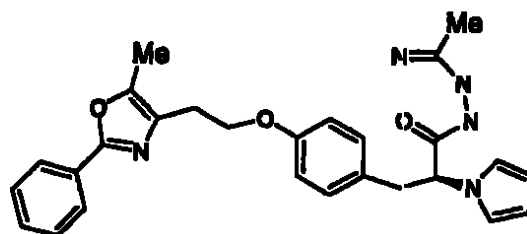
Se suspendió N'-(1-imino-etil)-hidrazida del ácido 20 (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (150, 0,860 g, 1,82 mmol) en para xileno (15 ml) y se calentó a 120°C en un tubo hermético durante 24 horas. El producto se aisló por cromatografía en 1:1 de acetato de etilo:hexanos, dando el producto deseado 25 en forma de una espuma blanca. Rendimiento = 684 mg, 76%  $^1\text{H}$

634

RMN (400 MHz)  $\delta$  (CDCl<sub>3</sub>) 7,96 (2H, m), 7,40 (3H, m), 6,87 (2H, d,  $J$  = 8,54), 6,77 (2H, t,  $J$  = 1,95), 6,11 (2H, d,  $J$  = 8,54 Hz), 6,11 (2H, t,  $J$  = 1,95 Hz), 5,25 (1H, dd,  $J$  = 6,34, 9,27 Hz), 4,16 (2H, t,  $J$  = 6,83), 3,51 (1H, dd,  $J$  = 5 6,1, 14,16 Hz), 3,38 (1H, dd,  $J$  = 9,27, 14,16 Hz), 2,93 (2H, t,  $J$  = 6,59 Hz), 2,42 (3H, s), 2,34 (3H, s). MS  $m/z$  454 (M+1).

La N'-(1-imino-etil)-hidrazida del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-10 propiónico (150) se preparó de la siguiente forma.

(a) N'-(1-imino-etil)-hidrazida del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-15 propiónico (150).



150

20 Se disolvió hidrazida del ácido (S)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-pirrol-1-il-propiónico (146, 1,22 g, 2,83 mmol) en THF (20 ml) y se enfrió a 0°C. Se añadieron clorhidrato de acetimidato de etilo (420 mg, 3,40 mmol) y trietilamina (513  $\mu$ l, 3,68 mmol) y la mezcla 25 de reacción se agitó a 0°C durante 1,5 horas seguido de



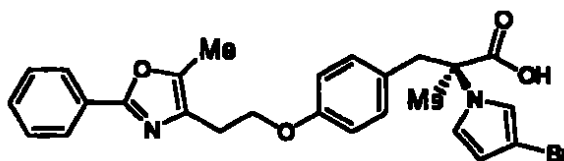
635

agitación a temperatura ambiente durante una noche. La mezcla de reacción se purificó por cromatografía en 1:20 a 1:4 de metanol a diclorometano. El producto deseado se obtuvo en forma de un sólido rosa. Rendimiento = 860 mg, 5 64%  $^1\text{H}$  RMN (400 MHz)  $\delta$  (DMSO- $d_6$ ) 7,85 (2H, m), 7,42 (3H, m), 6,95 (2H, d,  $J = 8,54$ ), 6,90 (2H, t,  $J = 8,30$ ), 6,73 (4H, m), 5,85 (1H, m), 4,08 (2H, t,  $J = 6,83$ ), 3,11-2,93 (4H, m), 2,83 (2H, m), 2,43 (3H, s), MS  $m/z$  472 (M+1).

Ejemplo 58

10 Ácido 2-(3-bromo-pirrol-1-il)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (154)

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154

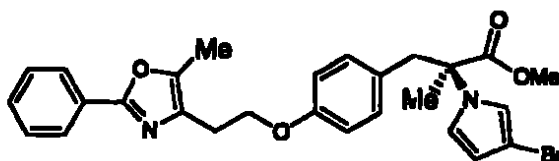
Se hidrolizó el éster metílico del ácido (S)-2-(3-bromo-pirrol-1-il)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-  
20 4-il)-etoxi]-fenil}-propiónico (153, 1,46 g, 2,79 mmol) como se describe en el procedimiento A. El producto deseado se aisló por cromatografía 1:1 de acetato de etilo:hexano. Rendimiento = 0,633, 45% p.f. 158-159°C.  $^1\text{H}$  RMN (400 MHz)  $\delta$  (CDCl $_3$ ) 8,06 (2H, m), 7,46 (3H, m), 6,75-6,61 (6H, m), 6,15  
25 (1H, m), 4,21 (2H, t,  $J = 6,1$ ), 3,25 (2H, m), 3,05 (2H, t,

$J = 6,1$ , 2,41 (3H, s), 1,58 (3H, s). MS  $m/z$  511 (M+1).

El éster metílico del ácido (S)-2-(3-bromo-pirrol-1-il)-2-metil-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-propiónico (153) se preparó de la siguiente forma.

- 5 (a) Éster metílico del ácido (S)-2-(3-bromo-pirrol-1-il)-2-metil-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]fenil)-propiónico (153).

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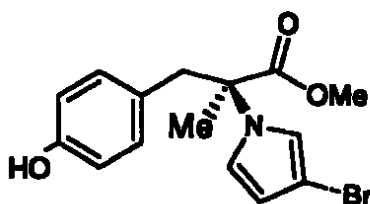
153

El éster metílico del ácido (S)-2-(3-bromo-pirrol-1-il)-3-(4-hidroxifenil)-2-metil-propiónico (152, 4,01 g, 15 11,8 mmol) se acopló como se describe en el procedimiento B. El éster se aisló por cromatografía de 1:10 a 1:1 de acetato de etilo:hexanos en forma de un aceite. Rendimiento = 1,46 g, 24%  $^1\text{H}$  RMN (400 MHz)  $\delta$  ( $\text{CDCl}_3$ ) 7,96 (2H, m), 7,40 (3H, m), 6,75-6,57 (6H, m), 6,15 (1H, m), 4,18 (2H, m), 20 3,73 (3H, s), 3,21 (2H, m), 2,35 (3H, s), 1,54 (3H, s) MS  $m/z$  525 (M+1).

- (b) Éster metílico del ácido (S)-2-(3-bromo-pirrol-1-il)-3-(4-hidroxifenil)-2-metil-propiónico (152).

63A

293



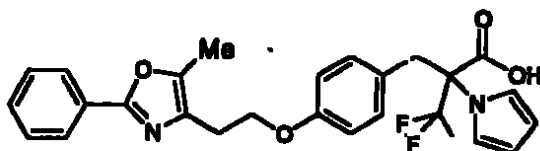
152

5

Se disolvió éster metílico del ácido (S)-3-(4-hidroxifenil)-2-metil-2-pirrol-1-il-propiónico (5,4 g, 20,8 mmol) en diclorometano (50 ml) y se enfrió a 78°C. Se añadió N-10 bromosuccinimida (4,08 g, 22,8 mmol) y la reacción se calentó a temperatura ambiente y se agitó durante 3 horas. El disolvente se retiró al vacío y el residuo se adsorbió sobre gel de sílice. La cromatografía usando de 1:10 a 1:1 de acetato de etilo:hexano, dio el producto deseado en 15 forma de una goma. Rendimiento = 6,44 g, 91%, <sup>1</sup>H RMN (400 MHz) δ (CDCl<sub>3</sub>) 6,71-6,58 (6H, m), 6,16 (1H, m), 3,75 (3H, s), 3,31-3,18 (2H, m), 1,55 (3H, s), MS m/z (M+1)

#### Ejemplo 59

Ácido 3,3,3-trifluoro-2-{4-[2-(5-metil-2-fenil-oxazol-20 4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico (159).



159

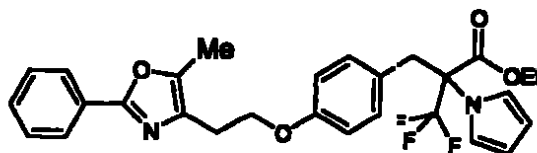
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Se hidrolizó éster etílico del ácido 3,3,3-trifluoro-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico (158, 0,83 g, 13,3 mmol) como se describe en el procedimiento B. El producto se recrystalizó 5 en acetato de etilo caliente, dando 2,03 g, 31% p.f. 201-203°C <sup>1</sup>H RMN (400 MHz) δ (D<sub>6</sub> DMSO) 7,85 (2H, m), 7,42 (3H, m), 7,71 (2H, d, J = 8,78), 6,93 (2H, s a), 6,79 (2H, d, J = 8,78), 6,06 (2H, t, J = 2,19), 4,12 (2H, t, J = 6,59), 3,74 (1H, d, J = 14,39 Hz), 3,62 (1H, d, J = 14,64), 2,85 10 (2H, t, J = 6,58 Hz), 2,29 (3H, s), MS m/z 485 (M+1).

El éster etílico del ácido 3,3,3-trifluoro-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico (158) se preparó de la siguiente forma.

(a) Éster etílico del ácido 3,3,3-trifluoro-2-{4-[2-15 (5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico (158)



158

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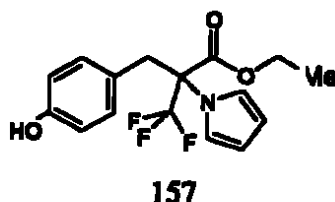
El éster etílico del ácido 3,3,3-trifluoro-2-(4-hidroxibencil)-2-pirrol-1-il-propiónico (157, 4,92 g, 15 mmol) se acopló como se describe en el procedimiento B. El 25 producto se purificó usando cromatografía, dando el

631

producto deseado. Rendimiento = 6,83 g, 88%.  $^1\text{H}$  RMN (400 MHz) ( $\text{CDCl}_3$ ) 8,05 (2H, m), 7,44 (3H, m), 6,98 (2H, d,  $J = 8,54$ ), 6,81 (2H, s a), 6,75 (2H, dd,  $J = 2,19, 6,06$ ), 6,23 (2H, t,  $J = 2,19$ ), 4,22 (4H, m), 3,67 (2H, 2d,  $J = 14,39$  5 Hz), 3,01 (2H, t,  $J = 6,58$  Hz), 2,38 (3H, s), 1,21 (3H, m) MS  $m/z$  513 (M+1)

(b) Éster etílico del ácido 3,3,3-trifluoro-2-(4-hidroxibencil)-2-pirrol-1-il-propiónico (157)

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15

Se disolvió éster etílico del ácido 2-(4-benciloxibencil)-2-terc-butoxicarbonilamino-3,3,3-trifluoropropiónico (156, 10,72 g) en THF y se hidrogenó usando 20 paladio sobre carbono. El producto éster etílico del ácido 2-terc-butoxicarbonilamino-3,3,3-trifluoro-2-(4-hidroxibencil)-propiónico (156a) se usó en bruto en la siguiente etapa.

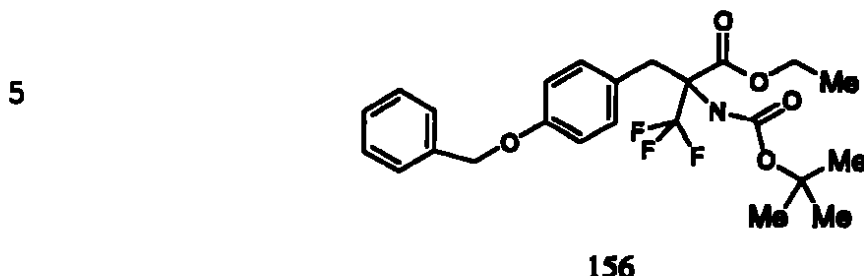
Se añadió cloruro de tionilo (3,46 ml, 47,4 mmol) a 25 metanol (100 ml) a 0°C. Se añadió éster etílico del ácido

2-terc-butoxicarbonilamino-3,3,3-trifluoro-2-(4-hidroxibencil)-propiónico (8,94 g, 23,7 mmol), se dejó que la mezcla de reacción alcanzara la temperatura ambiente y se agitó durante 24 horas. El disolvente se retiró al vacío y el producto bruto clorhidrato del éster etílico del ácido 2-amino-3,3,3-trifluoro-2-(4-hidroxibencil)-propiónico se usó directamente en la siguiente etapa. MS  $m/z$  278 (M+1).

Se disolvió clorhidrato del éster etílico del ácido 2-amino-3,3,3-trifluoro-2-(4-hidroxibencil)-propiónico (156a, 7,13 g, 22,7 mmol) en agua (40 ml) y ácido acético (40 ml). Se añadieron acetato sódico (2,98 g, 36,3 mmol) y 2,5-dimetoxi tetrahidrofurano (4,7 ml, 36,3 mmol) y la mezcla de reacción se calentó a 90°C durante 20 minutos hasta que no quedaba material de partida según se observó por análisis del espectro de masas. La mezcla de reacción se vertió en agua, se extrajo con acetato de etilo y se neutralizó usando carbonato sódico. La capa orgánica se secó sobre  $MgSO_4$  y el disolvente se retiró al vacío. El residuo se purificó por cromatografía de 1:10 a 1:1 de acetato de etilo:hexano, dando el producto deseado éster etílico del ácido 3,3,3-trifluoro-2-(4-hidroxibencil)-2-pirrol-1-il-propiónico en forma de un sólido blanco. Rendimiento = 4,95 g, 66%.  $^1H$  RMN (400 MHz) ( $CDCl_3$ ) 6,98 (2H, m), 6,83 (2H, s a), 6,75 (2H, m), 6,24 (2H, t,  $J$  = 2,44), 4,24 (2H, m), 3,70 (1H, d,  $J$  = 14,64 Hz), 3,66 (1H,

d,  $J = 14,64$ ), 1,21 (3H, t,  $J = 7,32$ ) MS  $m/z$  328 (M+1).

(c) Éster etílico del ácido 2-(4-benciloxi-bencil)-2-terc-butoxicarbonilamino-3,3,3-trifluoro-propiónico (156).



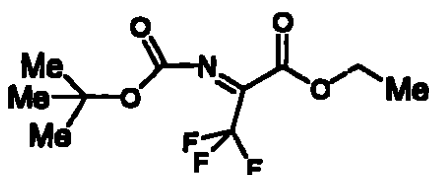
10 Se agitaron limaduras de magnesio (2,82 g, 0,16 mol) en tolueno (5 ml) a temperatura ambiente. Se añadió gota a gota cloruro de 4-benciloxi bencilo (11,3 g, 48,5 mmol) en THF (100 ml) con el control cuidadoso de la formación de Grignard. Una vez añadido todo el cloruro, la reacción se  
15 agitó hasta que no se observó cambio de color. Después, el reactivo de Grignard se transfirió por medio de una cánula a una solución de éster etílico del ácido 2-terc-butoxicarbonilimino-3,3,3-trifluoro-propiónico (155 g, 29,4 mmol) en THF (50 ml) a  $-78^{\circ}\text{C}$ . La reacción después se  
20 calentó a  $0^{\circ}\text{C}$  y se agitó durante 10 minutos. Se inactivó con cloruro amónico acuoso saturado y el producto se extrajo con acetato de etilo. La capa orgánica se secó sobre  $\text{MgSO}_4$  y el disolvente se retiró al vacío. El producto deseado se aisló usando cromatografía de 1:10 a 1:1 de  
25 acetato de etilo:hexano. Se obtuvo éster etílico del ácido

6/12

2-(4-benciloxi-bencil)-2-terc-butoxicarbonilamino-3,3,3-trifluoro-propiónico en forma de un sólido blanco. Rendimiento = 10,72 g, 78% (3 etapas)  $^1\text{H}$  RMN (400 MHz) ( $\text{CDCl}_3$ ) 7,43-7,32 (5H, m), 7,11 (2H, d,  $J = 8,78$ ), 6,87 (2H, 5 d,  $J = 8,78$ ), 5,52 (1H, s a), 5,02 (2H, s), 4,30 (2H, m), 3,70 (2H, d,  $J = 13,9$  Hz), 1,46 (9H, s), 1,33 (3H, t,  $J = 7,32$ ) MS  $m/z$  466 (M-1).

(d) Éster etílico del ácido 2-terc-butoxicarbonilimino-3,3,3-trifluoro-propiónico (155).

10



155

15 Se disolvió 3,3,3-trifluoropiruvato de etilo (5 g, 29,4 mmol) en diclorometano y se añadió carbamato de *t*-butilo (3,44 g, 29,4 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. El disolvente se retiró al vacío, dando un sólido blanco. El sólido se  
20 disolvió en éter (50 ml) y se añadió gota a gota anhídrido trifluoroacético (4,57 ml, 32,34 mmol) durante 30 minutos por agitación vigorosa. Después de agitar durante 30 minutos más, se añadió gota a gota piridina (5,23 ml, 64,7 mmol) y la reacción se agitó durante 2 h más. Se añadió  
25 hexano (100 ml) y la reacción se filtró rápidamente,

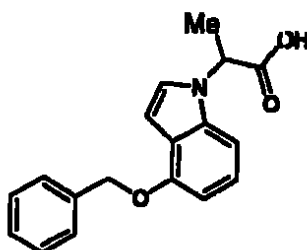


después de enfriarse a  $-78^{\circ}\text{C}$ . El producto éster etílico del ácido 2-terc-butoxicarbonilimino-3,3,3-trifluoro-propiónico aislado se almacenó al vacío y se usó sin purificación adicional.  $^1\text{H}$  RMN (400 MHz) ( $\text{CDCl}_3$ ) 4,30 (2H, q,  $J = 7,32$ ), 5 157 (9H, s), 1,37 (3H, t,  $J = 7,32$ ). MS  $m/z$  269 (M)

Ejemplo 60

Ácido 2-(4-benciloxi-indol-1-il)-propiónico (160).

10

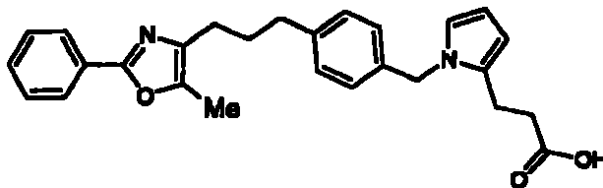


160

Preparado como en el Ejemplo 53 usando 2-15 bromopropionato de metilo. P.f.  $143^{\circ}\text{C}$ - $146^{\circ}\text{C}$  CHN; CALC.: C, 73,20; H, 5,80; N, 4,74; ENCONTRADO: C, 72,95; H, 5,86; N, 4,62.

Ejemplo 61

Ácido 3-(1-{4-[3-(5-metil-2-fenil-oxazol-4-il)-20 propil]-bencil}-1H-pirrol-2-il)-propiónico (165).



165

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644

Una mezcla de éster metílico del ácido 3-(1-[4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-bencil}-1H-pirrol-2-il)-propiónico (164, 0,44 g, 1,48 mmol) e hidróxido de litio (175 mg, 7,39 mmol) en 2-metoxietanol (12 ml) y agua (3 ml) se agitó a temperatura ambiente durante una noche. La reacción se diluyó con agua, se acidificó, se extrajo con acetato de etilo, se secó sobre  $\text{MgSO}_4$  y se concentró a presión reducida. El sólido bruto se recristalizó en EtOAc/hexanos, produciendo el ácido deseado. 400 MHz,  $^1\text{H}$  RMN (DMSO- $d_6$ )  $\delta$  7,84 (m, 2H), 7,43 (m, 3H), 7,11 (d, 2H,  $J = 8,1$  Hz), 6,88 (d, 2H,  $J = 8,1$  Hz), 6,67 (m, 1H), 5,88 (m, 1H), 5,75 (dd, 1H,  $J = 3,4, 2,7$  Hz), 5,00 (s, 2H), 2,55 (m, 4H), 2,38 (m, 4H), 2,23 (s, 3H), 1,82 (m, 2H). P.f. 139-141.

El éster metílico del ácido 3-(1-[4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-bencil}-1H-pirrol-2-il)-propiónico (164) se preparó de la siguiente forma.

(a) Éster metílico del ácido 3-(1-[4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-bencil}-1H-pirrol-2-il)-propiónico (164).

20 Una mezcla de éster metílico del ácido 3-(1-[4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-bencil}-1H-pirrol-2-il)-acrílico (163, 0,47 g, 1,07 mmol) y Pd al 10%/C (59 mg) en metanol (40 ml) y THF (10 ml) se agitó en una atmósfera de  $\text{H}_2$  durante 17 horas. La reacción se filtró y se concentró, 25 produciendo el producto deseado.

625

(b) Éster metílico del ácido 3-(1-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-bencil}-1H-pirrol-2-il)-acrílico (163).

A una solución del éster metílico del ácido 3-(1H-5 pirrol-2-il)-acrílico (162, 265 mg, 1,75 mmol) en dimetilformamida (15 ml) se le añadió hidruro sódico (60%, 85 mg, 2,10 mmol) y la mezcla se agitó a temperatura ambiente durante 15 minutos. Se añadió 4-[3-(4-clorometil-fenil)-propil]-5-metil-2-fenil-oxazol (161, 1,14 g, 3,50 mmol) y la reacción se calentó a 60°C durante una noche. La reacción se diluyó con agua, se acidificó, se extrajo con acetato de etilo, se secó sobre MgSO<sub>4</sub>, y se concentró a presión reducida. En la siguiente etapa se tomó una mezcla del producto y del material de partida.

15 (c) Éster metílico del ácido 3-(1H-pirrol-2-il)-acrílico (162).

Una solución de pirrol-2-carboxaldehído (2,5 g, 26,3 mmol) y (trifenilfosforanilidina)-acetato de metilo (9,23 g, 27,6 mmol) en tolueno (250 ml) se calentó a 45°C durante 20 una noche. La reacción se concentró a presión reducida. El aceite bruto se cromatografió eluyendo con EtOAc al 20%-30% en hexanos, produciendo el producto deseado (2,70 g, 68%).

(d) 4-[3-(4-Clorometil-fenil)-propil]-5-metil-2-fenil-oxazol (161).

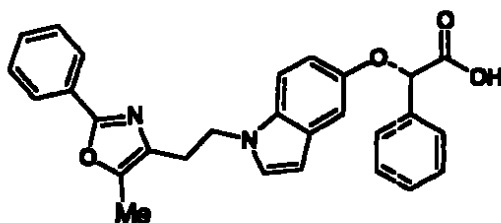
25 Una solución de {4-[3-(5-metil-2-fenil-oxazol-4-il)-

546

propil]-fenil}-metanol (2,0 g, 6,51 mmol) en diclorometano (25 ml) se enfrió a 0°C. Se añadieron cloruro de metanosulfanilo (550 µl, 7,16 mmol) y trietilamina (1,81 ml, 13,0 mmol) y la mezcla se calentó a temperatura ambiente durante una noche. La reacción se diluyó con una solución de NH<sub>4</sub>Cl saturada, se extrajo con CH<sub>2</sub>Cl<sub>2</sub>, se lavó con salmuera, se secó sobre MgSO<sub>4</sub> y se concentró a presión reducida, produciendo el producto deseado.

Ejemplo 62

10      Ácido      (1-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-1H-indol-5-iloxi)-fenil-acético (169).



169

20

Una mezcla de éster metílico del ácido {1-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-1H-indol-5-iloxi}-fenil-acético

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(168, 1,44 g, 3,09 mmol) y LiOH (370 mg, 15,4 mmol) en 2-metoxietanol (24 ml) y agua (6 ml) se agitó a temperatura ambiente durante una noche. La reacción se diluyó con agua, se acidificó con HCl 2 N, se extrajo con acetato de etilo, se secó sobre MgSO<sub>4</sub> y se concentró a presión reducida. El aceite bruto se cromatografió, eluyendo con EtOAc al 30% (con HOAc al 20%) en hexanos. El sólido resultante se recristalizó en EtOAc/hexanos, produciendo el ácido deseado (140 mg). 400 MHz, <sup>1</sup>H RMN (DMSO-*d*<sub>6</sub>) δ 7,88 (m, 2H), 7,49 (m, 5H), 7,35 (m, 3H), 7,26 (d, 1H, *J* = 9,0 Hz), 7,17 (d, 1H, *J* = 2,9 Hz), 7,00 (d, 1H, *J* = 2,4 Hz), 6,77 (dd, *J* = 9,0, 2,4 Hz), 6,25 (d, 1H, *J* = 2,9 Hz), 5,68 (s, 1H), 4,34 (t, 2H, *J* = 6,6 Hz), 2,87 (t, 2H, *J* = 6,6 Hz), 1,87 (s, 3H) p.f. 176-178.

15 El éster metílico del ácido {1-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-1H-indol-5-iloxi}-fenil-acético (168) se preparó de la siguiente forma.

(a) Éster metílico del ácido {1-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-1H-indol-5-iloxi}-fenil-acético (168).

20 Una mezcla de 1-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-1H-indol-5-ol (167, 1,16 g, 3,64 mmol), carbonato de cesio (2,37 g, 7,29 mmol) y α-bromofenilacetato de metilo (1,15 ml, 7,29 mmol) en DMF (35 ml) se calentó a 55°C durante una noche. La reacción se diluyó con agua, se acidificó con HCl 2 N, se extrajo con acetato de etilo, se

secó sobre  $\text{MgSO}_4$  y se concentró a presión reducida. El aceite bruto se cromatografió, eluyendo con EtOAc al 15%-25% (con HOAc al 20%) en hexanos, produciendo el producto deseado (1,44 g, 85%).

5 (b) 1-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-1H-indol-5-ol (167).

Una mezcla de éster metílico del ácido 3-(5-benciloxi-indol-1-il)-propiónico (166, 1,93 g, 4,72 mmol) y Pd al 20%/C (360 mg) en etanol (40 ml) y THF (10 ml) se agitó en  
10 una atmósfera de  $\text{H}_2$  durante 18 horas. La reacción se filtró y se concentró. Se purificó por cromatografía, produciendo el producto desprotegido con un rendimiento casi cuantitativo.

(c) 5-benciloxi-1-[2-(5-metil-2-fenil-oxazol-4-il)-  
15 etil]-1H-indol (166).

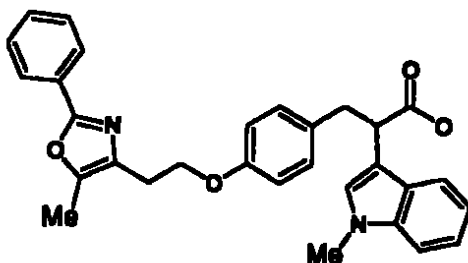
Se disolvió 5-benciloxiindol (2,0 g, 8,96 mmol) en dimetilformamida (90 ml) y se añadió hidruro sódico al 60% (540 mg, 13,4 mmol). Se añadió 2-(5-metil-2-fenil-oxazol-4-il)-etil ester del ácido tolueno-4-sulfónico (600  $\mu\text{l}$ , 5,37  
20 mmol). La reacción se agitó a temperatura ambiente durante una noche. La reacción se diluyó con agua, se acidificó, se extrajo con acetato de etilo, se secó sobre  $\text{MgSO}_4$  y se concentró a presión reducida. Se purificó usando cromatografía. Rendimiento 1,93 (60%).

25 Ejemplo 63

619

Ácido 2-(1-metil-1H-indol-3-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (173).

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173

Se disolvió éster metílico del ácido 2-(1-metil-1H-  
10 indol-3-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
fenil}-propiónico (172, 250 mg, 0,51 mmol) en 2-  
metoxietanol (4 ml) y H<sub>2</sub>O (1 ml). Se añadió monohidrato de  
LiOH (60 mg, 2,53 mmol) en una porción y la suspensión se  
agitó durante una noche. La reacción se diluyó con agua, se  
15 extrajo con acetato de etilo, se secó sobre MgSO<sub>4</sub>, y se  
concentró a presión reducida, produciendo el producto  
deseado. Rendimiento casi cuantitativo. 400 MHz, <sup>1</sup>H RMN  
(DMSO-d<sub>6</sub>) δ 7,85 (m, 2H), 7,58 (d, 1H, J = 7,8 Hz), 7,44 (m,  
3H), 7,32 (t, 1H, J = 6,6 Hz), 7,17 (s, 1H), 7,08 (m, 3H),  
20 6,96 (m, 1H), 6,75 (dd, 2H, J = 8,5, 6,6 Hz), 4,10 (m, 2H),  
3,97 (m, 1H), 3,67 (s, 3H), 2,95 (m, 2H), 2,84 (t, 2H, J =  
6,3 Hz), 2,29 (s, 3H). MS m/z 481 (M+1).

El éster metílico del ácido 2-(1-metil-1H-indol-3-il)-  
3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
25 propiónico (172) se preparó de la siguiente forma.

(a) Éster metílico del ácido 2-(1-metil-1H-indol-3-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (172).

Una solución de éster metílico del ácido (1-metil-1H-5 indol-3-il)-acético (171, 450 mg, 2,21 mmol) en tetrahidrofurano (14 ml) se enfrió a 0°C. Se añadió bis(trimetilsilil)amida de litio (1,0 M en THF, 2,32 ml, 2,32 mmol) y la mezcla se agitó a 0°C durante una hora. Se añadió una solución de 4-[2-(4-clorometil-fenoxi)-etil]-5-10 metil-2-fenil-oxazol (835 mg, 2,55 mmol) en THF (4 ml) y la mezcla de reacción se calentó a temperatura ambiente y se agitó durante 6 horas. La reacción se diluyó con agua, se extrajo con acetato de etilo, se secó sobre MgSO<sub>4</sub> y se concentró a presión reducida. El aceite bruto se 15 cromatografió, eluyendo con EtOAc al 15%-20% (con HOAc al 20%) en hexanos, produciendo el producto deseado (250 mg, 23%).

(b) 4-[2-(4-clorometil-fenoxi)-etil]-5-metil-2-fenil-oxazol (171).

20 Una solución de {4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-metanol (170, 2,0 g, 6,46 mmol) en diclorometano (25 ml) se enfrió a 0°C. Se añadieron cloruro de metanosulfanilo (550 µl, 7,16 mmol) y trietilamina (1,80 ml, 12,9 mmol) y la mezcla se calentó a temperatura 25 ambiente durante una noche. La reacción se diluyó con una



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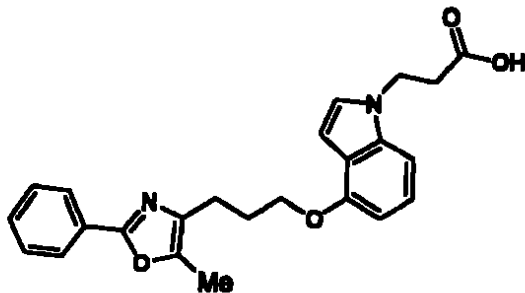
solución de  $\text{NH}_4\text{Cl}$  saturada, se extrajo con  $\text{CH}_2\text{Cl}_2$ , se lavó con salmuera, se secó sobre  $\text{MgSO}_4$  y se concentró a presión reducida, produciendo el producto deseado.

(c) Éster metílico del ácido (1-metil-1H-indol-3-il)-5 acético (170).

Se añadió TMS-diazometano (7,93 ml, 15,9 mmol, 2,0 M en hexanos) a una solución del ácido 1-metil-3-indolacético (2,0 g, 10,6 mmol) en tolueno (80 ml) y metanol (20 ml). La reacción se agitó a temperatura ambiente durante 30 10 minutos, se inactivó con ácido acético y se concentró. El éster deseado se obtuvo con un rendimiento casi cuantitativo.

#### Ejemplo 64

Ácido 3-(4-[3-(5-metil-2-fenil-oxazol-4-il)-propoxi]-15 indol-1-il)-propiónico (174).



174

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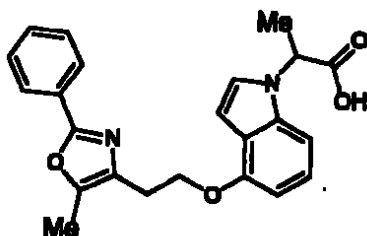
152

Preparado como se describe en el Ejemplo 53 usando 4-(3-bromo-propil)-5-metil-2-fenil-oxazol. P.f. 133-134 CHN (teórico): 71,27% C, 5,98% H, 6,93% N. Encontrado: 71,19% C, 5,92% H, 6,93% N.

Ejemplo 65

Ácido 2-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il)-propiónico (175)

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175

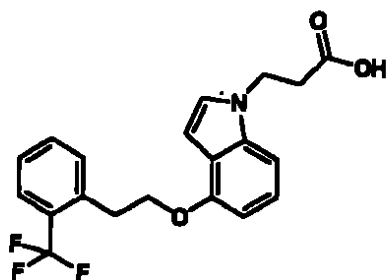
15 Preparado como se describe en el Ejemplo 53 usando 2-bromopropionato de metilo. P.f. 157°C-159°C, CHN (teórico): 70,75% C, 5,68% H, 7,17% N. Encontrado: 70,82% C, 5,74% H, 7,13% N.

Ejemplo 67

20 Ácido 3-(4-[2-(2-trifluorometil-fenil)-etoxi]-indol-1-il)-propiónico (176).

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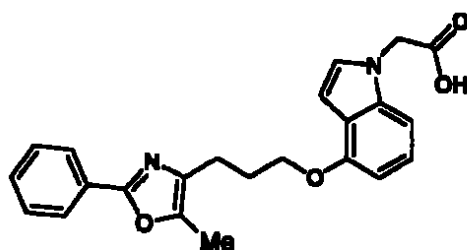
Preparado como se describe para el Ejemplo 53, con la excepción de que la alquilación en el oxígeno del indol se completó de la siguiente forma. Se disolvieron éster metílico del ácido 3-(4-hidroxi-indol-1-il)-propiónico (1,73 g, 7,89 mmol), trifenilfosfina (2,07 g, 7,89 mmol) y 2-(2-trifluorometil-fenil)-etanol (1,25 ml, 7,89 mmol) en tetrahidrofurano (35 ml). Se añadió gota a gota azodicarboxilato de dietilo (1,28 ml, en 5 ml de THF, 7,89 mmol) y la reacción se agitó a temperatura ambiente durante una noche. La mezcla se concentró y se purificó por cromatografía. Rendimiento = 290 mg, 10% p.f. = 126-129, TEÓRICO: 63,66% C, 4,81% H, 3,71% N. REAL: 63,68% C, 4,97% H, 3,71% N.

#### Ejemplo 67

Ácido (4-[3-(5-metil-2-fenil-oxazol-4-il)-propoxi]-indol-1-il)-acético (177).

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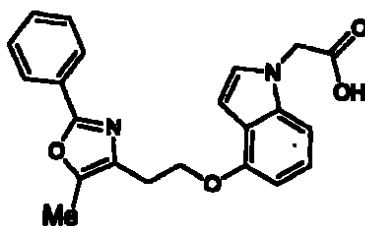
177

Preparado a partir de 4-(3-bromo-propil)-5-metil-2-fenil-oxazol como se describe en el Ejemplo 69. CHN: TEÓRICO: 70,75% C, 5,68% H, 7,17% N. REAL: 69,37% C, 5,59% 10 H, 6,82% N. MS  $m/z$  391 (M+1).

#### Ejemplo 68

Ácido 4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-acético (178).

15



178

20 Se disolvió 4-benciloxiindol (1,0 g, 4,48 mmol) en dimetilformamida (45 ml) y se añadió hidruro sódico al 60% (180 mg, 4,48 mmol). Se añadió bromoacetato de etilo (600  $\mu$ l, 5,37 mmol). La reacción se agitó a temperatura ambiente durante una noche. La reacción se diluyó con agua, se 25 extrajo con acetato de etilo, se secó sobre  $MgSO_4$  y se

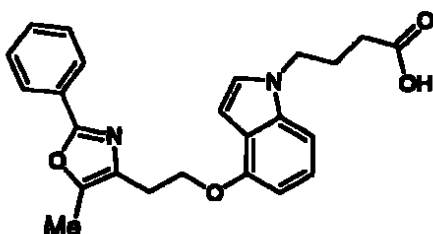
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concentró a presión reducida. Rendimiento casi cuantitativo. Después, el compuesto se preparó como se describe para el Ejemplo 53. PM=376,41, p.f. 193-196, CNH: TEÓRICO: 70,20% C, 5,36% H, 7,44% N. REAL: 69,89% C, 5,33% H 7,39% N.

Ejemplo 69

Ácido 4-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-butírico (179).

10



179

15 Se disolvió 4-benciloxiindol (2,0 g, 8,96 mmol) en tolueno (5 ml) y se añadió hidruro sódico al 60% (360 mg, 8,96 mmol). La mezcla se calentó a 100°C durante 20 minutos. El residuo se recogió en dimetilformamida (20 ml) y se añadió  $\gamma$ -butirolactona (1,38 ml, 17,9 mmol). La  
20 reacción se calentó a 150°C durante 72 horas. La reacción se diluyó con agua, se acidificó con HCl 2 N, se extrajo con acetato de etilo, se secó sobre MgSO<sub>4</sub> y se concentró a presión reducida. Después, el compuesto se preparó como se describe para PD n° 0333941-0000. 73140x27, pm=404,4, p.f.  
25 151-154; CHN; TEÓRICO: 71,27% C, 5,98% H, 6,93% N; REAL:

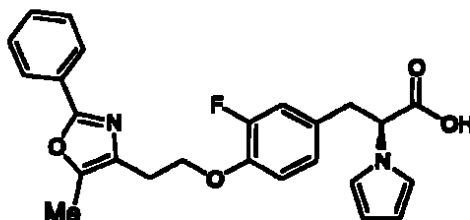
656

71,01% C, 6,02% H 6,83% N.

Ejemplo 70

Ácido 3-(3-fluoro-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-(S)-pirrol-1-il-propiónico (180).

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180

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Preparado como se describe para el Ejemplo 1 usando 5-fluoro-L-tirosina. 73140x37 PM=434,4, p.f. = 154-155, CHN; TEÓRICO: 69,11% C 5,34% H 6,45% N; REAL: 69,09% C, 5,25% H, 6,26%.

15 Ejemplo 71

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-4-il-propiónico (181).

El compuesto del título se sintetizó como se describe en el Ejemplo 12 usando 4-piridil acetato de etilo como material de partida (45 mg, 7%). <sup>1</sup>H RMN d<sub>6</sub>-DMSO δ 2,30 (s, 3H), 2,85 (m, 3H), 3,02 (m, 2H), 4,11 (t, 2H), 6,80 (d, 2H), 7,06 (d, 2H), 7,44 (m, 3H), 7,65 (d, 2H), 7,84 (d, 2H), 8,63 (s, 2H) ... MS (M-44) (menos carboxilato): 385,1.

25 Análisis Calculado para C<sub>26</sub>H<sub>24</sub>O<sub>4</sub>N<sub>2</sub>·1,67 H<sub>2</sub>O: C, 68,05; H,

657

5,82; N, 6,11. Encontrado: C, 68,03; H, 6,00; N, 6,11.

Ejemplo 72

2-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-fenil}-1-fenil-etil)-2H-tetrazol (186a) y 1-metil-5-  
5 (2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-  
fenil-etil)-1H-tetrazol (186b).

Una mezcla de 5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-fenil}-1-fenil-etil)-1H-tetrazol (185a) y 5-(2-  
{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-  
10 etil)-2H-tetrazol (185b) (0,23 g, 0,51 mmol), yoduro de  
metilo (0,20 ml, 3,2 mmol) y TEA (0,22 ml, 1,6 mmol) se  
calentó a reflujo en acetonitrilo durante 1 hora. La  
reacción se enfrió y se concentró. El residuo se disolvió  
en EtOAc, se lavó con agua y se secó (MgSO<sub>4</sub>). Los productos  
15 se aislaron por cromatografía en columna (de 25% a 35% de  
EtOAc/hex).

2-metil tetrazol (186a): mancha de desplazamiento  
frontal (13%) C<sub>28</sub>H<sub>27</sub>N<sub>5</sub>O<sub>2</sub> Masa Calculada = 465,555; M+1 (obs)  
= 466,2. HPLC: columna C-18, 87%, 20/80 (CH<sub>3</sub>CN/H<sub>2</sub>O) a 90/10  
20 durante 20 min, tr=18,876 min, 254 nm. Ausencia de NOE  
entre H35/H23, regiosiomera confirmada.

1-metil-tetrazol (186b): mancha de desplazamiento  
inferior (24%). C<sub>28</sub>H<sub>27</sub>N<sub>5</sub>O<sub>2</sub> Masa Calculado = 465,555; M+1  
(obs) = 466,2. HPLC: columna C-18, 85%, 20/80 (CH<sub>3</sub>CN/H<sub>2</sub>O) a  
25 90/10 durante 20 min; tr=17,438 min, 254 nm. Presencia de

NOE entre H35/H23, regioisomería confirmada.

El 5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-1H-tetrazol (185a) y el 5-(2-{4-2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-2H-5 tetrazol (185b) se prepararon de la siguiente forma.

(a) 5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-1H-tetrazol (185a) y 5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-2H-tetrazol (185b).

10 Se calentó a reflujo 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil-propionitrilo (184, 1,81 g, 4,47 mmol) con azidotributilestaño (2,3 ml, 8,4 mmol) en 20 ml de dioxano durante 25 horas. La reacción se concentró y el residuo se disolvió en Et<sub>2</sub>O. Se burbujeó gas HCl a través de  
15 la solución. La solución se concentró y se trituró con hexanos y la capa de hexanos se decantó. El residuo que quedaba se purificó por cromatografía en columna (25% a 100% de EtOAc/hex) obteniéndose una mezcla de 5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-  
20 1H-tetrazol (185a) y 5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-2H-tetrazol (185b) (material de partida recuperado 23%, producto 14%).

(b) 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil-propionitrilo (184).

25 El compuesto del título se preparó de acuerdo con el



Procedimiento General B usando 3-(4-hidroxifenil)-2-fenilpropionitrilo (183) y 2-(5-metil-2-feniloxazol-4-il)etanol como materiales de partida.

(c) 3-(4-Hidroxifenil)-2-fenilpropionitrilo (183).

5 El grupo bencilo en 3-(4-benciloxifenil)-2-fenilpropionitrilo (182) se retiró por hidrogenólisis usando Pd al 10%/C como catalizador.

(d) 3-(4-Benciloxifenil)-2-fenilpropionitrilo (182).

Este compuesto se sintetizó de la misma forma que el  
10 Compuesto 89 usando cianuro de bencilo (2,4 ml, 21 mmol) y el compuesto 88 (5,85 g, 21 mmol) como materiales de partida.

#### Ejemplo 73

Ácido 2-metil-3-{4-[2-(5-metil-2-feniloxazol-4-il)-  
15 etoxi]-fenil}-2-tiofen-2-il-propiónico (189).

Este compuesto se preparó como se describe en el Ejemplo 32 usando éster etílico del ácido 2-tiofen-3-il-propiónico (188) y el compuesto 88 como materiales de partida. P.f. 165-166°C. Análisis Calculado para  $C_{26}H_{25}O_4NS$ :  
20 C, 69,78; H, 5,63; N, 3,13. Encontrado: C, 69,65; H, 5,88; N, 3,00.

El éster etílico del ácido 2-tiofen-2-il-propiónico se preparó de la siguiente forma.

(a) Éster etílico del ácido 2-tiofen-2-il-propiónico  
25 (188).

Este compuesto se preparó como se describe para el compuesto 89, usando 2-tiofeno acetato de etilo y yoduro de metilo como materiales de partida.

Ejemplo 74

5      Ácido      2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-3-il-propiónico (191).

Este compuesto se preparó como se describe en el Ejemplo 32 usando éster etílico del ácido 2-tiofen-3-il-propiónico (191) y el compuesto 88 como material de  
10 partida. P.f.: 165-166°C. Análisis Calculado para  $C_{26}H_{25}O_4NS$ : C, 69,78; H, 5,63; N, 3,13. Encontrado: C, 69,65; H, 5,88; N, 3,00.

El éster etílico del ácido 2-tiofen-3-il-propiónico (190) se preparó de la siguiente forma.

15      (a) Éster etílico del ácido 2-tiofen-3-il-propiónico (190).

Este compuesto se preparó como se describe para el compuesto 89, usando 3-tiofeno acetato de etilo y yoduro de metilo como materiales de partida.

20 Ejemplo 75

N-(2,2-Dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propionil)-metanosulfonamida (192).

Se combinaron el compuesto 102 (0,493 g, 1,3 mmol), 4-DMAP (0,169 g, 1,4 mmol), EDC (0,266 g, 1,4 mmol) y  
25 metanosulfonamida (0,132 g, 1,4 mmol) en 10 ml de  $CH_2Cl_2$  y

la mezcla se agitó a temperatura ambiente durante una noche. La reacción se lavó con HCl 1 N y H<sub>2</sub>O y se secó (MgSO<sub>4</sub>). Se usó cromatografía en columna (25% a 40% de EtOAc/hex) para aislar el compuesto puro, que se cristalizó 5 en Et<sub>2</sub>O/hex (73 mg, 12%). P.f. 112-113°C. Análisis Calculado para C<sub>24</sub>H<sub>28</sub>O<sub>5</sub>N<sub>2</sub>S: C, 63,14; H, 6,18; N, 6,14. Encontrado: C, 63,46; H, 6,20; N, 6,09.

#### Ejemplo 76

N-(2-Fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
10 etoxi]-fenil}-2-fenil-propionil)-metanosulfonamida (193).

El compuesto 103 (1,003 g, 2,3 mmol) se sometió a las mismas condiciones que se han indicado anteriormente para PD 0333437. (32 mg, 2%). P.f. 118-120°C. Análisis Calculado para C<sub>28</sub>H<sub>27</sub>O<sub>5</sub>N<sub>2</sub>SF: C, 64,35; H, 5,21; N, 5,36. Encontrado: C, 15 64,02; H, 5,00; N, 5,15.

#### Ejemplo 77

Ácido 3-{3-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-isoxazol-5-il}-2-pirrol-1-il-propiónico (199).

Se hidrolizó éster metílico del ácido 3-{3-[2-(5-  
20 metil-2-fenil-oxazol-4-il)-etoxi]-isoxazol-5-il}-2-pirrol-1-il-propiónico (198, 0,2 g, 0,5 mmol) usando el Procedimiento General A. (0,16 g, 81%). P.f. 143-144°C. Análisis Calculado para C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>· 0,17 H<sub>2</sub>O: C, 64,32; H, 5,20; N, 10,23. Encontrado; C, 64,37; H, 5,24; N, 9,79.  
25 C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>. Masa Calculada = 407,426; M+1 (obs) = 408,2.

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El éster metílico del ácido 3-{3-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-isoxazol-5-il}-2-pirrol-1-il-propiónico (198) se preparó de la siguiente forma.

(a) Éster metílico del ácido 3-{3-[2-(5-metil-2-fenil-5 oxazol-4-il)-etoxi]-isoxazol-5-il}-2-pirrol-1-il-propiónico (198).

El compuesto del título se sintetizó como se describe para el Compuesto 89 usando éster metílico del ácido pirrol-2-il-acético (197, 0,139 g, 1 mmol) y 5-bromometil-10 3-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-isoxazol (196, 0,359 g, 0,99 mmol) como materiales de partida (0,20 g, 48%).

(b) Éster metílico del ácido pirrol-2-il-acético (197).

15 Se usó el Procedimiento General C (para la síntesis del compuesto 1) para sintetizar éster metílico del ácido pirrol-2-il-acético usando clorhidrato del éster metílico de glicina (1,26 g, 10 mmol) como material de partida, calentando solamente hasta que la reacción empezó a 20 adquirir un color amarillo (7-10 min). (1,01 g, 73%).

(c) 5-Bromometil-3-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-isoxazol (196).

Se añadió tetrabromuro de carbono (1,99 g, 6 mmol) a una solución a 0°C de {3-[2-(195,5-metil-2-fenil-oxazol-4-25 il)-etoxi]-oxazol-5-il}-metanol (0,91 g, 3 mmol) y  $\text{Ph}_3\text{P}$

(1,99 g, 7,6 mmol) en 15 ml de THF. La reacción se agitó a 0°C durante 1 hora. La reacción se concentró y se aisló por cromatografía en columna (15% a 20% de EtOAc/hex). (0,62 g, 57%)

5 (d) {3-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-oxazol-5-il}-metanol (195).

Se añadió borohidruro sódico (0,20 g, 5,3 mmol) en porciones a una suspensión de éster metílico del ácido 3-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-oxazol-5-  
10 carboxílico (194, 0,57 g, 1,7 mmol) en 15 ml de MeOH a 0°C. La reacción se dejó calentar a temperatura ambiente durante 2 horas. La reacción se inactivó con agua y el disolvente se retiró. El residuo se disolvió en Et<sub>2</sub>O, se lavó con agua y salmuera, se secó (MgSO<sub>4</sub>) y se concentró dando un sólido  
15 blanco (0,47 g, 90%).

(e) Éster metílico del ácido 3-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-oxazol-5-carboxílico (194).

Se usó el Procedimiento General B para sintetizar este compuesto usando 3-hidroxi-5-isoxazol carboxilato de metilo  
20 (1,423 g, 10 mmol) y 2-(5-metil-2-fenil-oxazol-4-il)etanol (2,141 g, 10,5 mmol) como material de partida (2,71 g, 83%).

#### Ejemplo 78

Ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[3-(5-  
25 metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (204).

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Se usó el Procedimiento General A para hidrolizar el éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-r-il)-propel]-fenil}-2-pirrol-1-il-propiónico (203), produciendo el producto final (0,54 g, 80%).  $C_{32}H_{30}N_2O_4$  Masa 5 Calculada = 506,601;  $M+1$  (obs) = 507,3. Análisis Calculado para  $C_{32}H_{30}O_4N_2$  0,17  $H_2O$ : C, 75,35; H, 5,95; N, 5,49. Encontrado: C, 75,19, H, 6,06; N, 5,28.

El éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-r-il)-propel]-fenil}-2-pirrol-1-il-propiónico (203) 10 se preparó de la siguiente manera.

(a) Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-r-il)-propel]-fenil}-2-pirrol-1-il-propiónico (203).

El compuesto del título se sintetizó como se describe para el compuesto 89 usando 2-(5-metil-2-fenil-1,3-oxazol-15 4-il)acetato de metilo (0,55 g, 2,3 mmol) y 4-[3-(4-bromometil-fenil)-propil]-5-metil-2-fenil-oxazol (202, 0,78 g, 2,1 mmol) como materiales de partida.

(b) 4-[3-(4-Bromometil-fenil)-propil]-5-metil-2-fenil-oxazol (202).

20 Se añadió tetrabromuro de carbono (2,65 g, 8 mmol) a una solución a 0°C de {4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-metanol (202, 1,25 g, 4 mmol) y  $Ph_3P$  (2,67 g, 10 mmol) en 40 ml de THF. La reacción se agitó a 0°C durante 1 hora. La reacción se concentró y se aisló por 25 cromatografía en columna (5% de EtOAc/hex). (0,83 g, 53%).

(c) {4-[3-(5-Metil-2-fenil-oxazol-4-il)-propil]-fenil}-metanol (202).

Se reduce {4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-metanol (201, 6,63 g, 21,8 mmol) usando níquel 5 Raney en 1:1 de MeOH/THF. El catalizador se filtró y el filtrado se concentró obteniéndose un sólido amarillo pálido (6,45 g, 100%).

(d) {4-[3-(5-Metil-2-fenil-oxazol-4-il)-prop-1-in-il]-fenil}-metanol (202).

10 Se añadió 5-metil-2-fenil-4-prop-2-iniloxazol (compuesto 117, 11,74 g, 60 mmol) en 50 ml de pirrolidina a una suspensión de 4-yodobencil alcohol (10,71 g, 46 mmol), tetraquis(trifenilfosfina)paladio (0) (5,30 g, 4,6 mmol) y yoduro de cobre (I) (0,431 g, 2,3 mmol) en 50 ml de 15 pirrolidina. La reacción se completó después de la adición de alquino. La reacción se concentró y el residuo se disolvió en EtOAc. La capa orgánica se lavó con NH<sub>4</sub>Cl saturado y salmuera, se filtró y se secó (MgSO<sub>4</sub>). El material bruto se trituró con CH<sub>2</sub>Cl<sub>2</sub> y se filtró. Este 20 proceso se repitió dos veces para obtener dos extracciones del material deseado, que se recristalizó en EtOAc/hex. (6,63 g, 48%).

#### Ejemplo 79

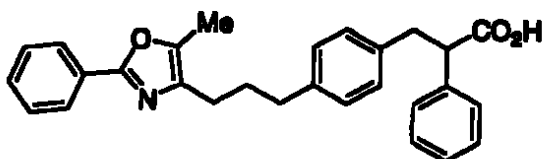
Ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[2-(5- 25 metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (205).

Este compuesto se sintetizó como se describe en el Ejemplo 32 usando 2-(5-metil-2-fenil-1,3-oxazol-4-il)acetato de metilo y el compuesto 88 como materiales de partida. P.f.: 120°C. MS(M+1):509,2.

#### 5 Ejemplo 80

Ácido 3-{4-[3-(5-metil-2-feniloxazol-4-il)-propil]-fenil}-2-fenilpropiónico (211).

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Una solución de 3-{4-[3-(5-metil-2-feniloxazol-4-il)-15 propil]-fenil}-2-fenilpropiónico (210, 0,86 g, 1,96 mmol) en MeOH se trató con un exceso de LiOH (1,0 M) y se agitó a temperatura ambiente. Después de esto, la reacción se diluyó con NH<sub>4</sub>Cl saturado y se extrajo con EtOAc. Los extractos orgánicos reunidos se secaron con salmuera 20 seguido de Na<sub>2</sub>SO<sub>4</sub> y se cromatografió (5 a 60% de EtOAc en hexanos), proporcionando 120 mg del compuesto del título. MS *m/z* 426 (M+H)<sup>+</sup>.

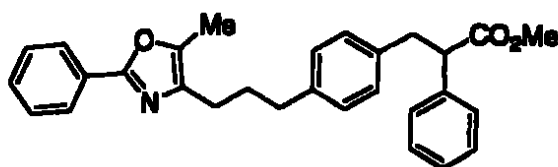
El éster metílico del ácido 3-{4-[3-(5-metil-2-feniloxazol-4-il)-propil]-fenil}-2-fenilpropiónico (210) se 25 preparó de la siguiente forma.



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(a) Éster metílico del ácido 3-{4-[3-(5-metil-2-feniloxazol-4-il)-propil]-fenil}-2-fenilpropiónico (210).

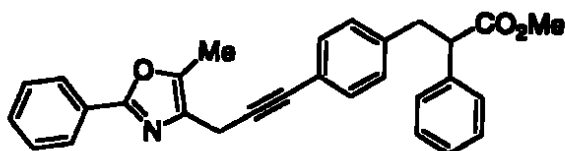


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210

Una solución del éster metílico del ácido 3-{4-[3-(5-metil-2-feniloxazol-4-il)-prop-1-inil]-fenil}-2-fenilpropiónico (209, 0,89 g, 2,0 mmol) en MeOH (50 ml) con Pd al 20%/C (0,13 g) se agitó en una atmósfera de H<sub>2</sub> durante 13,5 horas. La filtración proporcionó el compuesto deseado con un rendimiento del 96%.

(b) Éster metílico del ácido 3-{4-[3-(5-metil-2-feniloxazol-4-il)-prop-1-inil]-fenil}-2-fenilpropiónico (208).



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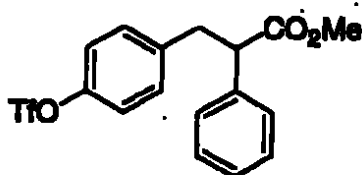
208

Una mezcla de 5-metil-2-fenil-4-prop-iniloxazol (1,0, 5,07 mmol), éster metílico del ácido 2-fenil-3-(4-trifluorometanosulfonilfenil)-propiónico (207, 1,52 g, 3,9 mmol) y tetraquis(trifenilfosfina)paladio (0) (0,32 g, 0,27

mmol) se combinaron en 3 ml de DMF. La mezcla se purgó con nitrógeno antes de añadir TEA (0,163 ml, 1,17 mmol) y CuI (15 mg, 0,078 mmol). Después de agitar a 80°C durante 18 horas, la mezcla se diluyó con EtOAc y se lavó con agua y 5 salmuera, se secó sobre Na<sub>2</sub>SO<sub>4</sub>, y se cromatografió (5% de EtOAc en hexanos), dando 0,89 g del compuesto del título.

(c) Éster metílico del ácido 2-fenil-3-(4-trifluorometanosulfonilfenil)-propiónico (207).

10



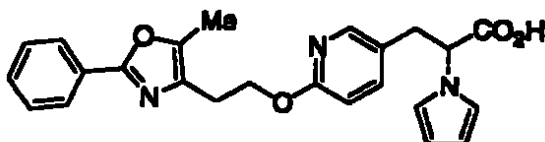
Una solución de éster metílico del ácido 2-fenil-3-(4-15 hidroxifenil)-propiónico (2,0 g, 7,8 mmol) en CH<sub>2</sub>Cl<sub>2</sub> (25 ml) se purgó con nitrógeno. Se añadió TEA (1,2 ml, 8,6 mmol) y la mezcla se enfrió a 0°C. Se añadió anhídrido trifluorometanosulfónico (1,38 ml, 8,2 mmol) y la reacción se dejó calentar a temperatura ambiente. Después de 18 h, 20 la reacción se diluyó con EtOAc, se lavó con NaHCO<sub>3</sub> al 5%, agua y salmuera, se secó sobre Na<sub>2</sub>SO<sub>4</sub> y se cromatografió (10% de EtOAc en hexanos), proporcionando 2,84 g del compuesto del título.

#### Ejemplo 81

25      Ácido      3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-il}-2-pirrol-1-il-propiónico (216).

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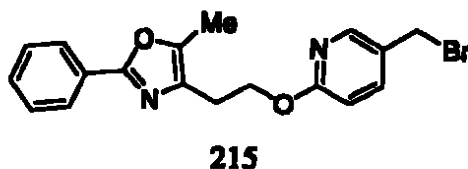
216

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Una solución de 5-bromometil-2-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridina (215, 0,73 g, 1,96 mmol) y éster metílico del ácido pirrol-1-il-acético (0,54 g, 3,91 mmol) en 20 ml de THF anhidro se purgó con nitrógeno seco y se trató con bis(trimetilsilil)amida de litio (1,0 M en THF, 3,9 ml). Después de agitar a temperatura ambiente durante 18 horas, la reacción se diluyó con EtOAc y se lavó con NH<sub>4</sub>Cl saturado. La TLC y la MS de la capa orgánica indican hidrólisis de parte del éster metílico. La capa orgánica se lavó con salmuera y se evaporó a sequedad. El aceite resultante se disolvió en MeOH y se trató con exceso de LiOH (1 M en agua). Después de agitar durante 18 horas a temperatura ambiente, la mezcla se evaporó a sequedad y se repartió entre EtOAc y tampón de pH 7. Tras el lavado de la capa orgánica con salmuera, el producto se precipitó. El sólido se recogió, se lavó con agua y éter, y se secó al vacío hasta un peso constante, proporcionando 287 mg (34%) del compuesto del título. MS m/z 465 (M+H)<sup>+</sup>.

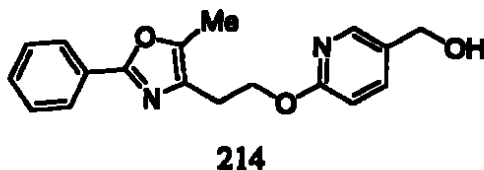
La 5-bromometil-2-[2-(5-metil-2-fenil-oxazol-4-il)-25 etoxi]-piridina (215) se preparó de la siguiente forma.

(a) 5-Bromometil-2-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridina (215).



Se disolvió {6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-il}-metanol (214, 1,50 g, 4,83 mmol) en CH<sub>2</sub>Cl<sub>2</sub> anhidro (40 ml), se purgó con nitrógeno seco y se enfrió a 0°C. Se añadió trifenilfosfina (1,34 g, 5,12 mmol), seguido de N-bromosuccinimida (0,95 g, 5,36 mmol). Después de 30 minutos, la mezcla de reacción se concentró y se cromatografió (5 a 25% de EtOAc en hexanos), dando 1,19 g (66%) de bromuro.

(b) {6-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-il}-metanol (214).

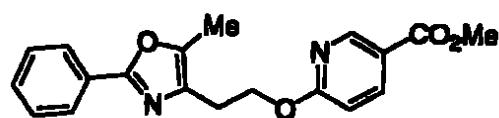


A una solución purgada con nitrógeno del éster metílico del ácido 6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-nicotínico (213, 1,87 g, 5,53 mmol) en éter anhidro (50 ml) se le añadió hidruro de litio y aluminio (1,0 M en THF, 11,1 ml) durante aproximadamente 5 minutos. El baño se

621

retiró, y la reacción se dejó en agitación a temperatura ambiente durante 4 horas. Se añadió HCl (1,0 M) y la reacción se agitó a temperatura ambiente durante una noche. Se añadió Na<sub>2</sub>CO<sub>3</sub> (5%) a pH 8. La mezcla se extrajo con 5 EtOAc. Los extractos orgánicos reunidos se lavaron con agua y salmuera, se secaron sobre Na<sub>2</sub>SO<sub>4</sub> anhidro y se evaporaron, proporcionando el compuesto del título con un rendimiento del 62%.

(c) Éster metílico del ácido 6-[2-(5-metil-2-fenil-10 oxazol-4-il)-etoxi]-nicotínico (213).



213

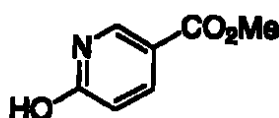
15 Se combinaron éster metílico del ácido 6-hidroxinicotínico (212, 3,47 g, 22,7 mmol), 2-(5-metil-2-fenil-oxazol-4-il)-etanol (5,53 g, 27,2 mmol) y trifenilfosfina (7,1 g, 27,2 mmol) en THF anhidro (100 ml), la mezcla se purgó con nitrógeno seco y se enfrió a 0°C. Se  
20 añadió DEAD (5,9 g, 34,0 mmol) durante 5 minutos, y la mezcla se dejó calentar lentamente a temperatura ambiente durante una noche. El THF se retiró a presión reducida, y el residuo se repartió entre EtOAc y NaHCO<sub>3</sub> al 5%. La capa orgánica se lavó con NaHCO<sub>3</sub> al 5%, agua y salmuera, se secó  
25 sobre Na<sub>2</sub>SO<sub>4</sub> anhidro y se cromatografió (de 5 a 40% de EtOAc

672

en hexanos), proporcionando 2,98 g (39%) del compuesto del título.

(d) Éster metílico del ácido 6-hidroxinicotínico (212).

5



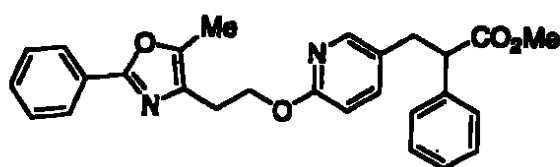
212

Una suspensión del ácido 6-hidroxinicotínico (10,0 g, 71,9 mmol) en CH<sub>2</sub>Cl<sub>2</sub> anhidro (80 ml, más 3 gotas de DMF) se purgó con nitrógeno, se enfrió a 0°C y se trató con cloruro de oxalilo (7,53 ml, 86,3 mmol). Después de 18 horas a temperatura ambiente, se añadió cuidadosamente un exceso de metanol. La reacción se evaporó y se cromatografió (20% de EtOAc en hexanos), proporcionando 2,74 g (25%) del compuesto del título.

# Ejemplo 82

Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-il}-2-fenilpropiónico (217).

20



217

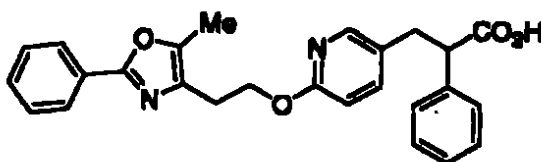
25 El compuesto del título se preparó de una forma

193

análoga a PD-341440-0000 utilizando fenilacetato de metilo con un rendimiento del 79%. MS  $m/z$  443 (M+H)<sup>+</sup>.

Ejemplo 83

Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-5 piridin-3-il}-2-fenil-propiónico (218).



218

10

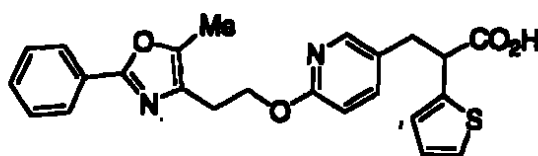
Una solución del éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-il}-2-fenilpropiónico (0,52 g, 1,18 mmol) en 10 ml de MeOH se trató con un exceso de LiOH 1 M. Después de esto, la 15 reacción se diluyó con NH<sub>4</sub>Cl saturado y se extrajo con EtOAc. Los extractos orgánicos reunidos se secaron con salmuera seguido de Na<sub>2</sub>SO<sub>4</sub> y se cromatografiaron (5 a 60% de EtOAc en hexanos), proporcionando 323 mg del compuesto del título. MS  $m/z$  429 (M+H)<sup>+</sup>.

20 Ejemplo 84

Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-il}-2-tiofen-2-il-propiónico (219).

674

330



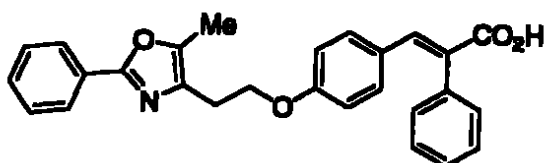
219

5

El compuesto del título (155 mg) se preparó de una forma análoga a PD 341440-0000, utilizando tiofeno-2-ilacetato de metilo. MS  $m/z$  435  $(M+H)^+$ .

#### Ejemplo 85

10      Ácido      3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-acrílico (222).



222

15

Una solución de éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-acrílico (221, 0,31 g, 0,71 mmol) en 10 ml de MeOH se trató con un 20 exceso de LiOH 1 M. Después de esto, la reacción se diluyó con  $\text{NH}_4\text{Cl}$  saturado y se extrajo con EtOAc. Los extractos orgánicos reunidos se secaron con salmuera seguido de  $\text{Na}_2\text{SO}_4$  y se cromatografiaron (5 a 60% de EtOAc en hexanos), proporcionando 241 mg del compuesto del título. MS  $m/z$  426 25  $(M+H)^+$ .

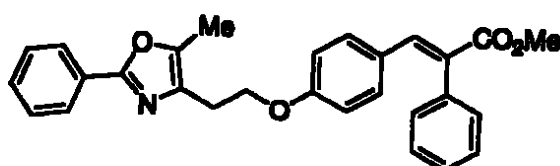


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331

El éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-acrílico (221) se preparó de la siguiente forma.

(a) Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-5 oxazol-4-il)-etoxi]-fenil}-2-fenil-acrílico (221).



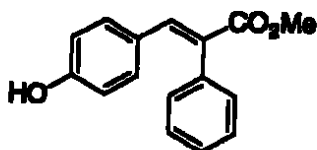
221

10

Se combinaron trifenilfosfina (0,57 g, 2,17 mmol), éster metílico del ácido 3-(4-hidroxifenil)-2-fenilacrílico (220, 0,46 g, 1,81 mmol) y 2-(5-metil-2-feniloxazol-4-il)-etanol (0,44 g, 2,17 mmol) en THF (10 ml), la mezcla se purgó con nitrógeno y se enfrió a 0°C. Se añadió DEAD (0,43 ml, 2,71 mmol) y la mezcla se dejó calentar a temperatura ambiente durante una noche. La reacción se diluyó con EtOAc y se lavó con NaHCO<sub>3</sub> al 5%, agua y salmuera, se secó sobre Na<sub>2</sub>SO<sub>4</sub> y se cromatografió (0 a 60% de EtOAc en hexanos), proporcionando 0,31 g del compuesto del título.

(b) Éster metílico del ácido 3-(4-hidroxifenil)-2-fenilacrílico (220).

332



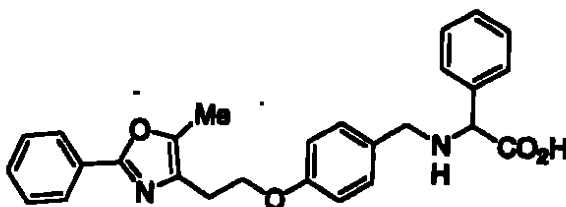
220

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Una suspensión del ácido 3-(4-hidroxifenil)-2-fenilacrílico (2,5 g, 10,4 mmol) en MeOH (50 ml) se trató con H<sub>2</sub>SO<sub>4</sub> (1 ml) y se calentó a reflujo durante 72 horas. La mayor parte del disolvente se retiró a presión reducida y el residuo se diluyó con EtOAc y se lavó con NaHCO<sub>3</sub> al 5%, agua y salmuera. La cromatografía (5 a 60% de EtOAc en hexanos) proporcionó 0,46 g del compuesto del título en forma de un sólido blanco.

#### Ejemplo 87

15 Ácido {4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (223).



223

20

Una solución de éster metílico del ácido {4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (0,30 g, 0,66 mmol) en 10 ml de MeOH se trató con un exceso

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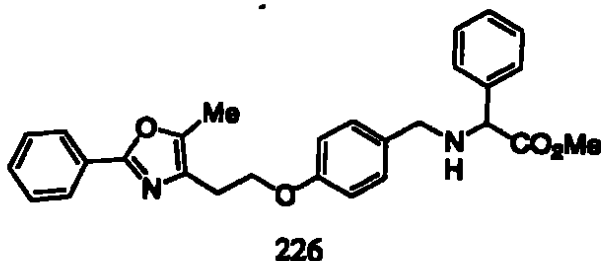
637

de LiOH 1 M. Después de esto, la reacción se diluyó con NH<sub>4</sub>Cl saturado y se extrajo con EtOAc. Los extractos orgánicos reunidos se secaron con salmuera seguido de Na<sub>2</sub>SO<sub>4</sub> y se cromatografiaron (5 a 60% de EtOAc en hexanos), proporcionando el compuesto del título con un rendimiento del 71%. MS m/z 443 (M+H)<sup>+</sup>.

Ejemplo 87

Éster metílico del ácido {4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (226).

10



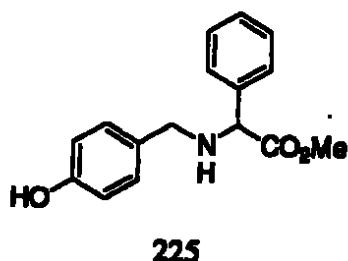
15

Se combinaron trifenilfosfina (2,00 g, 7,65 mmol), éster metílico del ácido (4-hidroxibencilamino)-fenilacético (225, 1,73 g, 6,38 mmol) y 2-(5-metil-2-feniloxazol-4-il)-etanol (1,56 g, 7,65 mmol) en THF (25 ml), la mezcla se purgó con nitrógeno y se enfrió a 0°C. Se añadió DEAD (1,20 ml, 7,65 mmol) y la mezcla se dejó calentar a temperatura ambiente durante una noche. La reacción se diluyó con EtOAc y se lavó con NaHCO<sub>3</sub> al 5%, agua y salmuera, se secó sobre Na<sub>2</sub>SO<sub>4</sub> y se cromatografió (0 a 60% de EtOAc en hexanos), proporcionando 1,52 g del

compuesto del título. MS  $m/z$  457 (M+H)<sup>+</sup>.

El éster metílico del ácido (4-hidroxibencilamino)-fenilacético (225) se preparó de la siguiente forma.

(a) Éster metílico del ácido (4-hidroxibencilamino)-5 fenilacético (225).



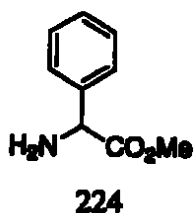
10

Se combinaron éster metílico de fenilglicina (224, 1,63 g, 9,87 mmol) y 4-hidroxibenzaldehído (0,80 g, 6,58 mmol) en HOAC al 1% en MeOH (100 ml). Se añadió 15 cianoborohidruro sódico (0,62 g, 9,87 mmol) y la mezcla se dejó en agitación a temperatura ambiente. Después de 18 horas, la reacción se concentró a presión reducida y se repartió entre EtOAc y NaHCO<sub>3</sub> al 5%. La capa orgánica se lavó con agua y salmuera, se secó sobre Na<sub>2</sub>SO<sub>4</sub> y se 20 cromatografió (0 a 50% de EtOAc en hexanos), proporcionando el compuesto del título con un rendimiento del 97%.

(b) Éster metílico de fenilglicina (224).

62d

335



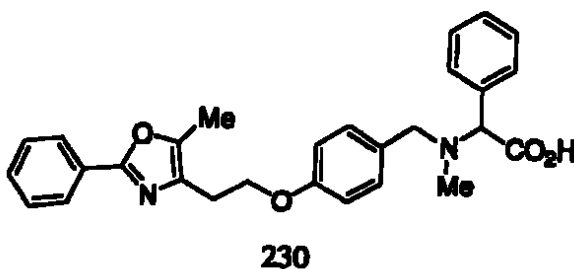
5

Se disolvió fenilglicina (10,0 g, 66,2 mmol) en 100 ml de MeOH con 2 ml de H<sub>2</sub>SO<sub>4</sub> y se calentó a reflujo durante una noche. La reacción se concentró a presión reducida y se repartió entre éter y agua. Se añadió NaHCO<sub>3</sub> sólido a pH 7.

10 La capa acuosa se extrajo con éter y EtOAc. Los extractos orgánicos reunidos se lavaron con agua y salmuera, y se secaron sobre Na<sub>2</sub>SO<sub>4</sub>, proporcionando 1,63 g del compuesto del título.

Ejemplo 88

15      Ácido            metil-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (230).



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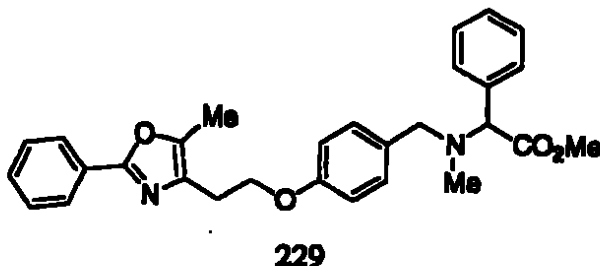
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Una solución de éster metílico del ácido metil-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (229, 0,18 g, 0,38 mmol) en 5 ml de MeOH se trató con un exceso de LiOH 1 M. Después de esto, la reacción se diluyó con NH<sub>4</sub>Cl saturado y se extrajo con EtOAc. Los extractos orgánicos reunidos se secaron con salmuera seguido de Na<sub>2</sub>SO<sub>4</sub> y se cromatografiaron (5 a 60% de EtOAc en hexanos), proporcionando el compuesto del título 10 con un rendimiento del 62%. MS m/z 457 (M+H)<sup>+</sup>.

El éster metílico del ácido metil-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (229) se preparó de la siguiente forma.

(a) Éster metílico del ácido metil-{4-[2-(5-metil-2-15 fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (229).



20

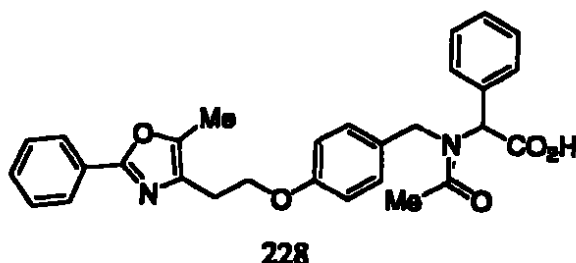
Una solución de éster metílico del ácido {4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (228, 0,30 g, 0,66 mmol), formaldehído (37% en agua, 0,26 25 ml, 3,10 mmol) y HOAc (0,056 ml, 0,99 mmol) en CH<sub>3</sub>CN (5 ml)

63

se trató con cianoborohidruro sódico (45 mg, 0,72 mmol). Después de 18 horas, el producto se purificó como en la preparación de éster metílico del ácido (4-hidroxibencilamino)-fenilacético, dando el compuesto del 5 título con un rendimiento del 65%. MS  $m/z$  471 (M+H)<sup>+</sup>.

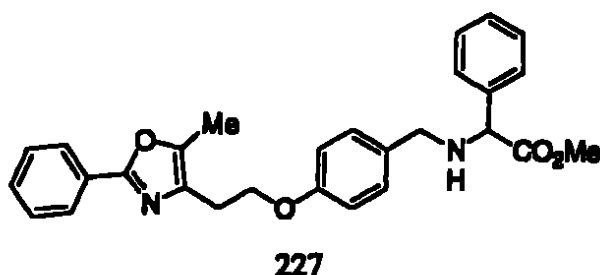
(b) Ácido acetil-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (228).

10



Una solución de éster metílico del ácido acetil-{4-[2-15 (5-metil-2-fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (227, 0,25 g, 0,50 mmol) en 5 ml de MeOH se trató con un exceso de LiOH 1 M. Después de esto, la reacción se diluyó con NH<sub>4</sub>Cl saturado y se extrajo con EtOAc. Los extractos orgánicos reunidos se secaron con 20 salmuera seguido de Na<sub>2</sub>SO<sub>4</sub> y se cromatografiaron (5 a 60% de EtOAc en hexanos), proporcionando el compuesto del título con un rendimiento del 55%. MS  $m/z$  485 (M+H)<sup>+</sup>.

(c) Éster metílico del ácido acetil-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (227).

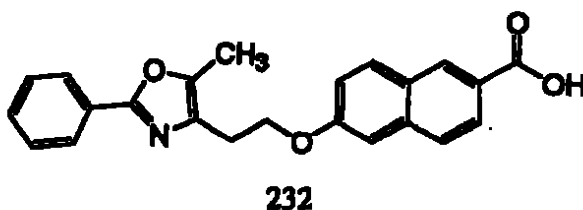


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Una solución de éster metílico del ácido {4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencilamino}-fenilacético (0,30 g, 0,66 mmol) y trietilamina (0,10 ml, 0,72 mmol) en 10 CH<sub>2</sub>Cl<sub>2</sub> (5 ml) se trató con cloruro de acetilo (0,050 ml, 0,69 mmol). Después de 18 horas, la mezcla de reacción se evaporó y se cromatografió (5 a 20% de EtOAc en hexanos), dando el compuesto del título con un rendimiento del 85%. MS *m/z* 499 (M+H)<sup>+</sup>.

#### 15 Ejemplo 89

Ácido 6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-naftaleno-2-carboxílico (231).



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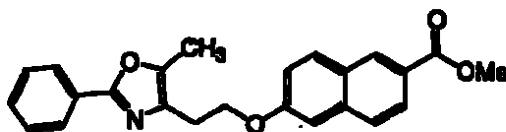
Una solución de éster metílico del ácido 6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-naftaleno-2-carboxílico (231) en MeOH (5 ml) se trató con un exceso de LiOH (1,0 M)



y se agitó a temperatura ambiente. Después de esto, la reacción se diluyó con  $\text{NH}_4\text{Cl}$  saturado y se extrajo con EtOAc. Los extractos orgánicos reunidos se secaron con salmuera seguido de  $\text{Na}_2\text{SO}_4$  y se cromatografiaron (5 a 60% de 5 EtOAc en hexanos), proporcionando 131 mg del compuesto del título. MS  $m/z$  374 ( $\text{M}+\text{H}$ )<sup>+</sup>.

El éster metílico del ácido 6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-naftaleno-2-carboxílico (231) se preparó de la siguiente forma.

- 10 (a) Éster metílico del ácido 6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-naftaleno-2-carboxílico (231)



15

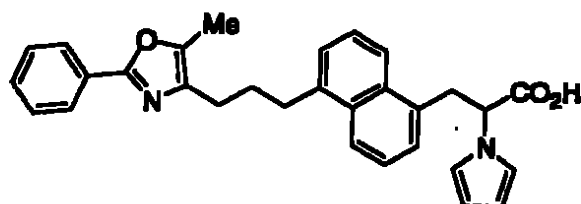
Se combinaron trifenilfosfina (1,65 g, 6,29 mmol), éster metílico del ácido 6-hidroxinaftaleno-2-carboxílico (1,06 g, 5,24 mmol) y 2-(5-metil-2-feniloxazol-4-il)-etanol (1,28 g, 6,29 mmol) en THF (25 ml), la mezcla se purgó con 20 nitrógeno y se enfrió a 0°C. Se añadió DEAD (1,00 ml, 6,29 mmol) y la mezcla se dejó calentar a temperatura ambiente durante una noche. La reacción se diluyó con EtOAc y se lavó con  $\text{NaHCO}_3$  al 5%, agua y salmuera, se secó sobre  $\text{Na}_2\text{SO}_4$  y se cromatografió (0 a 60% de EtOAc en hexanos), 25 proporcionando 0,58 g del compuesto del título.

654

Ejemplo 90

Ácido 3-{5-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-naftalen-1-il]-2-pirrol-1-il}-propiónico (237).

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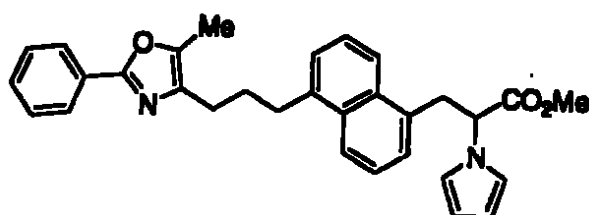
237

Una solución de éster metílico del ácido 3-{5-[3-(5-  
10 metil-2-fenil-oxazol-4-il)-propil]-naftalen-1-il}-2-pirrol-  
1-il}-propiónico (236, 0,15 g, 0,31 mmol) en metanol se  
trató con un exceso de LiOH (1 M en agua). Después de  
agitar a temperatura ambiente durante una noche, la mezcla  
de reacción se diluyó con agua y se lavó con éter. La capa  
15 acuosa se acidificó con HCl 1 M y se extrajo con EtOAc. Los  
extractos reunidos se lavaron con salmuera, se secaron  
sobre Na<sub>2</sub>SO<sub>4</sub> y se evaporaron proporcionando 84 mg (56%) del  
compuesto del título.

El éster metílico del ácido 3-{5-[3-(5-metil-2-fenil-  
20 oxazol-4-il)-propil]-naftalen-1-il}-2-pirrol-1-il-  
propiónico (236) se preparó de la siguiente forma.

585

341



236

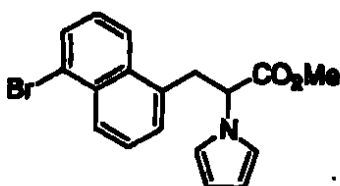
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(a) Éster metílico del ácido 3-{5-[3-(5-metil-2-fenil-oxazol-4-il)-propíl]-naftalen-1-il}-2-pirrol-1-il-propiónico (236).

10 Una solución de 4-alil-5-metil-2-fenil-oxazol (0,38 g, 1,89 mmol) se purgó con nitrógeno, se enfrió a 0°C y se trató con 9-borabicyclo[3.3.1]nonano (0,5 M en THF, 7,6 ml). La reacción se dejó calentar lentamente a temperatura ambiente durante una noche. La solución del aducto de 9-BBN  
15 se transfirió a una mezcla purgada de éster metílico del ácido 3-(5-bromo-naftalen-1-il)-2-pirrol-1-il-propiónico (235, 0,52 g, 1,45 mmol), complejo de [1,1'-bis(difenilfosfino)ferroceno]dicloro paladio (II) con diclorometano (1:1) (0,10 g, 0,15 mmol), carbonato de cesio  
20 (1,32 g, 4,06 mmol), trifenilarsina (44 mg, 0,15 mmol), agua (0,31 ml, 17,4 mmol) y DMF (4 ml). La mezcla de reacción se agitó a temperatura ambiente durante 24 horas, antes de enfriarse a 0°C y de añadir NaOAc (3,0 M, 6 ml) y H<sub>2</sub>O<sub>2</sub> (30%, 3 ml). Después de 2 horas, la mezcla se diluyó  
25 con agua y se extrajo con una mezcla de 7:1 de éter/EtOAc.

Los extractos orgánicos reunidos se lavaron con agua y salmuera, se secaron sobre  $\text{Na}_2\text{SO}_4$  anhidro, se evaporaron y se lavaron abundantemente (5 a 50% de EtOAc en hexanos), dando 0,15 g (22%) del compuesto del título.

- 5 (b) Éster metílico del ácido 3-(5-bromo-naftalen-1-il)-2-pirrol-1-il-propiónico (235)



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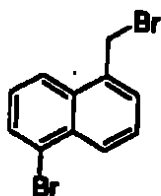
235

Una solución de 1-bromo-5-bromometil-naftaleno (234, 1,05 g, 3,50 mmol) y éster metílico del ácido pirrol-1-il-acético (0,97 g, 7,00 mmol) en THF anhidro (20 ml) se purgó con nitrógeno y se trató con  $\text{LiN}(\text{TMS})_2$  (1,0 M 7,0 ml). Después de aproximadamente 30 minutos a temperatura ambiente, la reacción se calentó a 50°C durante 48 horas. La mezcla de reacción se concentró y se cromatografió (5 a 50% de EtOAc en hexanos), proporcionando 0,80 g (64%) del compuesto del título.

- (c) 1-Bromo-5-bromometil-naftaleno (234).

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343



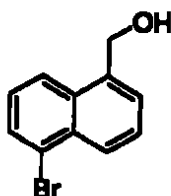
234

5

Una solución de (5-bromo-naftalen-1-il)-metanol (233, 1,13 g, 4,77 mmol) en  $\text{CH}_2\text{Cl}_2$  anhidro (20 ml) se purgó con nitrógeno y se enfrió a  $0^\circ\text{C}$ . Se añadió trifenilfosfina 10 (1,33 g, 5,05 mmol) seguido de NBS (0,94 g, 5,29 mmol). Después de 30 minutos a  $0^\circ\text{C}$ , la mezcla se concentró y se cromatografió dos veces (5 a 25% de EtOAc en hexanos), dando 1,05 g, (73%) del compuesto del título.

(d) (5-Bromo-naftalen-1-il)-metanol (233).

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233

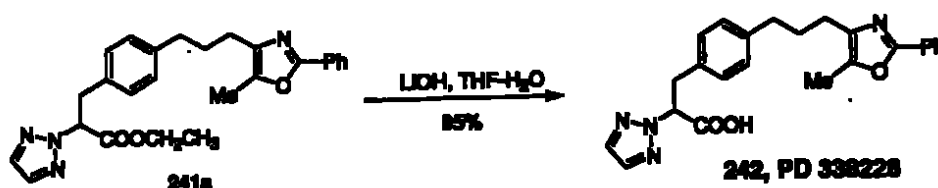
20 Una solución del ácido 5-bromonaftalen-1-carboxílico (2,50 g, 9,96 mmol, PD-59348, Lote P) en THF anhidro (100 ml) se purgó con nitrógeno. Se añadió borano (1,0 M en THF, 20 ml) y la reacción se calentó a reflujo durante 6 horas. La reacción se enfrió a temperatura ambiente, se trató con 25 10 ml de MeOH, y se agitó a temperatura ambiente durante

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una noche. La mezcla se concentró, se disolvió en éter, se lavó con NaOH 1 M, agua y salmuera, y se secó sobre Na<sub>2</sub>SO<sub>4</sub> anhidro. El producto bruto se purificó por cristalización en CH<sub>2</sub>Cl<sub>2</sub>/hexanos proporcionando 1,5 g (64%) del compuesto 5 del título.

### Ejemplo 91

Ácido 3-(4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-2-1,2,3-triazol-1-il-propiónico (242).



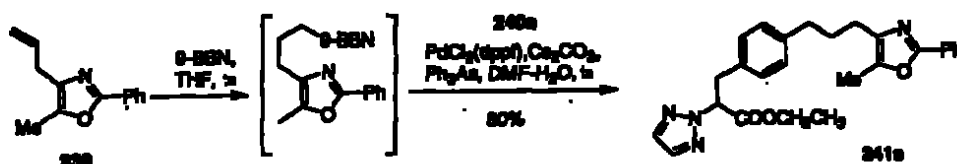
- 10 PROCEDIMIENTO GENERAL 91. Se disolvió éster etílico del ácido 3-(4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-2-1,2,3-triazol-2-il-propiónico (241a) (2,37 g, 5,331 mmol) en THF (60 ml) y se añadió agua (15 ml). Se incorporó hidróxido de litio monohidrato (0,335 g, 8,00 mmol) y la
- 15 mezcla se agitó a temperatura ambiente durante 1 hora. El disolvente orgánico se retiró por evaporación rotatoria a temperatura ambiente. El residuo acuoso se diluyó con agua y se extrajo con Et<sub>2</sub>O (2 x 45 ml). Se pasó un flujo de aire a través de la fase acuosa para retirar el éter residual.
- 20 Después, la fase acuosa se acidificó con HCl al 10%. El

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sólido precipitado se separó por filtración al vacío y se lavó con agua. Después, el sólido se secó al aire durante una noche a 45°C durante 14 horas, dando el compuesto del título en forma de un sólido blanquecino (2,11 g, 95%):  
 5 p.f. (se reblandece o se funde a 50-85°C, forma otro sólido que se funde a 153-153,5°C);  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,98-7,96 (m, 2H), 7,62 (s, 2H), 7,43-7,40 (m, 3H), 7,03 (d,  $J$  = 8,1 Hz, 2H), 6,98 (d,  $J$  = 8,1 Hz, 2H), 5,52 (dd,  $J$  = 10,4 y 5,0 Hz, 1H), 3,65-3,49 (m, 2H), 2,58 (t,  $J$  = 7,6 Hz, 2H),  
 10 2,48 (t,  $J$  = 7,6 Hz, 2H), 2,27 (s, 3H), 1,93 (m,  $J$  = 7,6 Hz, 2H); CIMS  $m/z$  417 ( $M+1$ ). HPLC: pureza: 100%; columna: symmetry  $\text{C}_{18}$ , 4,6 x 150 mm, 5  $\mu\text{M}$ , fase móvil: A: agua + TFA al 0,1%, B: acetonitrilo + TFA al 0,1%; tiempo de retención 15,914 min; longitud de onda: 254 nm.

15 El éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-1,2,3-triazol-2-il-propiónico (241a) se preparó de la siguiente forma.

(a) Éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-1,2,3-triazol-2-il-propiónico  
 20 (241a).



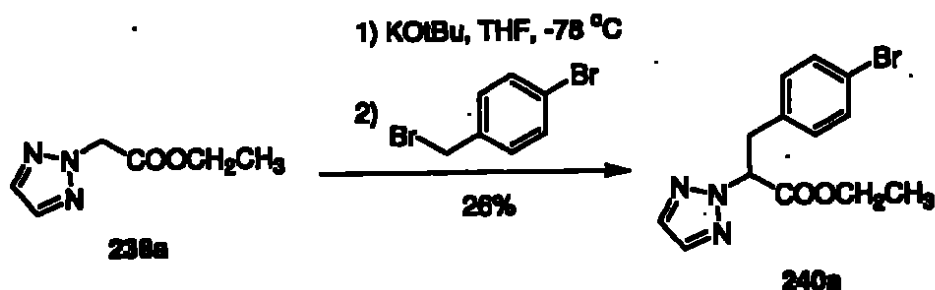
PROCEDIMIENTO GENERAL 92-a. Se añadió una solución de 5-metil-2-fenil-4-prop-2-eniloxazol (compuesto 239) (1,716 g, 8,614 mmol) en THF seco (25 ml) a una solución de 9-BBN 0,5 M en THF (34,45 ml) a 0°C en una atmósfera de 5 nitrógeno. El baño de hielo se retiró y la mezcla se agitó a temperatura ambiente durante una noche. Después se añadió el aducto de 9-BBN a un matraz que contenía el bromuro 238a (2,148 g, 6,626 mmol), PdCl<sub>2</sub> (dppf) (0,485 g, 0,662 mmol), Cs<sub>2</sub>CO<sub>3</sub> (3,88 g, 11,927 mmol), Ph<sub>3</sub>As (0,203 g, 0,662 10 mmol), agua (1,4 ml, 79,5 mmol) y DMF (15 ml). La mezcla de reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 2 días. Al finalizar este tiempo, la mezcla se enfrió en un baño de hielo y se añadió NaOAc 3 M (16 ml) seguido de H<sub>2</sub>O<sub>2</sub> al 30% (8 ml). Se continuó agitando 15 durante 2 horas y después, la mezcla se calentó lentamente a temperatura ambiente. Se añadió agua (100 ml) seguido de Et<sub>2</sub>O y EtOAc. Las fases se separaron y la fase acuosa se extrajo con Et<sub>2</sub>O-EtOAc (60:10 ml x 4). Los extractos orgánicos reunidos se lavaron con salmuera, se secaron 20 sobre sulfato de magnesio y el disolvente se retiró. La purificación por cromatografía en columna sobre gel de sílice eluyendo con EtOAc en hexanos (0 a 22%) produjo el éster 241a en forma de un aceite espeso. (2,37 g, 80%): <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,98-7,95 (m, 2H), 7,61 (s, 2H), 25 7,44-7,38 (m, 3H), 7,03 (d, J = 8,3 Hz, 2H), 7,00 (d, J =



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8,3 Hz, 2H), 5,50 (dd,  $J = 10,2$  y  $5,6$  Hz, 1H), 4,18 (q,  $J = 7,1$  Hz, 2H), 3,71-3,57 (m, 2H), 2,58 (t,  $J = 7,6$  Hz, 2H), 2,46 (t,  $J = 7,6$  Hz, 2H), 2,24 (s, 3H), 1,93 (m,  $J = 7,6$  Hz, 2H), 1,19 (t,  $J = 7,1$  Hz, 3H); CSMS  $m/z$  445 ( $M+1$ ).

5 (b) Bromuro 240a (PD 0341554).



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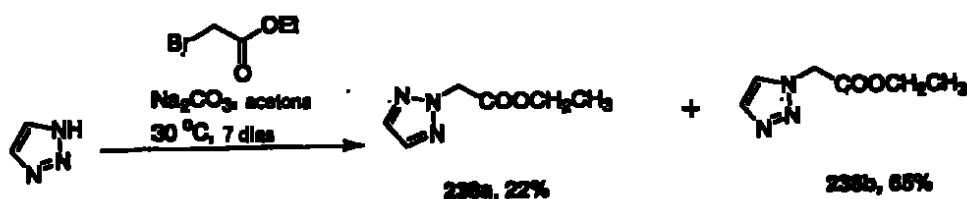
Procedimiento General 91-b. Se disolvió el éster 238a (3,0 g, 19,336 mmol) en THF seco (60 ml) y se enfrió a -15 78°C en una atmósfera de nitrógeno. Se añadió una solución de terc-butoxido potásico 1,0 M en THF (20,3 ml, 20,3 mmol). La mezcla se agitó a -78°C durante 45 minutos. Se añadió una solución de bromuro de 4-bromobencilo (5,56 g, 22,236 mmol) en THF (20 ml). Se dejó que la reacción 20 alcanzará lentamente la temperatura ambiente y después se

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agitó durante 6 días. La mezcla se inactivó con agua (60 ml) y se diluyó con Et<sub>2</sub>O y EtOAc. Las fases se separaron y la fase acuosa se extrajo con Et<sub>2</sub>O-EtOAc (50:5 ml x 3). Los extractos orgánicos reunidos se lavaron con salmuera, se 5 secaron sobre sulfato de magnesio y el disolvente se retiró. Se purificaron por cromatografía en columna sobre gel de sílice eluyendo con EtOAc en hexanos (0 a 16%), produjo el compuesto del título en forma de un aceite (1,668 g, 26%): <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,62 (s, 2H), 7,32 10 (d, J = 8,5 Hz, 2H), 6,97 (d, J = 8,5 Hz, 2H), 5,48 (dd, J = 10,4 y 5,4 Hz, 1H), 4,19 (q, J = 7,1 Hz, 2H), 3,70-3,55 (m, 2H), 1,20 (t, J = 7,1 Hz, 3H); CIMS m/z 324 (M)<sup>+</sup>.

(c) Acetato de 2-(2H-1,2,3-triazol-2-il)etilo (238a).

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El compuesto del título se preparó siguiendo el 20 procedimiento descrito por Kume y col. (Kume, M.; Kubota,

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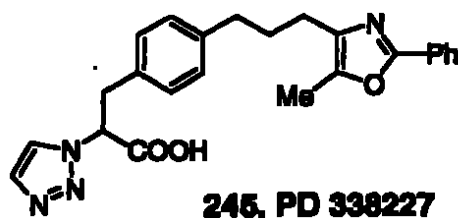
T.; Kimura, Y.; Nakashimizu, H.; Motokawa, K.; Nakano, M. *J. Antibiotics* **1993**, *46*, 177-192). Siguiendo este procedimiento y partiendo de 1H-1,2,3-triazol (18,17 g, 0,263 mmol), se obtuvo el éster 238a en forma de un líquido 5 (9,2 g, 22%) después de cromatografía en columna sobre gel de sílice, eluyendo con EtOAc en hexanos (del 0 al 55%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,68 (s, 2H), 5,23 (s, 2H), 4,24 (q,  $J = 7,1$  Hz, 2H), 1,27 (t,  $J = 7,1$  Hz, 3H); CIMS  $m/z$  156 (M+1).

10 A partir de la misma purificación, se obtuvo el producto N-1 alquilado 238 b como el producto principal (26,45 g, 65%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,75 (d,  $J = 1,0$  Hz, 1H), 7,71 (d,  $J = 1,0$  Hz, 1H), 5,19 (s, 2H), 4,25 (q,  $J = 7,1$  Hz, 2H), 1,28 (t,  $J = 7,1$  Hz, 3H); CIMS  $m/z$  156 15 (M+1).

#### Ejemplo 92

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-1,2,3-triazol-1-il-propiónico (245).

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**245, PD 338227**

25 Preparado a partir del éster 244 (1,0 g, 2,249 mmol) siguiendo el Procedimiento General 92. El compuesto del

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título se obtuvo en forma de un sólido blanco (0,854 g, 91%), p.f. 162-163,5°C;  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,93 (m, 2H), 7,66 (s, 1H), 7,63 (s, 1H), 7,41 (m, 3H), 7,01 (d,  $J = 8,0$  Hz, 2H), 6,92 (d,  $J = 8,0$  Hz, 2H), 5,62 (dd,  $J = 8,3$  y 5 6,1 Hz, 1H), 3,46-3,35 (m, 2H), 2,56 (t,  $J = 7,3$  Hz, 2H), 2,48 (t,  $J = 7,3$  Hz, 2H), 2,28 (s, 3H), 1,89 (m, 2H); CIMS  $m/z$  417 (M+1).

El éster metílico del ácido 3-(4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-2-1,2,3-triazol-1-il-propiónico 10 (244) se preparó de la siguiente forma.

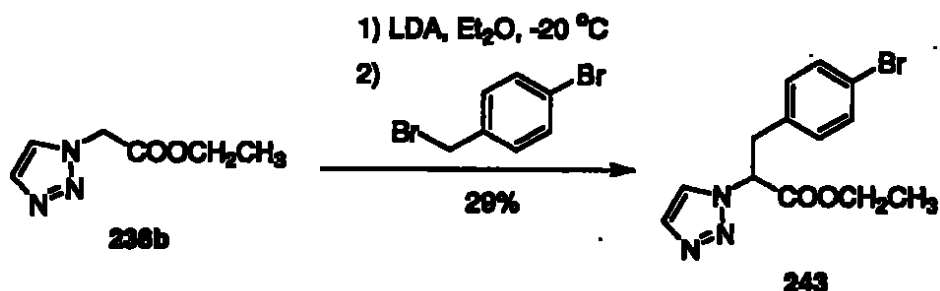
(a) Éster metílico del ácido 3-(4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-2-1,2,3-triazol-1-il-propiónico (244).

El compuesto del título se preparó a partir del 15 bromuro 243 (1,2 g, 3,702 mmol) usando el Procedimiento General 92a. El éster 244b se obtuvo en forma de un aceite espeso (1,00 g, 61%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,98 (m, 2H), 7,66 (s, 1H), 7,63 (s, 1H), 7,44-7,38 (m, 3H), 7,06 (d,  $J = 8,0$  Hz, 2H), 6,93 (d,  $J = 8,0$  Hz, 2H), 5,59 (dd,  $J = 8,3$  y 20 6,6 Hz, 1H), 4,19 (q,  $J = 7,3$  Hz, 2H), 3,49-3,38 (m, 2H), 2,61 (t,  $J = 7,6$  Hz, 2H), 2,48 (t,  $J = 7,3$  Hz, 2H), 2,27 (s, 3H), 1,96 (m, 2H), 1,21 (t,  $J = 7,1$  Hz, 3H); CIMS  $m/z$  445 (M+1).

(b) Bromuro 243

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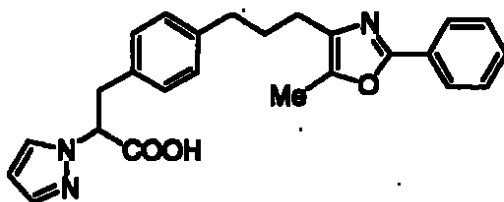
Se enfrió una solución de diisopropilamina (2,0 ml, 14,18 mmol) en Et<sub>2</sub>O (30 ml) a -20°C en una atmósfera de nitrógeno. Se añadió una solución de BuLi 1,6 M en hexanos (9,7 ml, 15,47 mmol). La mezcla se agitó durante 25 minutos. Se añadió una solución del éster 238b (2,0g, 12,89 mmol) en Et<sub>2</sub>O (20 ml). La mezcla se agitó durante 30 minutos. Se incorporó una solución de bromuro de 4-bromobencilo (3,70 g, 14,82 mmol) en Et<sub>2</sub>O (20 ml). La mezcla de reacción se mantuvo a -20°C durante 2,5 horas y después se dejó calentar lentamente a la temperatura ambiente. Se continuó agitando a temperatura ambiente durante 24 horas. En ese momento, la mezcla se inactivó con agua y se diluyó con Et<sub>2</sub>O. Las fases se separaron y la capa acuosa se extrajo con Et<sub>2</sub>O (3 x 40 ml). Los extractos orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato de magnesio y el disolvente se retiró. La purificación por cromatografía en columna sobre gel de sílice produjo el bromuro 243 en forma de un aceite amarillo pálido (1,21 g, 29%): <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,67 (d, J = 0,7 Hz, 1H), 7,63 (d, J = 1,0 Hz, 1H), 7,35 (d, J = 8,5 Hz, 2H), 6,89

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(d,  $J = 8,5$  Hz, 2H), 5,54 (dd,  $J = 8,7$  y  $6,5$  Hz, 1H), 4,21 (q,  $J = 7,1$  Hz, 2H), 3,51-3,39 (m, 2H), 1,22 (t,  $J = 7,3$  Hz, 3H); CIMS  $m/z$  324 (M)<sup>+</sup>.

Ejemplo 93

5 Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirazol-1-il-propiónico (249).



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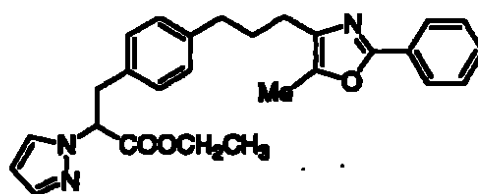
**249, PD 339165**

El compuesto del título se preparó a partir de 248 (0,735 g, 1,657 mmol) por el Procedimiento General 92, PD 0339165, obtenido en forma de un sólido amarillo (0,602 g, 15 87%): p.f. 75-77°C; <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,96 (m 2H), 7,61 (d,  $J = 2,0$  Hz, 1H), 7,40 (m, 3H), 7,09 (d,  $J = 2,0$  Hz, 1H), 7,02 (d,  $J = 8,0$  Hz, 2H), 6,80 (d,  $J = 8,0$  Hz, 2H), 6,19 (t,  $J = 2,2$  Hz, 1H), 5,02 (dd,  $J = 10,0$  y  $4,6$  Hz, 1H), 3,45-3,27 (m, 2H), 2,59 (t,  $J = 7,6$  Hz, 2H), 2,47 (t, 20  $J = 7,6$  Hz, 2H), 2,27 (s, 3H), 1,93 (m, 2H); CIMS  $m/z$  416 (M+1). Análisis Calculado para C<sub>25</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>·0,4 H<sub>2</sub>O: C, 71,04; H, 6,15; N, 9,94. Encontrado: C, 70,76; H, 6,08; N, 9,91.

El éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirazol-1-il-propiónico (248) 25 se preparó de la siguiente forma.

(a) Éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]fenil}-2-pirazol-1-il-propiónico (4c).

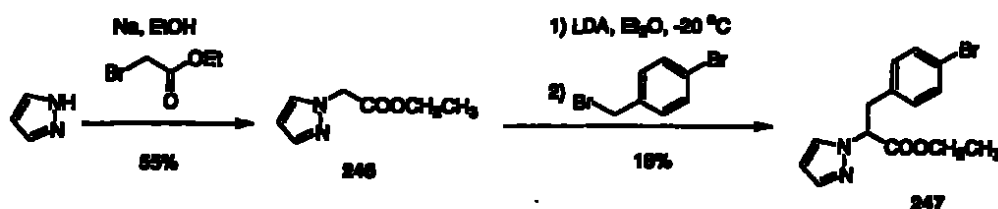
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Preparado a partir de bromuro 247 (0,760 g, 2,351 mmol) por el Procedimiento General 95. La purificación por 10 cromatografía en columna, produjo 248 (0,735 g, 70%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,96 (m, 2H), 7,52 (d,  $J = 1,5$  Hz, 1H), 7,44–7,38 (m, 4H), 7,05 (d,  $J = 8,0$  Hz, 2H), 6,94 (d,  $J = 8,0$  Hz, 2H), 6,22 (t,  $J = 2,1$  Hz, 1H), 5,11 (t,  $J = 7,7$  Hz, 1H), 4,16 (q,  $J = 7,1$  Hz, 2H), 2,60 (t,  $J = 7,6$  Hz, 2H), 15 2,47 (t,  $J = 7,3$  Hz, 2H), 2,26 (s, 3H), 1,95 (m, 2H), 1,18 (t,  $J = 7,1$  Hz, 3H); CIMS  $m/z$  444 ( $M+1$ ).

(b) Éster etílico del ácido pirazol-1-il acético (247).



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Se disolvió sodio (3,7 g, 161 mmol) en etanol (150 ml) con refrigeración con hielo. Se añadió pirazol (10 g, 146 mmol). Se añadió gota a gota bromoacetato de etilo (32 ml, 5 292 mmol). El baño de hielo se retiró después de terminar la adición y la mezcla se agitó a temperatura ambiente durante 5 días. El disolvente se retiró y el residuo se diluyó con HCl 6 N frío y se extrajo con Et<sub>2</sub>O (2 x 50 ml). La capa acuosa se neutralizó con carbonato sódico sólido y 10 después se extrajo con cloroformo. Los extractos orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato de magnesio y el disolvente se retiró. La purificación por destilación produjo 247 en forma de un aceite (12,495 g, 55%): p.e. 65-80°C a 2 mm de Hg; <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 15 7,55 (d, J = 1,7 Hz, 1H), 7,47 (d, J = 2,2 Hz, 1H), 6,32 (t, J = 2,0 Hz, 1H), 4,92 (s, 2H), 4,22 (q, J = 7,1 Hz, 2H), 1,27 (t, J = 7,1 Hz, 3H); CIMS m/z 155 (M+1).

**Bromuro 246.** El compuesto del título se preparó a partir del éster 246 (2,0 g, 12,97 mmol) por el Procedimiento 20 General 92-b. El bromuro 247 se obtuvo en forma de un aceite espeso. (0,768 g, 18%): <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,53 (d, J = 1,7 Hz, 1H), 7,36 (d, J = 2,0 Hz, 1H), 7,33 (d, J = 8,5 Hz, 2H), 6,88 (d, J = 8,3 Hz, 2H), 5,07-5,03 (m, 1H), 4,18 (q, J = 7,0 Hz, 2H), 3,49-3,39 (m, 2H), 1,20 25 (t, J = 7,1 Hz, 3H); CIMS m/z 323 (M)<sup>+</sup>.

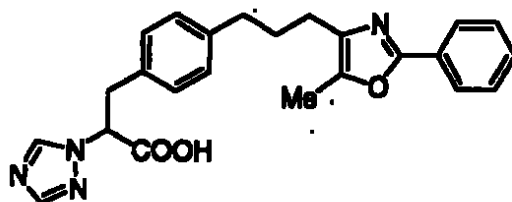


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Ejemplo 94

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-1,2,4-triazol-1-il-propiónico (253).

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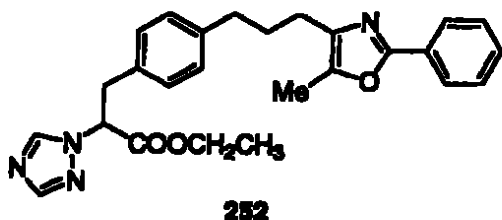


**253, PD 336683**

Preparado a partir del éster 252 (0,492 g, 1,106 mmol)  
10 por el Procedimiento General 92. El compuesto del título se  
obtuvo en forma de un sólido blanco (0,33 g, 72%): p.f.  
169-171°C; <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 8,16 (s, 1H), 8,00 (m,  
2H), 7,98 (s, 1H), 7,45-7,40 (m, 3H), 7,01 (d, J = 8,0 Hz,  
2H), 6,87 (d, J = 8,0 Hz, 2H), 5,24 (t, J = 7,1 Hz, 1H),  
15 3,42 (d, J = 7,1 Hz, 2H), 2,57 (t, J = 7,6 Hz, 2H), 2,52  
(t, J = 7,6 Hz, 2H), 2,28 (s, 3H), 1,93 (m, 2H); CIMS m/z  
417 (M+1).

El éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propil]-fenil}-2-1,2,4-triazol-1-il-propiónico  
20 (252) se preparó de la siguiente forma.

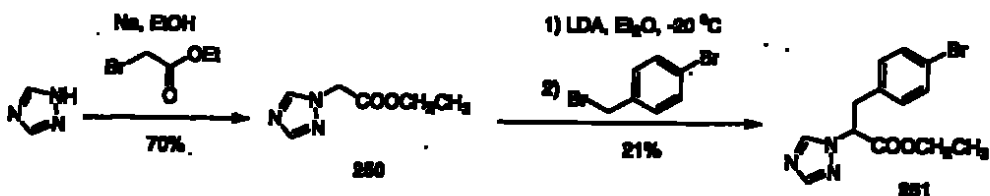
(a) Éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propil]-fenil}-2-1,2,4-triazol-1-il-propiónico  
(252).



5

Preparado a partir del bromuro 251 (0,440 g, 1,357 mmol) por el Procedimiento General 95-a. El compuesto del título se obtuvo en forma de un aceite espeso (0,492 g, 82%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8,08 (m, 2H), 8,00 (s, 1H), 7,94 (s, 1H), 7,48-7,41 (m, 3H), 7,06 (d,  $J = 8,0$  Hz, 2H), 6,88 (d,  $J = 8,0$  Hz, 2H), 5,17 (dd,  $J = 8,0$  y 6,6 Hz, 1H), 4,21 (q,  $J = 7,1$  Hz, 2H), 3,43 (d,  $J = 7,3$  Hz, 2H), 2,62 (t,  $J = 7,6$  Hz, 2H), 2,53 (d,  $J = 7,3$  Hz, 2H), 2,28 (s, 3H), 1,23 (t,  $J = 7,1$  Hz, 3H); CIMS  $m/z$  445 ( $M+1$ ).

15 (b) 2-1,2,4-Triazol-1-il acetato de etilo (250) y bromuro (251).



El éster 250 se preparó siguiendo el procedimiento descrito por Ainsworth y Jones (Ainsworth, C; Jones, R.G. *J. Am. Chem. Soc.* 1955, 77, 621-624).  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8,19 (s, 1H), 7,97 (s, 1H), 4,96 (s, 2H), 4,25 (q,  $J$

20

701 700

= 7,1 Hz, 2H), 1,28 (t,  $J$  = 7,1 Hz, 3H); CIMS  $m/z$  156 (M+1).

**Bromuro 251.** El título del compuesto se preparó a partir del éster 250 (1,0 g, 6,445 mmol) siguiendo el 5 Procedimiento General III. El bromuro 251 se obtuvo en forma de un aceite espeso (0,447 g, 21%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8,10 (s, 1H), 7,98 (s, 1H), 7,35 (d,  $J$  = 8,3 Hz, 2H), 6,86 (d,  $J$  = 8,5 Hz, 2H), 5,16 (dd,  $J$  = 8,1 y 6,7 Hz, 1H), 4,22 (q,  $J$  = 7,1 Hz, 2H), 3,46 (d,  $J$  7,6 Hz, 2H), 1,23 10 (t,  $J$  = 7,1 Hz, 3H); CIMS  $m/z$  324 (M)<sup>+</sup>.

#### Ejemplo 95

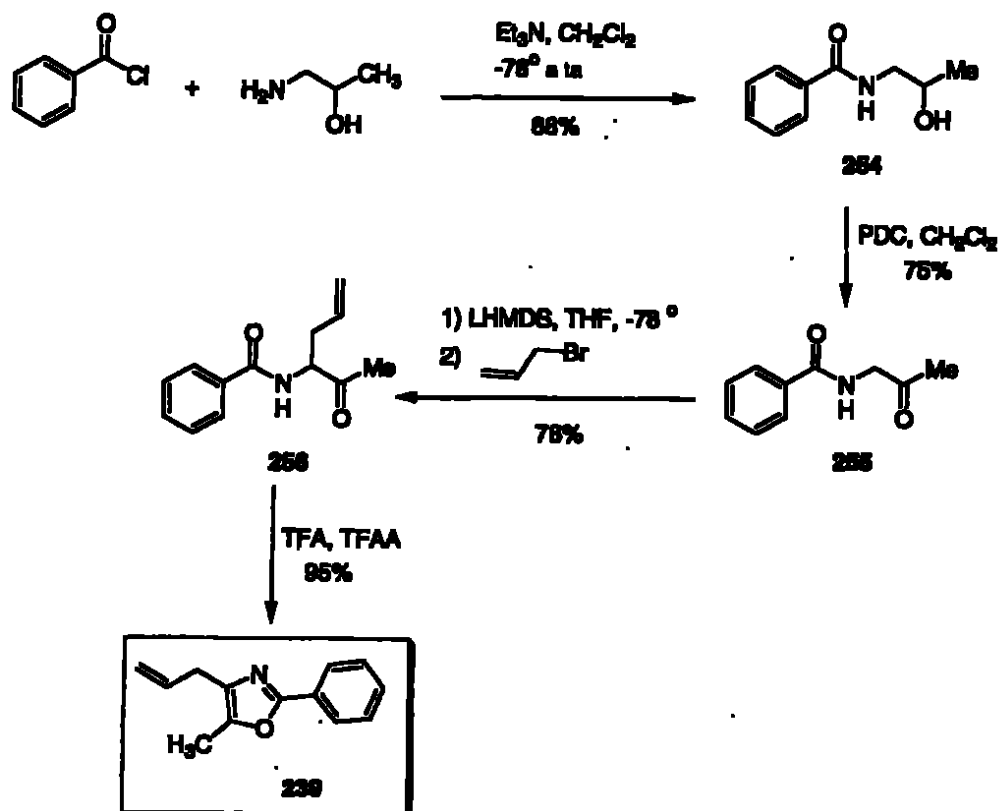
5-Metil-2-fenil-4-prop-2-eniloxazol (239).

Se disolvió la amida 256 (2,00 g, 9,205 mmol) en TFA (16 ml) y se añadió TFAA (8 ml). La mezcla se calentó a 35- 15 40°C durante 16 horas. La mezcla se dejó enfriar y los disolventes se retiraron a presión reducida. El residuo se diluyó con  $\text{NaHCO}_3$  saturado (50 ml) y se añadió  $\text{NaHCO}_3$  sólido para neutralizar la mezcla. Después se extrajo con acetato de etilo (3 x 60 ml). Los extractos orgánicos reunidos se 20 lavaron con salmuera, se secaron sobre  $\text{MgSO}_4$ , se filtraron y el disolvente se retiró. La purificación por cromatografía ultrarrápida sobre gel de sílice, eluyendo con hexanos:acetato de etilo (15:1), dio el oxazol 239 (1,75 g, 95%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,98 (d,  $J$  = 7,8 Hz, 2H), 25 7,43-7,35 (m, 3H), 6,03-5,93 (m, 1H), 5,13 (dq,  $J$  = 16,9 y

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1,7 Hz, 1H), 5,09 (dq,  $J = 10,0$  y  $1,5$  Hz, 1H), 3,29 (d,  $J = 6,3$  Hz, 2H), 2,32 (s, 3H); CIMS  $m/z$  200 ( $M+H$ )<sup>+</sup>; IR 3070, 2924, 1638, 1450  $\text{cm}^{-1}$ .



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La amida (256) se preparó de la siguiente forma.

(a) *N*-(1-acetilbut-3-enil)benzamida (256).

Se disolvió la amida 255 (2,098 g, 11,839 mmol) en THF 5 (120 ml) y se enfrió a -78°C en una atmósfera de nitrógeno. Se añadió una solución de LHMDs 1,0 M en THF (11,9 ml, 11,9 mmol) y la mezcla se agitó durante 40 minutos. Se añadió una solución de bromuro de alilo (1,33 ml, 15,39 mmol) en THF (10 ml). La mezcla se dejó calentar a temperatura 10 ambiente y se agitó durante una noche. La mezcla se diluyó con salmuera y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (3 x 50 ml) y los extractos orgánicos reunidos se secaron sobre MgSO<sub>4</sub>, se filtraron y el disolvente se retiró. La purificación por cromatografía 15 ultrarrápida sobre gel de sílice, eluyendo con hexanos:acetato de etilo (2:1 a 1:1), dio la amida 256 (2,02 g, 78%): <sup>1</sup>H RMN (CDCl<sub>3</sub>, 400 MHz) δ 7,79 (d, *J* = 7,1 Hz, 2H), 7,51-7,41 (m, 3H), 6,95 (bd, *J* = 5,4 Hz, 1H), 5,74-5,64 (m, 1H), 5,17-5,12 (m, 2H), 4,88 (dt, *J* = 6,8 y 20 5,4 Hz, 1H), 2,85-2,78 (m, 1H), 2,61-2,54 (m, 1H), 2,28 (s, 3H); CIMS *m/z* 218 (M+H)<sup>+</sup>; IR 3263, 3081, 1719, 1632, 1556 cm<sup>-1</sup>. Análisis Calculado para C<sub>13</sub>H<sub>15</sub>NO<sub>2</sub>: C, 71,87; H, 6,96; N, 6,45. Encontrado: C, 71,91; H, 7,03; N, 6,52.

(b) Amida (255).

25 De acuerdo con el procedimiento de Ellinger, L.P.;

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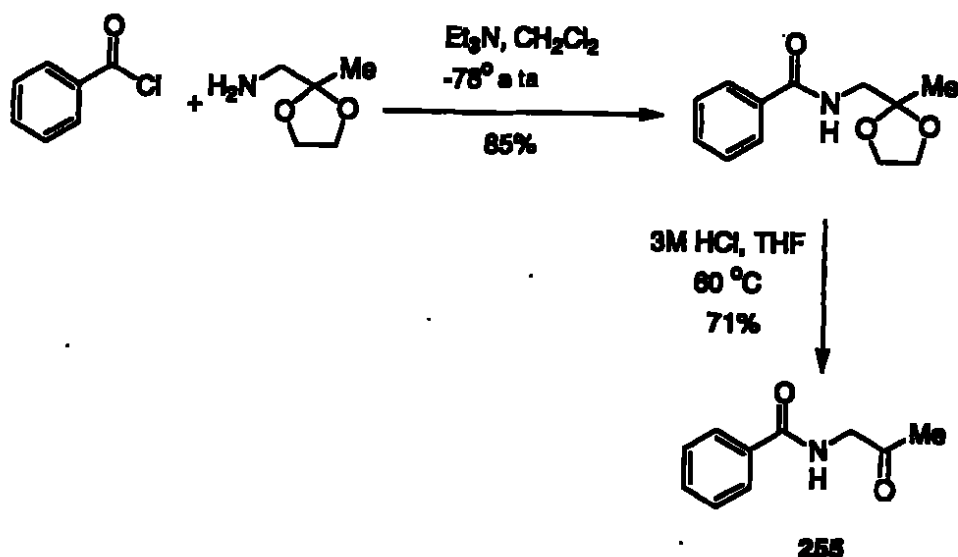
Goldberg, A.A. *J. Chem. Soc.* 1949, 263. Se disolvió el alcohol 254 (3,0 g, 16,7 mmol) en  $\text{CH}_2\text{Cl}_2$  (60 ml) y se añadió PDC (9,42 g, 25,0 mmol). La mezcla se agitó a temperatura ambiente durante 24 horas y se añadió más PDC (9,42 g, 25,0 5 mmol). Se continuó agitando durante 24 horas. La mezcla se diluyó con acetato de etilo y se filtró a través de una capa de celite. Después, el residuo se paso a través de una columna de gel de sílice a temperatura ambiente eluyendo con acetato de etilo. El disolvente se retiró y el residuo 10 se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con hexanos:acetato de etilo (1:1) que contenía MeOH (del 0 al 4%). Esta purificación produjo la amida 225 en forma de un sólido blanco (2,21 g, 75%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,76 (dd,  $J = 7,0$  y  $1,5$  Hz, 2H), 7,48-15 7,36 (m, 3H), 6,96 (s a, 1H), 4,30 (d,  $J = 4,6$  Hz, 2H), 2,21 (s, 3H): CIMS  $m/z$  178 ( $\text{M}+\text{H}$ ) $^+$ .

(b-1) A continuación se muestra una ruta alternativa para la benzamidoacetona 255.

Esta ruta elimina la oxidación de PDC que es un 20 tratamiento muy laborioso. Este procedimiento no requiere purificación cromatográfica y produce la amida 6 con un rendimiento del 63% para las dos etapas.

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(c) *N*-(2-hidroxil-propil)benzamida (254).

El compuesto del título se preparó de acuerdo con el procedimiento de Arai, K.; Tamura, S.; Masumizu, T.; Kawai, S K-I.; Nakajima, S.; Ueda, A. *Can. J. Chem.* 1990, 68:903-907. Se enfrió a  $-78^\circ\text{C}$  en nitrógeno una solución de DL-1-amino-2-propanol (3,4 ml, 43,2 mmol) y trietilamina (16,4 ml, 117,9 mmol) en  $\text{CH}_2\text{Cl}_2$  (60 ml). Se añadió gota a gota cloruro de benzoilo (4,6 ml, 39,3 mmol). La mezcla se dejó calentar lentamente y se agitó a temperatura ambiente durante una noche. Después se diluyó con  $\text{CH}_2\text{Cl}_2$  (100 ml) y se lavó con HCl al 5% frío y salmuera. Las fases se separaron y la fase acuosa se extrajo con  $\text{CH}_2\text{Cl}_2$  (2 x 50 ml). Los extractos orgánicos reunidos se secaron sobre 15  $\text{MgSO}_4$ , se filtraron y el disolvente se retiró. El residuo se

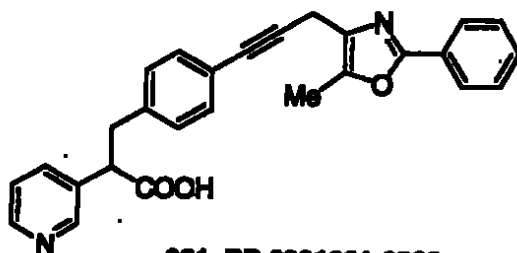
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secó al vacío, dando la amida 254 en forma de un sólido amarillo pálido (6,21 g, 88%):  $^1\text{H}$  RMN ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7,75 (d,  $J = 6,8$  Hz, 2H), 7,49-7,39 (m, 3H), 6,57 (s a, 1H), 4,00 (m, 1H), 3,67-3,61 (m, 1H), 3,31-3,24 (m, 1H), 1,22 (d,  $J = 6,3$  Hz, 3H).

Ejemplo 96

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-2-piridin-3-il-propiónico (261).

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261, PD 0331961-0000

15 Procedimiento General 96. Se disolvió éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-2-piridin-3-il-propiónico 4a (0,284 g, 0,630 mmol) en THF (15 ml) y se añadió agua (5 ml). Se incorporó hidróxido de litio monohidrato (0,040 g, 0,945 mmol) y la  
20 mezcla se agitó durante 1 hora. El disolvente orgánico se retiró por un evaporador rotatorio a temperatura ambiente. El residuo acuoso se diluyó con agua y se extrajo con  $\text{Et}_2\text{O}$  (2 x 45 ml). Después, la fase acuosa se acidificó con HCl al 10%. El producto se extrajo con  $\text{CH}_2\text{Cl}_2$ - $\text{CHCl}_3$ . Los  
25 extractos se secaron sobre sulfato de magnesio, se

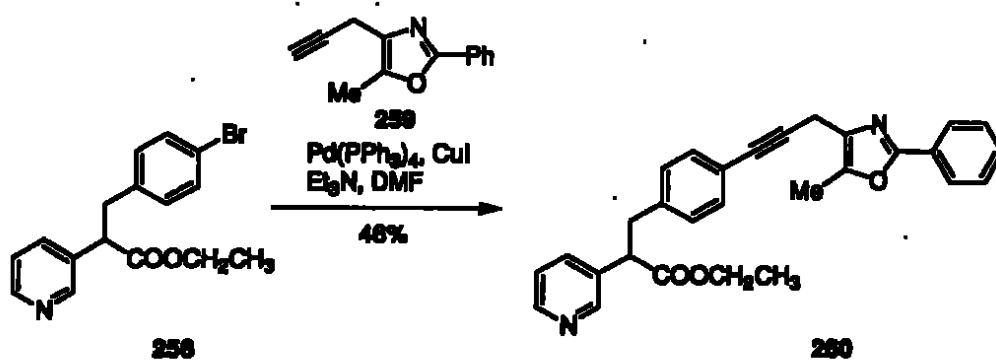


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filtraron y el disolvente se retiró. La purificación por cromatografía en columna sobre gel de sílice, eluyendo con metanol en cloroformo (del 0 al 10%) produjo el compuesto del título en forma de un sólido (0,100 g, 37%): p.f. 115-5 117°C; CIMS  $m/z$  423,1 ( $M+1$ ).

El éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-2-piridin-3-il-propiónico (260) se preparó de la siguiente forma.

(a) Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-2-piridin-3-il-propiónico (260).

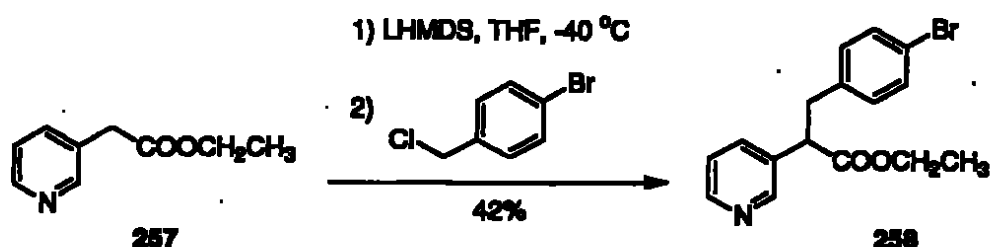


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Procedimiento General 96a. Se disolvieron el bromuro (258,354 g, 4,051 mmol) y el alquino (259,04 g, 5,266 mmol) en DMF seca (14 ml). Se añadió trietilamina (1,7 ml, 12,153 mmol) y se pasó nitrógeno a través de la mezcla de reacción durante 0,5 h. Se añadió  $\text{Pd(PPh}_3)_4$  (0,328 g, 0,284 mmol) seguido de  $\text{CuI}$  (0,154 g, 0,810 mmol). La mezcla se calentó a 80°C durante 24 h en una atmósfera de nitrógeno. La mezcla se dejó enfriar y se diluyó con agua (100 ml) y  $\text{Et}_2\text{O}$  10 (70 ml). Las fases se separaron y la fase acuosa se extrajo con  $\text{Et}_2\text{O}$  (4 x 60 ml). Los extractos orgánicos reunidos se lavaron con agua y salmuera. Se añadió carbono activado y la mezcla se hirvió durante 15-20 minutos. Después de enfriar a temperatura ambiente, la mezcla se secó sobre 15  $\text{MgSO}_4$ , se filtró y el disolvente se retiró. La purificación por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo en hexanos (del 0 al 30%) dio 260 puro en forma de un aceite espeso (0,838 g, 46%); CIMS  $m/z$  451 ( $\text{M}+\text{H}$ )<sup>+</sup>.

20 (b) éster etílico del ácido 3-(4-bromo-fenil)-2-piridin-3-il-propiónico (258).

709 208



Procedimiento General 96-b. Se disolvió el éster 257 (63 g, 9,861 mmol) en THF seco (20 ml) y se enfrió a -78°C 5 en una atmósfera de nitrógeno. Se añadió una solución 1,0 M de LHMDS en THF (10,8 ml, 10,8 mmol). La mezcla se agitó de -78°C a -40°C durante 1,25 h. Se añadió una solución de bromuro de 4-clorobencilo (2,43 g, 11,833 mmol) en THF (5 ml). Se dejó que la reacción alcanzará la temperatura 10 ambiente durante una noche. La mezcla se inactivó con agua (40 ml) y se diluyó con EtOAc (30 ml). Las fases se separaron y la capa acuosa se extrajo con EtOAc (30 ml x 3). Los extractos orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato de magnesio y el 15 disolvente se retiró. La purificación por cromatografía sobre gel de sílice eluyendo con EtOAc en hexanos (0 a 45%) produjo el bromuro 258 en forma de aceite (1,37 g, 42%): CIMS  $m/z$  334,0 (M)<sup>+</sup>.

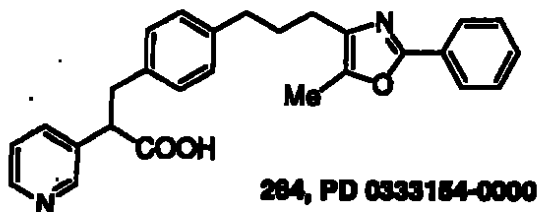
#### Ejemplo 97

20 Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)propil]fenil}-2-

710 208

piridin-3-il-propiónico (264)

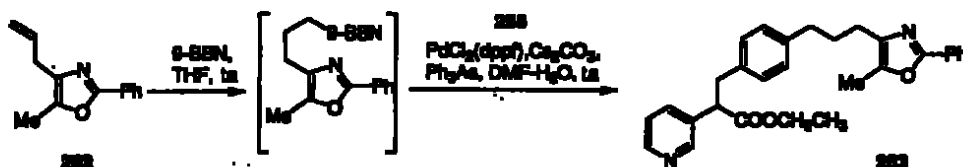
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Este compuesto se preparó a partir del éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-piridin-3-il-propiónico 263 siguiendo el Procedimiento General 100. Se obtuvo el compuesto del título en forma de un sólido con un rendimiento del 58%: p.f. 138-141°C: CIMS  $m/z$  427,2 (M+1). Análisis Calculado para  $C_{27}H_{26}N_2O_3 \cdot 1,0H_2O$ : C, 72,95; H, 6,35; N, 6,30. Encontrado: 15 C, 72,64; H, 6,32; N, 5,97.

El éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-piridin-3-il-propiónico (263) se preparó de la siguiente forma.

(a) Éster etílico del ácido 2-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-piridin-3-il-propiónico (263).



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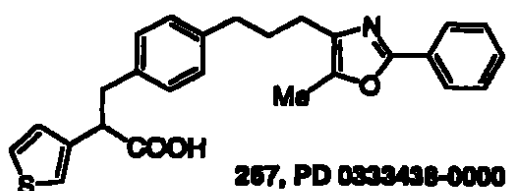
Procedimiento General 97-a. Se añadió una solución del 5 5-metil-2-fenil-4-prop-2-eniloxazol (262) (0,20 g, 1,003 mmol) en THF seco (5 ml) a una solución de 9-BBN 0,5 M en THF (4 ml, 2,0 mmol) a 0°C en una atmósfera de nitrógeno. El baño de hielo se retiró y la mezcla se agitó a temperatura ambiente durante una noche. Después, se añadió 10 el aducto de 9-BBN a un matraz que contenía el bromuro 258 (0,351 g, 1,053 mmol), PdCl<sub>2</sub> (dppf) (0,073 g, 0,1 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0,588 g, 1,805 mmol), Ph<sub>3</sub>As (0,030 g, 0,1 mmol), agua (0,22 ml, 12 mmol) y DMF (5 ml). La mezcla de reacción se agitó a temperatura ambiente en una atmósfera de 15 nitrógeno durante una noche. Al final de este tiempo, la mezcla se enfrió en una baño de hielo y se le añadió NaOAc 3 M (6 ml) seguido de H<sub>2</sub>O<sub>2</sub> al 30% (3 ml). Se continuó agitando durante 2 horas, dejando calentar lentamente la reacción a temperatura ambiente. Se añadió agua (50 ml) 20 seguido de Et<sub>2</sub>O y EtOAc. Las fases se separaron y la fase acuosa se extrajo con Et<sub>2</sub>O-EtOAc (30:5 ml x 4). Los extractos reunidos se lavaron con salmuera, se secaron sobre sulfato de magnesio y el disolvente se retiró. La purificación por cromatografía en columna sobre gel de 25 sílice, eluyendo con EtOAc en hexanos (0 a 25%) produjo el

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éster 263 en forma de un aceite espeso (0,272 g, 60%): CIMS  $m/z$  455,2 (M+1).

Ejemplo 98

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-5 fenil}-2-piridin-3-il-propiónico (267).



10 Este compuesto se preparó a partir del éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-tiofen-3-il-propiónico (266). La purificación se realizó por cromatografía sobre gel de sílice, eluyendo con acetato de 15 etilo en hexanos (0 a 45%). El compuesto del título se obtuvo en forma de un sólido con un rendimiento del 58%: p.f. 112-114°C; CIMS  $m/z$  432,1 (M+1). Análisis Calculado para  $C_{26}H_{25}NO_3S$ : C, 72,36; H, 5,84; N, 3,25. Encontrado: C, 72,18; H, 5,97; N, 3,04.

20 El éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-tiofen-3-il-propiónico (266) se preparó de la siguiente forma.

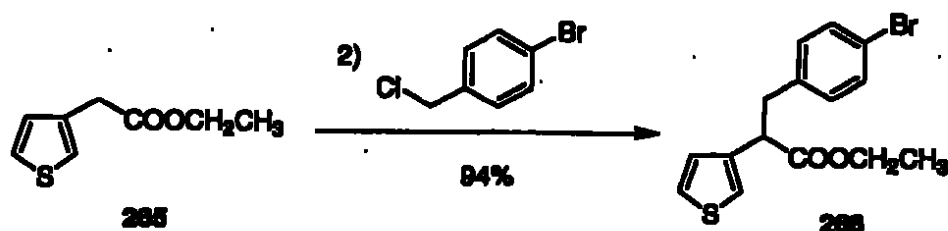
(a) Éster etílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-tiofen-3-il-propiónico (267).

25 Este compuesto se preparó siguiendo el Procedimiento

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General 98-a usando el bromuro 266 para el acoplamiento de Suzuki. Se obtuvo el éster 267 en forma de un aceite espeso con un rendimiento del 78%: CIMS  $m/z$  460,2 (M+1).

(b) éster etílico del ácido 3-(4-bromo-fenil)-2-5 tiofen-3-il-propiónico (266).

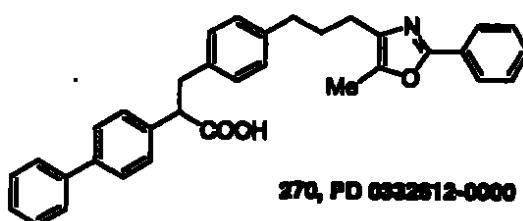


Este compuesto 266 se preparó a partir del éster 265 siguiendo el Procedimiento General 98-b y se obtuvo en forma de un aceite espeso con un rendimiento del 94%: CIMS  $m/z$  339,0 (M)<sup>+</sup>.

#### Ejemplo 99

Ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (270).

15



270, PD 0332812-0000

20 Este compuesto se preparó a partir del éster etílico

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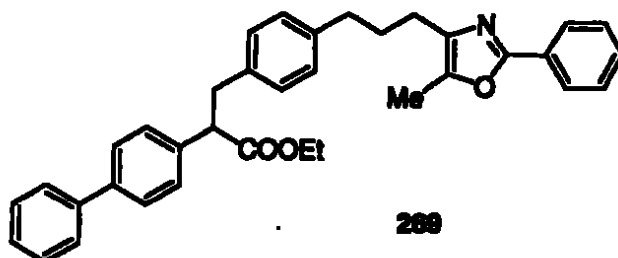
del ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (269) por hidrólisis. La purificación se realizó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo en hexanos (0 a 30%).

5 El compuesto del título se obtuvo en forma de un sólido con un rendimiento del 96%: p.f. 158-160°C; CIMS  $m/z$  502,3 (M+1). Análisis Calculado para  $C_{34}H_{31}NO_3$ : C, 81,41; H, 6,23; N, 2,79. Encontrado: C, 81,05; H, 6,42; N, 2,63.

El éster etílico del ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (269) se preparó de la siguiente forma.

(a) Éster etílico del ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (269).

15



20 Se disolvió éster etílico del ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-propiónico (268, Véase el Ejemplo 104) (0,325 g, 0,618 mmol) en THF (50 ml) y se hidrogenó sobre níquel Raney (1,0 g) durante una noche. La mezcla se retiró por filtración y

25 el disolvente se retiró. La purificación por cromatografía



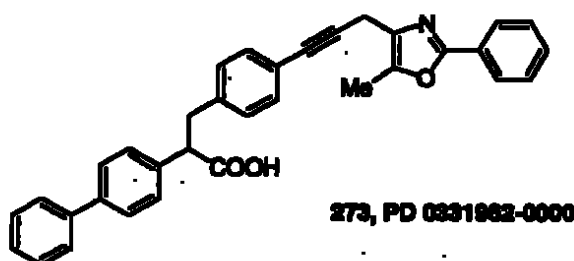
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sobre gel de sílice, eluyendo con acetato de etilo en hexanos, dio **6c** en forma de un aceite transparente (0,254 g, 77%): CIMS  $m/z$  530,2 (M+1).

Ejemplo 100

5        Ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-propiónico (273).

10



15        Este compuesto se preparó a partir del éster 272. La mezcla de reacción se calentó a 80°C durante 7 horas. La purificación se realizó por cromatografía sobre gel de sílice, eluyendo con metanol en cloroformo (del 0 a 6%). El compuesto del título se obtuvo en forma de un sólido  
20 naranja con un rendimiento del 54%: p.f. 163-165°C; CIMS  $m/z$  498,2 (M+1).

El éster etílico del ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-propiónico (268) se preparó de la siguiente forma.

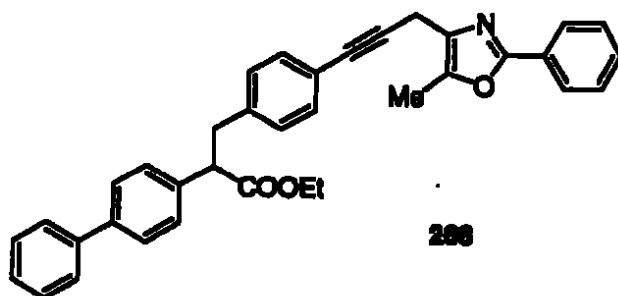
25        (a) Éster etílico del ácido 2-bifenil-4-il-3-{4-[3-(5-

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7/6

372

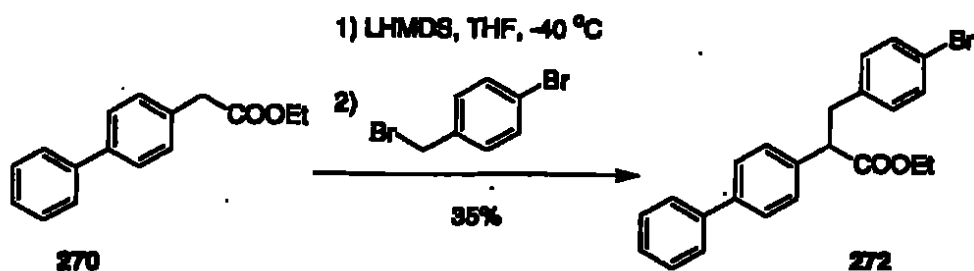
metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-propiónico  
(268).

5



Este compuesto se obtuvo a partir del bromuro 271  
10 siguiendo el Procedimiento General II. Se obtuvo el éster  
268 en forma de un aceite naranja espeso con un rendimiento  
del 37%: CIMS  $m/z$  526 ( $M+1$ ).

(b) Éster etílico del ácido 2-bifenil-3-(4-bromo-  
fenil)-propiónico (271).



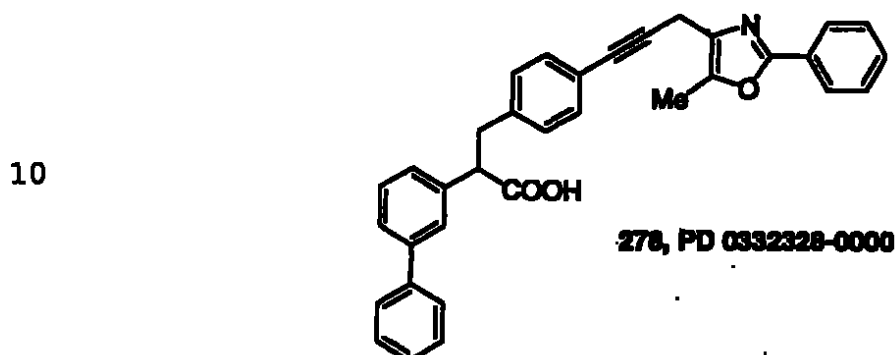
15

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Este compuesto se preparó a partir del 27. Se obtuvo en forma de un sólido blanco con un rendimiento 35%: CIMS  $m/z$  409,0 (M)<sup>+</sup>.

#### 5 Ejemplo 101

Ácido 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-propiónico (278).



15 Este compuesto se preparó a partir del éster 277. La purificación se realizó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo en hexanos (0 a 45%). El compuesto del título se obtuvo en forma de un sólido con un rendimiento del 96%: p.f. 105-107°C; CIMS  $m/z$  498,2  
20 (M+1). Análisis calculado para  $C_{34}H_{27}NO_3 \cdot 1,3H_2O$ : C, 78,38; H, 5,73; N, 2,69. Encontrado: C, 78,22; H, 5,57; M, 2,59.

El éster metílico del ácido 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-propiónico (277) se preparó de la siguiente forma.

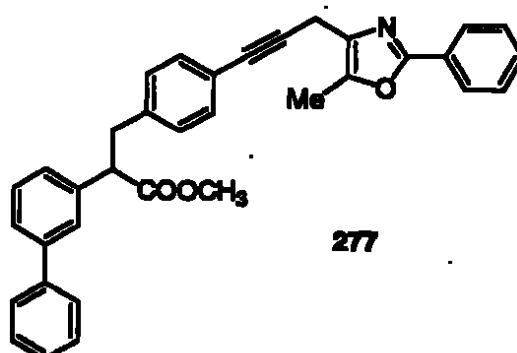
25 (a) Éster metílico del ácido 2-bifenil-3-il-3-{4-[3-

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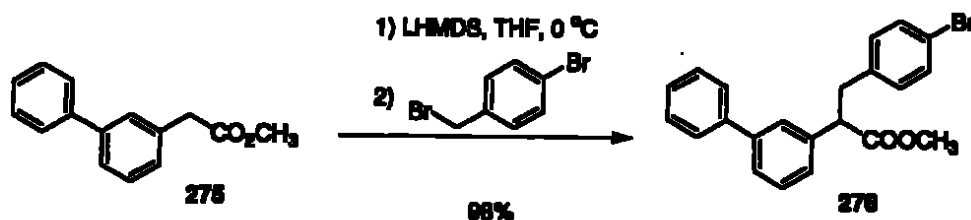
(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-  
propiónico (277).

5



10 Este compuesto se obtuvo a partir del bromuro 276 siguiendo el procedimiento General 100-a. Se obtuvo el éster 277 en forma de un aceite naranja espeso con un rendimiento del 12%: CIMS  $m/z$  512,2 ( $M+1$ ).

(b) Éster metílico del ácido 2-bifenil-3-il-3-(4-15 bromo-fenil)-propiónico (276).

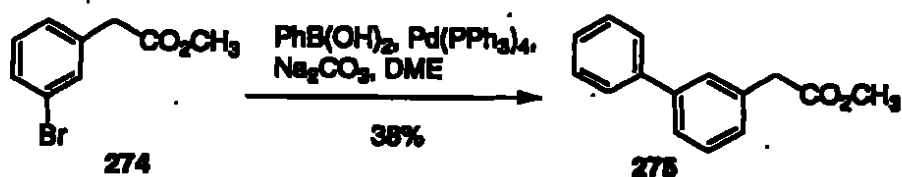


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Este compuesto se preparó a partir del éster 275. Se obtuvo como un aceite incoloro espeso con un rendimiento del 98%: CIMS  $m/z$  395,1 (M)<sup>+</sup>.

(c) Éster metílico del ácido 2-bifenil-3il-acético 5 (275).

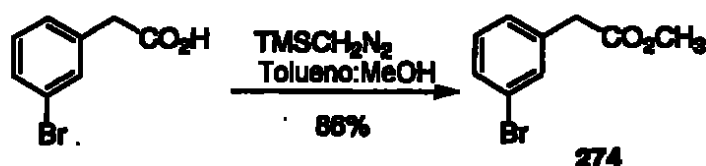


10 Se disolvieron el bromuro 274 (1,872 g, 8,172 mmol) y ácido fenilborónico (1,49 g, 12,258 mmol) en DME. Se añadió carbonato sódico (1,73 g, 16,344 mmol). Se burbujeó nitrógeno en la mezcla de reacción durante 25 min. Se añadió  $\text{Pd(PPh}_3)_4$  (0,471 g, 0,408 mmol) y la mezcla de  
15 reacción se calentó a 90°C durante 40 horas. La mezcla se enfrió a ta, se diluyó con acetato de etilo (30 ml) y se le añadió agua (30 ml). Las fases se separaron. La fase acuosa se extrajo con acetato de etilo (3 x 35 ml). Los extractos reunidos se secaron sobre sulfato de magnesio, se filtraron  
20 y el disolvente se retiró. El residuo se purificó por cromatografía en columna sobre gel de sílice, eluyendo con

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acetato de etilo en hexanos (0 a 5%). Se obtuvo el éster 275 en forma de un aceite espeso (0,706 g, 38%): CIMS  $m/z$  227,0 ( $M+1$ ).

(d) Éster etílico del ácido 2-(3-bromo-fenil)-acético 5 (274).



10 Se disolvió ácido 2-(3-bromo-fenil)-acético (5,00 g, 23,25 mmol) en tolueno/MeOH (10:5 ml). La solución se enfrió en un baño de hielo y se añadió gota a gota una solución de trimetilsilildiazometano 2,0 M en hexanos (14 ml, 28 mmol). La mezcla se agitó a temperatura ambiente  
15 durante una noche. La mezcla se inactivó con ácido acético y se agitó durante 0,5 horas. Los disolventes se retiraron y el residuo se purificó por cromatografía en columna sobre gel de sílice, eluyendo con acetato de etilo en hexanos (0 a 5%). Se obtuvo el éster 274 en forma de un aceite  
20 transparente (4,59 g, 86%): CIMS  $m/z$  228,9 ( $M$ )<sup>+</sup>.

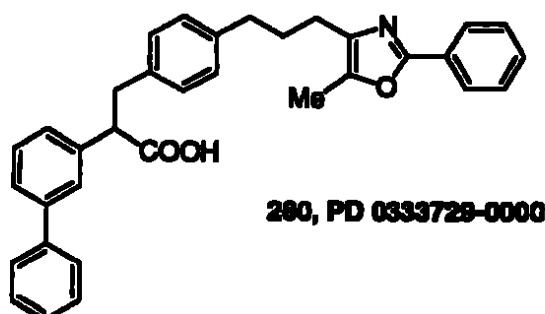
Ejemplo 102

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Ácido 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (280).

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Este compuesto se preparó a partir del éster 279 siguiendo el Procedimiento General 100. La purificación se realizó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo en hexanos (0 a 30%). El compuesto del  
15 título se obtuvo en forma de un sólido con un rendimiento del 69%; p.f. 75-80°C; CIMS  $m/z$  502,3 (M+1). Análisis Calculado para  $C_{34}H_{31}NO_3 \cdot 0,1H_2O$ : C, 81,12; H, 6,25; N, 2,78. Encontrado: C, 80,80; H, 6,33; N, 2,69.

El éster metílico del 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (279) se preparó de la siguiente forma.

(a) Éster metílico del ácido 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (279).

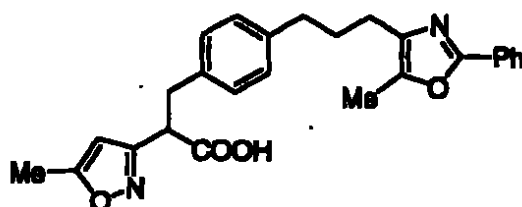
25 Este compuesto se preparó siguiendo el Ejemplo 104

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usando el bromuro 272 para el acoplamiento de Suzuki. Se obtuvo el éster 279 en forma de un aceite espeso con un rendimiento del 37%: CIMS  $m/z$  516,3 (M+1).

Ejemplo 103

5        Ácido        2-(5-metil-isoxazol-3-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (284).



284, PD 0338453-0000

10

Este compuesto se preparó a partir del éster etílico del ácido 3-(4-bromo-fenil)-2-(5-metil-isoxazol-3-il)-propiónico (283) por hidrólisis mediada por LiOH. La purificación se realizó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo en hexanos (0 a 30%). El compuesto del título se obtuvo en forma de un sólido con un rendimiento del 69%: p.f. 75-80°C; CIMS  $m/z$  502,3 (M+1). Análisis Calculado para  $C_{34}H_{31}NO_3 \cdot 0,1 H_2O$ : C, 81,12; H, 6,25; N, 2,78. Encontrado: C, 80,80; H, 6,33; N, 2,69.

El éster etílico del ácido 2-(5-metil-isoxazol-3-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (283) (PD 0335776-0000) se preparó de la siguiente forma.

25        (a) Éster etílico del ácido 2-(5-metil-isoxazol-3-il)-

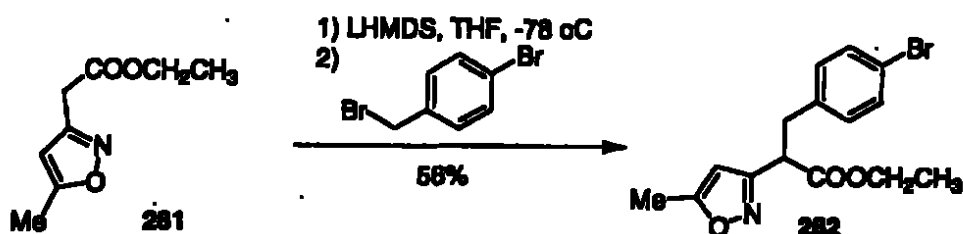


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3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-  
propiónico (283).

Este compuesto se preparó siguiendo el Procedimiento General 100-a usando el bromuro 282 para el acoplamiento de Suzuki. Se obtuvo el éster 283 en forma de un aceite espeso con un rendimiento del 84%: CIMS m/z 459,3 (M+1).

(b) Éster etílico del ácido 3-(4-bromo-fenil)-2-(5-metil-isoxazol-3-il)-propiónico (282).



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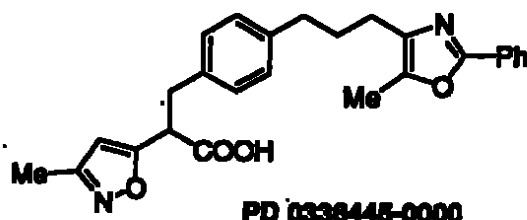
Este compuesto se preparó a partir del éster 281  
siguiendo el Procedimiento General 97-b y se obtuvo en  
forma de un aceite espeso con un rendimiento del 56%: CIMS  
m/z 338,0 (M)<sup>+</sup>.

#### Ejemplo 104

Ácido 2-(3-metil-isoxazol-5-il)-3-{4-[3-(5-metil-2-  
fenil-oxazol-4-il)-propil]-fenil}-propiónico (288).

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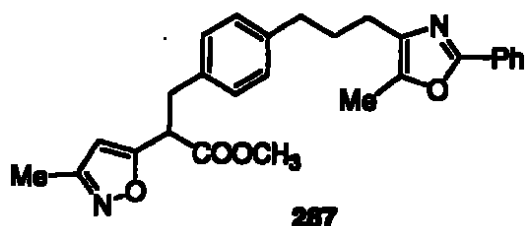


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Este compuesto se preparó a partir del éster metílico del ácido 2-(3-metil-isoxazol-5-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (287) siguiendo el Procedimiento General 96. La purificación se  
10 realizó por cromatografía sobre gel de sílice, eluyendo con metanol en cloroformo (del 0 a 5%). El compuesto del título se obtuvo en forma de un sólido blanco con un rendimiento del 85%: p.f. 133-135°C; CIMS m/z 431,2 (M+1). Análisis Calculado para  $C_{26}H_{26}N_2O_4$ : C, 72,54; H, 6,09; N, 6,51.  
15 Encontrado: C, 72,32; H, 6,28; N, 6,41.

El éster metílico del ácido 2-(3-metil-isoxazol-5-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}propiónico (287) se preparó de la siguiente forma.

(a) Éster metílico del ácido 2-(3-metil-isoxazol-5-il)-  
20 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (287).



25

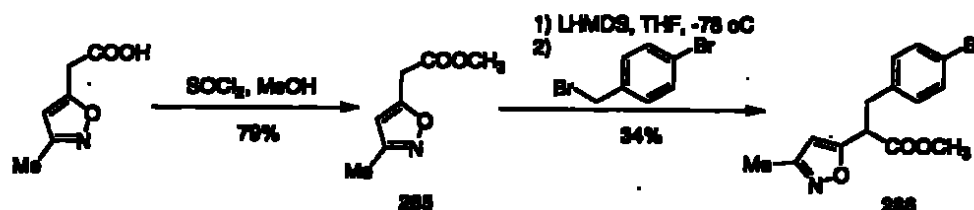
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Este compuesto se preparó siguiendo el Procedimiento General 96-a usando el bromuro 286 para el acoplamiento de Suzuki. Se obtuvo el éster metílico del ácido 2-(3-metil-5 isoxazol-5-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico (287) en forma de un aceite espeso con un rendimiento del 60%: CIMS  $m/z$  459,3 (M+1).

(b) Éster etílico del ácido 3-(4-bromo-fenil)-2-(3-metil-isoxazol-5-il)-propiónico (286).

10



15

Este compuesto se preparó a partir del éster 285 siguiendo el Procedimiento 96-b y se obtuvo en forma de un 20 aceite espeso con un rendimiento del 34%: CIMS  $m/z$  324,0

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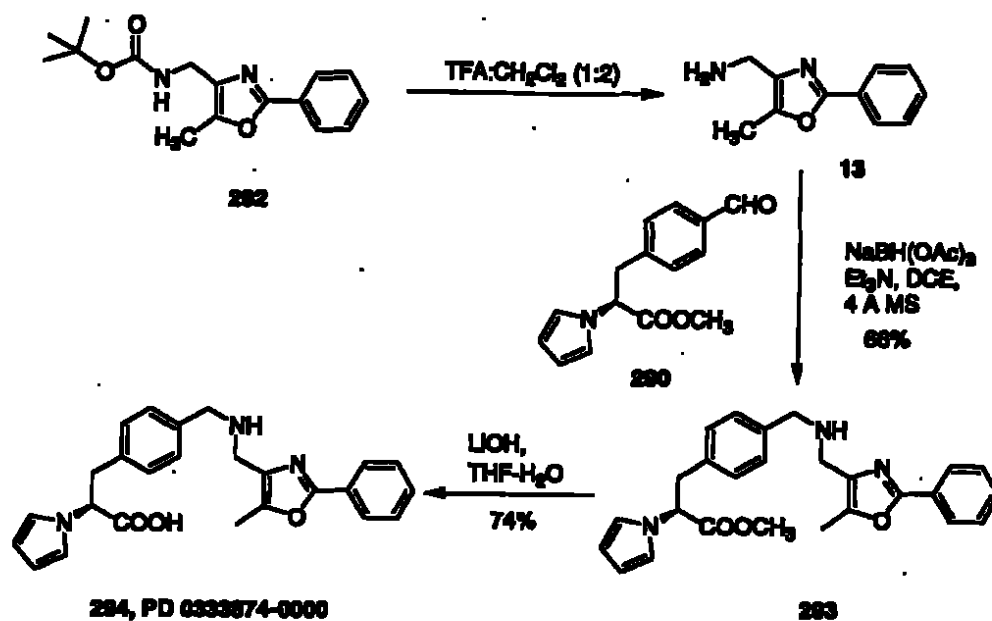
(M)<sup>+</sup>.

(c) Éster metílico del ácido 3-metil-isoxazol-5-il-acético (285).

Se disolvió ácido 3-metil-isoxazol-5-il-acético (3,05 g, 21,257 mmol) en MeOH (50 ml) y se enfrió en un baño de hielo. Se añadió cloruro de tionilo (2,3 ml, 31,9 mmol) y el baño de hielo se retiró. La mezcla se calentó a 40°C durante 24 horas. El disolvente se retiró y el residuo se purificó por destilación. El compuesto del título se obtuvo 10 en forma de un aceite transparente (2,62 g, 79%): p.e. 81-82°C (a 0,7 mm Hg); CIMS *m/z* 154,1 (M+1).

#### Ejemplo 105

Ácido (S)-3-(4-[[[(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil]-fenil)-2-pirrol-1-il-propiónico (294).



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Este compuesto se preparó a partir del éster 293 siguiendo el Procedimiento General 100. La purificación se realizó por cromatografía sobre gel de sílice, eluyendo con metanol en cloroformo (0 a 5%). El compuesto del título se 5 obtuvo en forma de un sólido blanco con un rendimiento del 74%: p.f. 163-165°C. C; CIMS m/z 416,2 (M+1). Análisis Calculado para  $C_{25}H_{25}N_3O_3 \cdot 0,42 CHCl_3$ : C, 65,57; H, 5,50; N, 9,02. Encontrado: C, 65,26; H, 5,81; N, 8,86.

El éster metílico del ácido (S)-3-(4-([(5-metil-2- 10 fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico (293) se preparó de la siguiente forma.

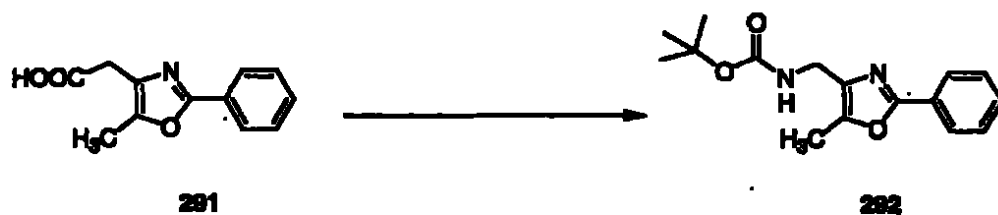
(a) Éster metílico del ácido (S)-3-(4-([(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico (293).

15 Se disolvió el carbamato 292 (0,326 g, 1,130 mmol) en diclorometano (6 ml) y se enfrió en un baño de hielo. Se añadió TFA (3 ml), la mezcla se agitó durante 10 minutos y el baño de hielo se retiró. La mezcla de reacción se agitó a temperatura ambiente durante 3 horas. Los disolventes se 20 retiraron y el residuo se secó a alto vacío. Después, el residuo se disolvió en 1,2-dicloroetano (15 ml) y se añadió  $Et_3N$  (0,39 ml, 2,825 mmol). Después de 5 minutos se añadió el aldehído 290 (0,215 g, 0,837 mmol), seguido de  $NaBH(OAc)_3$  (0,283 g, 1,339 mmol) después de 10 minutos. La mezcla se 25 agitó a temperatura ambiente durante 18 horas. Se añadió

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más  $\text{NaBH}(\text{OAc})_3$  (0,300 g) y se continuó agitando durante 5 horas. La mezcla se diluyó con diclorometano y se filtró a través de una capa de celite. Se añadió  $\text{NaHCO}_3$  saturado y las fases se separaron. La fase acuosa se extrajo con 5 diclorometano (3 x 25 ml). Los extractos reunidos se secaron sobre sulfato de magnesio, se filtraron y el disolvente se retiró. Los disolventes se retiraron y el residuo se purificó por cromatografía en columna de gel de sílice, eluyendo con metanol en cloroformo (0 a 5%). Se  
10 obtuvo el éster 293 en forma de un aceite espeso (0,236 g, 66%): CIMS  $m/z$  430,2 (M+1).

(b) Preparación del éster terc-butílico del ácido (5-metil-2-fenil-oxazol-4-ilmetil)-carbámico.



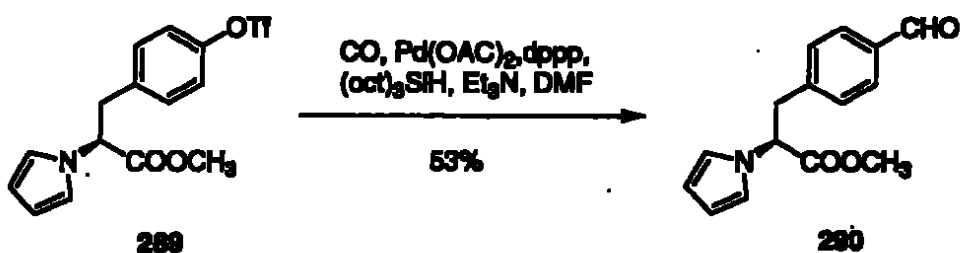
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Se disolvió el ácido 291 (3,0 g, 13,8 mmol) en diclorometano (70 ml) en una atmósfera de nitrógeno. La mezcla se enfrió en un baño de hielo y después se añadió cloruro de oxalilo (1,7 ml, 19,32 mmol), seguido de DMF  
20 (0,053 ml, 0,69 mmol). El baño de hielo se retiró después

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de 20 minutos y la mezcla de reacción se agitó a temperatura ambiente durante 5 h. El disolvente se retiró. El residuo se disolvió en acetona y se enfrió a 0°C. Se añadió una solución de azida sódica (1,19 g, 18,354 mmol) en agua (4,2 ml). La mezcla se agitó a 0°C durante 1 hora, después se diluyó con agua y se extrajo con tolueno (4 x 35 ml). Los extractos reunidos se secaron sobre sulfato de magnesio, se filtraron y el disolvente se retiró. El residuo se disolvió en tolueno (80 ml) y se añadió terc-  
10 BuOH (2,64 ml, 27,6 mmol). La solución se calentó a reflujo durante 18 horas. Los disolventes se retiraron y el residuo se purificó por cromatografía en columna sobre gel de sílice, eluyendo con acetato de etilo en hexanos (0 a 25%). Se obtuvo el carbamato 292 en forma de un sólido (2,33 g, 15 58%): CIMS  $m/z$  289,1 (M+1).

(c) Éster metílico del ácido (S)-2-pirrol-1-il-3-(4-formil-fenil)-propiónico (290).



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Una mezcla del triflato 289 (3,0 g, 7,950 mmol), Pd(OAc)<sub>2</sub> (0,065 g, 0,289 mmol), dppp (0,122 g, 0,295 mmol), 5 Et<sub>3</sub>N (0,92 ml, 6,60 mmol) y (octil)<sub>3</sub>SiH (2,38 ml, 5,298 mmol) en DMF (45 ml) se agitó y se calentó a 70°C en 3447,37 kPa de CO durante 14 horas. El disolvente se retiró y el residuo se diluyó con Et<sub>2</sub>O (50 ml) y se lavó con agua (70 ml). La fase acuosa se extrajo con Et<sub>2</sub>O (4 x 50 ml). Los 10 extractos reunidos se secaron sobre sulfato de magnesio, se filtraron y el disolvente se retiró. El residuo se purificó por cromatografía en columna sobre gel de sílice, eluyendo con acetato de etilo en hexanos (0 a 25%). El compuesto del título se obtuvo en forma de un sólido naranja (1,11 g, 15 54%): CIMS m/z 258,1 (M+1).

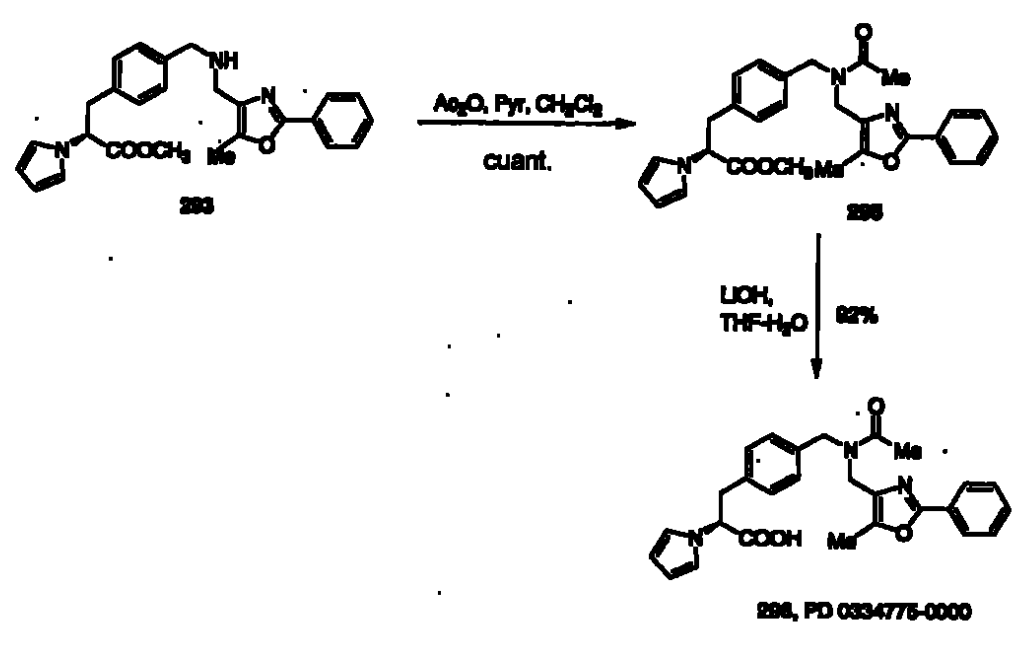
#### Ejemplo 106

Ácido (S)-3-(4-([acetil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico (296).



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Se disolvió el éster 295 (0,268 g, 0,570 mmol) en THF (15 ml) y se añadió agua (5 ml). Se incorporó hidróxido de litio monohidrato (0,036 g, 0,885 mmol) y la mezcla se agitó a temperatura ambiente durante 2,5 horas. El disolvente orgánico se retiró por evaporación rotatoria a temperatura ambiente. El residuo acuoso se diluyó con agua y se enfrió en un baño de hielo. Después, se acidificó con HCl al 10%. El sólido obtenido se separó por filtración, se lavó con agua y se secó a alto vacío a 50°C durante 12 horas, dando el compuesto del título en forma de un sólido amarillo- pálido-pardo (0,241 g, 92%): p.f. 97-100°C: CIMS m/z 458,2 (M+1). Análisis Calculado para  $C_{27}H_{27}N_3O_4 \cdot 0,5H_2O$ : C, 69,51; H, 6,05; N, 9,01. Encontrado: C, 69,32; H, 6,02; N, 8,73.

15 La preparación del éster metílico del ácido (S)-3-(4-([acetil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico (295) se realizó de la siguiente forma.

(a) Éster metílico del ácido (S)-3-(4-([acetil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico (15).

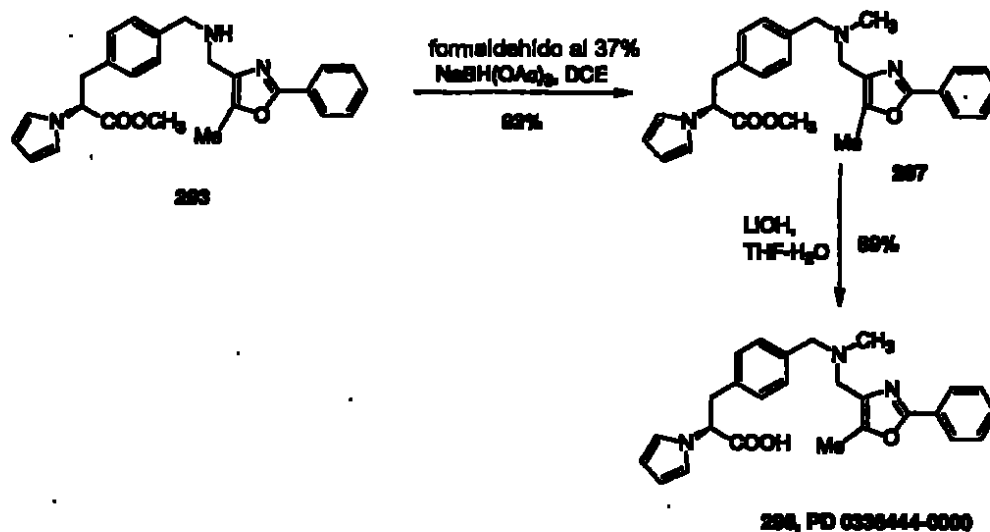
Se disolvió éster metílico del ácido (S)-3-(4-([(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico (293) (0,245 g, 0,570 mmol) en 25 diclorometano (10 ml) y se enfrió en un baño de hielo. Se

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añadió piridina (0,115 ml, 1,425 mol) seguido de Ac<sub>2</sub>O (0,107 ml, 1,14 mmol). El baño de hielo se retiró después de 30 minutos y la mezcla se agitó a temperatura ambiente durante 20 horas, se añadió diclorometano (50 ml) y la solución se lavó con HCl al 10%, NaHCO<sub>3</sub> saturado y NaCl saturado. La fase orgánica se secó sobre sulfato de magnesio, se filtró y el disolvente se retiró. Los disolventes se retiraron y el residuo se secó a alto vacío durante una noche, dando un aceite amarillo pálido (0,295 g): CIMS *m/z* 472 (M+1).

10 Ejemplo 107

Ácido (S)-3-(4-([metil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico (298).



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Este compuesto se preparó a partir del éster metílico del ácido (S)-3-(4-([metil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico

- 5 (297) siguiendo el Procedimiento General 96. La purificación se realizó por cromatografía sobre gel de sílice, eluyendo con metanol en cloroformo (0 a 10%). El compuesto del título se obtuvo en forma de un sólido con un rendimiento del 89%: p.f. 133-135°C; CIMS  $m/z$  430,3 (M+1).
- 10 Análisis Calculado para  $C_{26}H_{27}N_3O_3 \cdot 1,71 H_2O$ : C, 67,84; H, 6,66; N, 9,13. Encontrado: C, 67,85; H, 6,39; N, 8,73.

El éster metílico del ácido (S)-3-(4-([metil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico (297) se preparó de la siguiente forma.

- 15 (a) Éster metílico del ácido (S)-3-(4-([metil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico (16).

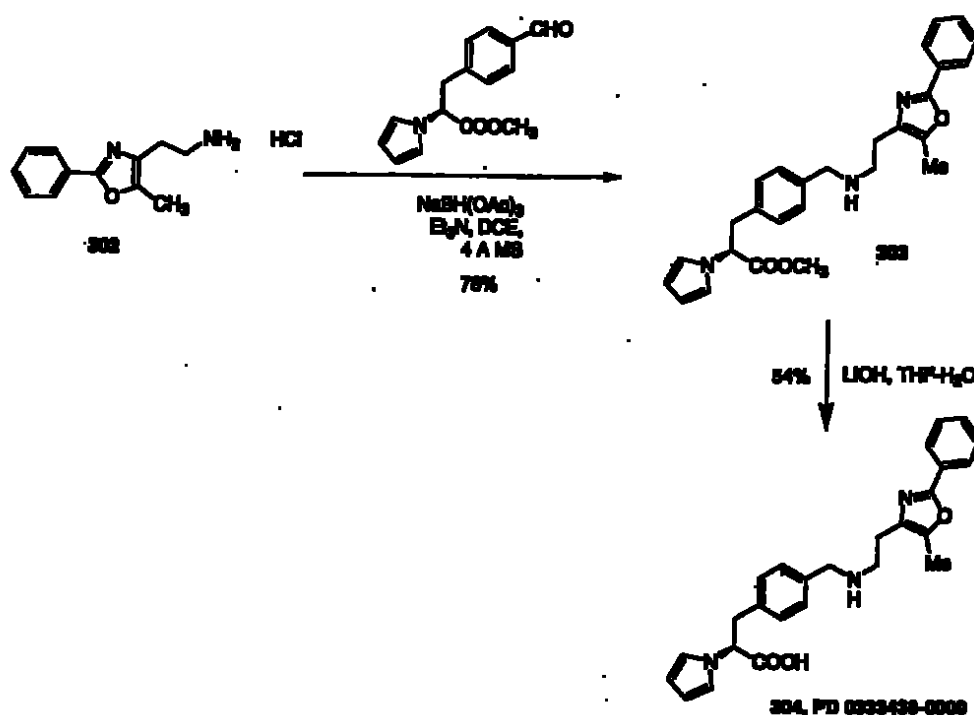
- Se disolvió éster metílico del ácido (S)-3-(4-([(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-propiónico (293) (0,432 g, 1,006 mmol) en 1,2-dicloroetano (10 ml) y se añadió una solución de formaldehído al 37% (0,090 ml, 1,106 mmol), seguido de  $NaBH(OAc)_3$  (0,300 g, 1,408 mmol). La mezcla se agitó a temperatura ambiente durante 24 horas en una atmósfera de
- 25 nitrógeno. Se añadió  $NaHCO_3$  saturado (30 ml) y la mezcla se

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agitó durante 20 minutos. En este momento, se diluyó con diclorometano y las fases se separaron. La fase acuosa se extrajo con diclorometano (3 x 30 ml). Los extractos reunidos se secaron sobre sulfato de magnesio, se filtraron y el disolvente se retiró. Los disolventes se retiraron y el residuo se purificó por cromatografía sobre gel de sílice, eluyendo con metanol en cloroformo (0 a 3%). Se obtuvo el éster 16 en forma de un aceite amarillo pálido (0,417 g, 93%): CIMS  $m/z$  444,2 (M+1).

10 Ejemplo 108

Ácido (S)-3-(4-{[2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-metil}-fenil)-2-pirrol-1-il-propiónico (304).



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Este compuesto se preparó a partir del éster metílico del ácido (S)-3-(4-([2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-metil)-fenil)-2-pirrol-1-il-propiónico (303) siguiendo el Procedimiento General 97. La purificación se realizó por cromatografía sobre gel de sílice, eluyendo con metanol en cloroformo (0 a 12%). El compuesto del título se obtuvo en forma de un sólido blanco con un rendimiento del 54%: p.f. 208-210°C; CIMS  $m/z$  430,2 (M+1). Análisis Calculado para  $C_{26}H_{27}N_3O_3 \cdot 0,6 H_2O$ : C, 70,92; H, 6,46; N, 9,54. 10 Encontrado: C, 70,60; H, 6,34; N, 9,48.

El éster metílico del ácido (S)-3-(4-([2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-metil)-fenil)-2-pirrol-1-il-propiónico (303) se preparó de la siguiente forma.

(a) Éster metílico del ácido (S)-3-(4-([2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-metil)-fenil)-2-pirrol-1-il-propiónico (303).

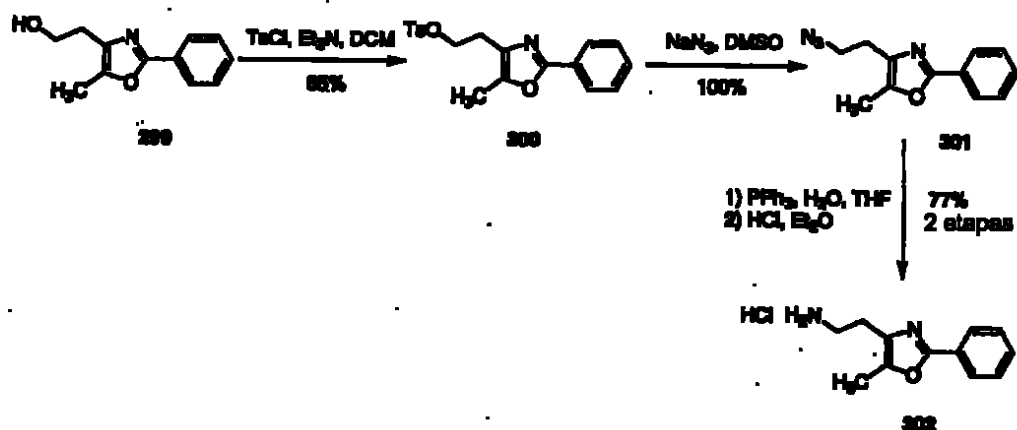
Se suspendió la amina 302 (0,392 g, 1,642 mmol) en 1,2-dicloroetano (15 ml). Se añadió  $Et_3N$  (0,252 ml, 1,806 mmol) y la mezcla se agitó durante 10 minutos. Se incorporó una solución del aldehído 290 (0,352 g, 1,368 mmol) en 1,2-dicloroetano (15 ml). Después de 10 minutos, se añadió  $NaBH(OAc)_3$  (0,405 g, 1,915 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas. Se añadieron  $NaBH(OAc)_3$  (0,290 g) y MS de 4A (0,4 g) y se continuó agitando durante 3 días. La mezcla se diluyó con

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diclorometano y se filtró a través de una capa de celite. Se añadió  $\text{NaHCO}_3$  saturado y las fases se separaron. La fase acuosa se extrajo con diclorometano (3 x 25 ml). Los extractos reunidos se secaron sobre sulfato de magnesio, se  
5 filtraron y el disolvente se retiró. Los disolventes se retiraron y el residuo se purificó por cromatografía sobre gel de sílice, eluyendo con metanol en cloroformo (del 0 al 5%). Se obtuvo el éster 21 en forma de un aceite amarillo (0,461 g, 76%): CIMS  $m/z$  444,2 (M+1).

10 (b) Clorhidrato de 2-(5-metil-2-fenil-oxazol-4-il)-etilamino (302).

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Se disolvió alcohol el 299 (3,87 g, 19,04 mmol) en

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diclorometano (60 ml) y se enfrió a 0°C. Se añadió TsCl (4,35 g, 22,85 mmol) seguido de Et<sub>3</sub>N (5,3 ml, 38,08 mmol). La mezcla se dejó calentar a temperatura ambiente durante una noche. Después, se diluyó con diclorometano (100 ml) y 5 la solución se lavó con HCl frío al 5% (2 x 50 ml) y NaHCO<sub>3</sub> saturado (50 ml), se secó sobre sulfato de magnesio, se filtró y el disolvente se retiró. Los disolventes se retiraron y el residuo se purificó por cromatografía en columna sobre gel de sílice, eluyendo con acetato de etilo 10 en hexanos (0 a 30%). Se obtuvo el tosilato 300 en forma de un sólido amarillento. (4,41 g, 65%): CIMS *m/z* 358,1 (M+1).

Se disolvió el tosilato 300 (4,41 g, 12,34 mmol) en DMSO y se añadió NaN<sub>3</sub> (1,04 g, 16,04 mmol). La mezcla se agitó a temperatura ambiente durante 3 días. La solución se 15 diluyó con agua (150 ml) y se extrajo con Et<sub>2</sub>O (5 x 100 ml). Los extractos reunidos se secaron sobre sulfato de magnesio, se filtraron y el disolvente se retiró. Se obtuvo la azida 301 en forma de un aceite naranja (2,86 g): CIMS *m/z* 229,1 (M+1).

20 Se disolvió la azida 301 (2,86 g, 12,53 mmol) en THF (50 ml) y se añadió PPh<sub>3</sub> (6,57 g, 25,06 mmol) seguido de agua (2,25 ml, 125,3 mmol). La mezcla se agitó a temperatura ambiente durante 20 horas. Los disolventes se retiraron, el residuo se disolvió en Et<sub>2</sub>O y la solución se 25 extrajo con HCl al 10% (3 x 20 ml). Los extractos acuosos



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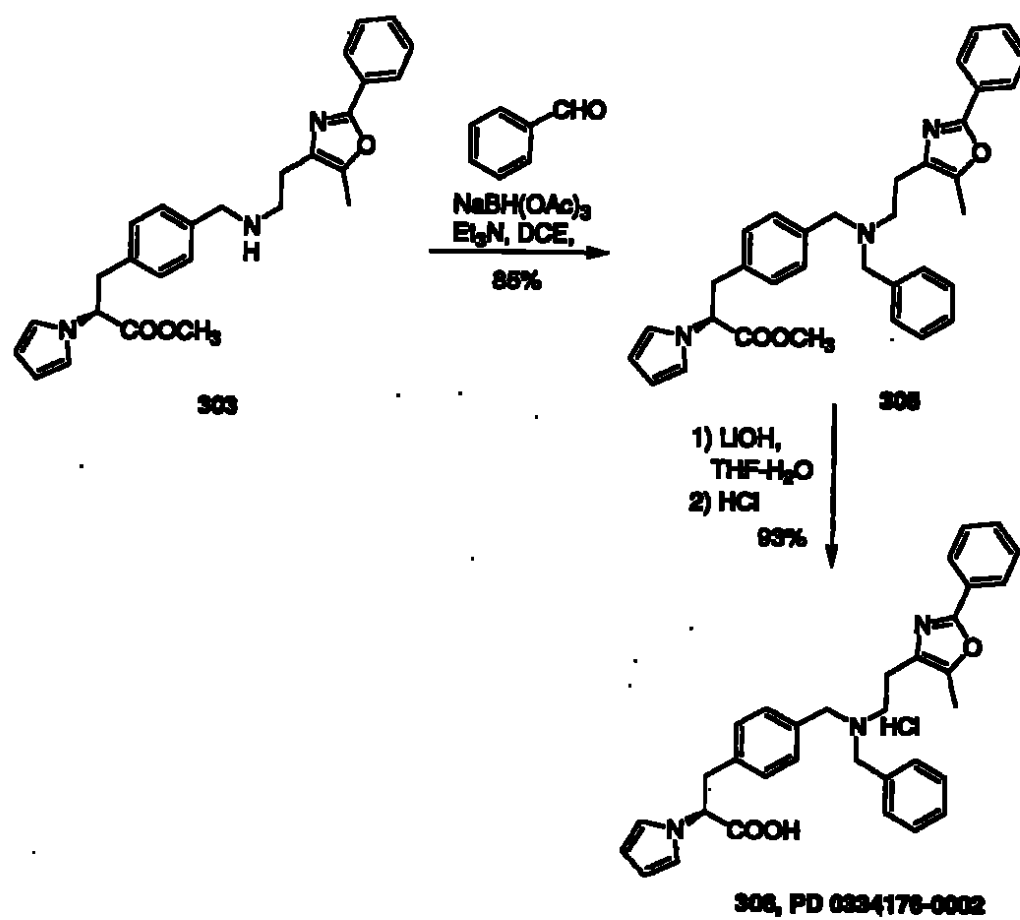
reunidos se lavaron con Et<sub>2</sub>O. El pH de la solución se ajustó a 14 con gránulos de hidróxido sódico. La mezcla se extrajo con Et<sub>2</sub>O (3 x 30 ml). Los extractos reunidos se secaron sobre sulfato de magnesio, se filtraron y el disolvente se retiró hasta dejar un pequeño volumen. Se añadió gota a gota una solución de HCl 1,0 N en Et<sub>2</sub>O. El sólido precipitado se separó por filtración, se lavó con Et<sub>2</sub>O y se secó durante una noche, dando la amina 302 en forma de la sal clorhidrato. Se obtuvo la amina 302 en forma de un sólido blanco (2,316 g, 77%): CIMS *m/z* 203,1 (M+1).

Ejemplo 109

Ácido (S)-3-[4-({bencil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico (306).

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Este compuesto se preparó a partir del éster metílico del ácido (S)-3-[4-({bencil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico

(22) siguiendo el Procedimiento General 96. Se obtuvo un sólido después de la acidificación con HCl al 10%. El sólido se separó por filtración, se lavó con agua y se secó a alto vacío, dando un sólido blanco (93%): p.f. 110-113°C; CIMS  $m/z$  520,3 (M+1). Análisis Calculado para  $C_{33}H_{33}N_3O_3 \cdot HCl$ ; C, 71,27, H, 6,16; N, 7,56. Encontrado. C, 71,22; H, 6,26; N, 7,42.

El éster metílico del ácido (S)-3-[4-({bencil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico (305) se preparó de la siguiente forma.

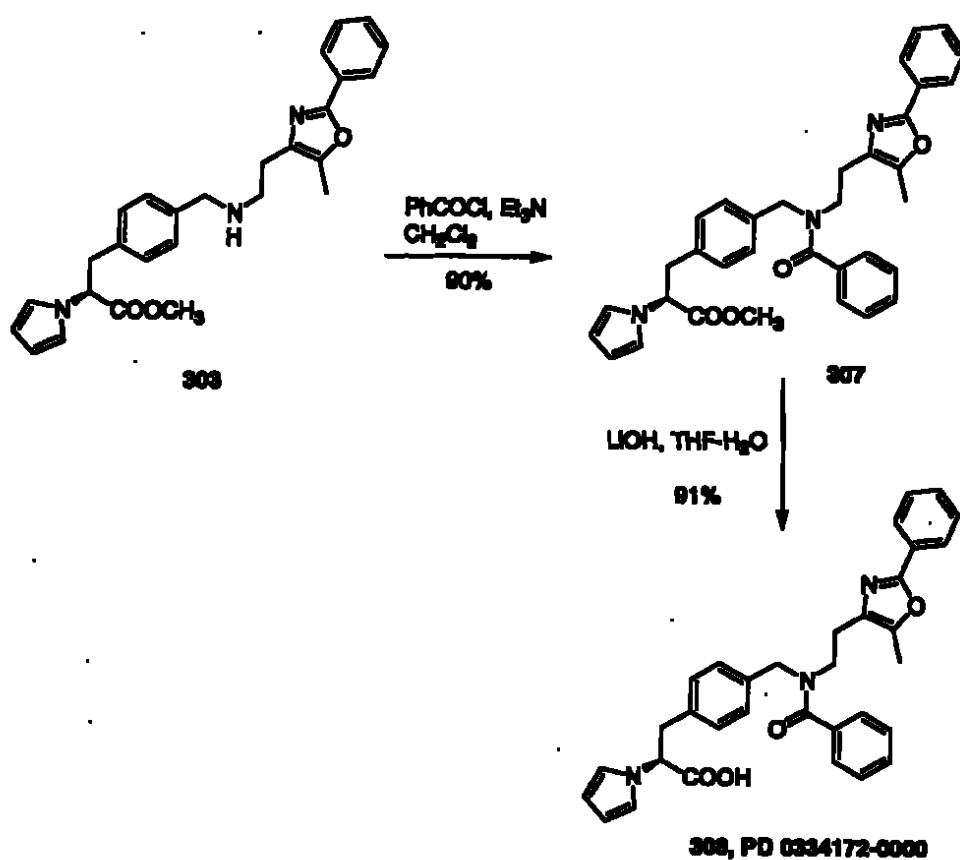
Este compuesto se preparó a partir del éster metílico del ácido (S)-3-[4-({[2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-metil}-fenil)-2-pirrol-1-il-propiónico (303) y benzaldehído siguiendo el Ejemplo 112, etapa a, y se obtuvo en forma de un aceite con un rendimiento del 85%: CIMS  $m/z$  534,3 (M+1).

#### Ejemplo 110

Ácido (S)-3-[4-({benzoil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico (308).

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Este compuesto se preparó a partir del éster metílico del ácido (S)-3-[4-((benzoil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino)-metil)-fenil]-2-pirrol-1-il-propiónico (307). El compuesto del título se obtuvo en forma de un 5 sólido blanco con un rendimiento del 91%: p.f. 105-110°C; CIMS  $m/z$  534,2 (M+1). Análisis Calculado para C<sub>33</sub>H<sub>31</sub>N<sub>3</sub>O<sub>4</sub>·0,2 H<sub>2</sub>O: C, 73,78; H, 5,89; N, 7,82. Encontrado C, 73,46; H, 5,76; N, 7,70.

El éster metílico del ácido (S)-3-[4-((benzoil-[2-(5-10 metil-2-fenil-oxazol-4-il)-etil]-amino)-metil)-fenil]-2-pirrol-1-il-propiónico (307) se preparó de la siguiente

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forma.

(a) Éster metílico del ácido (S)-3-{4-({benzoil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico (307).

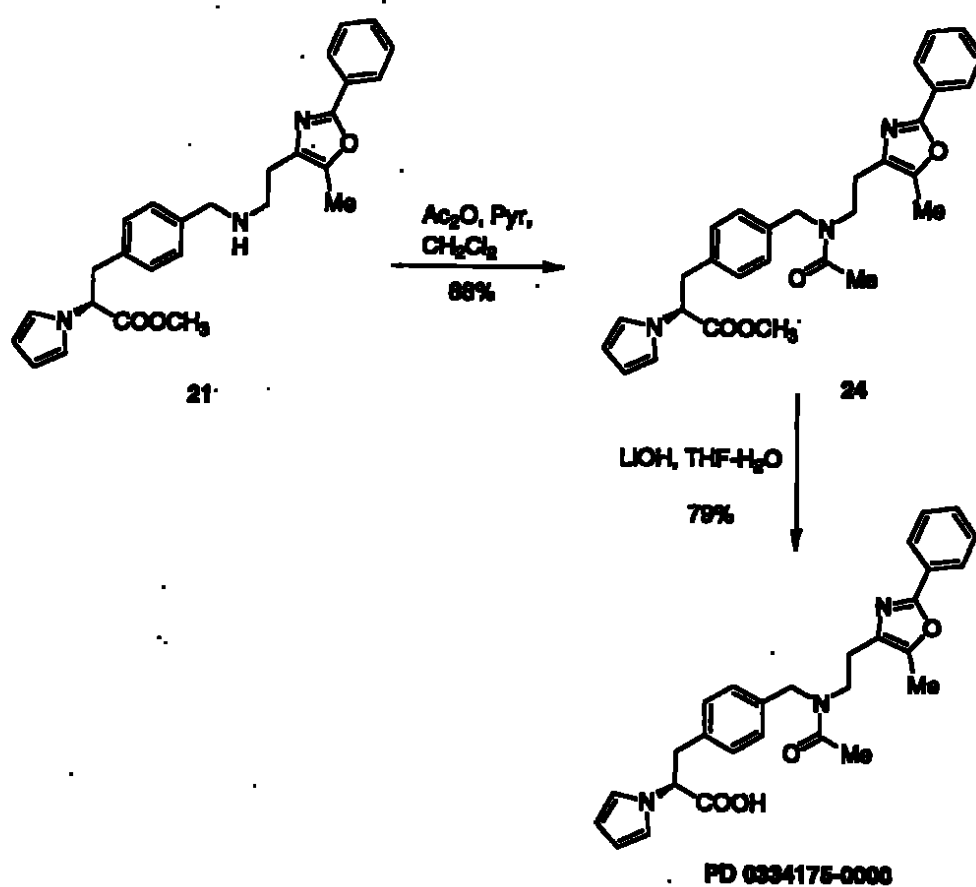
5 Se disolvió éster metílico del ácido (S)-3-(4-{[2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-metil}-fenil)-2-pirrol-1-il-propiónico (303) (0,286 g, 0,645 mmol) en diclorometano (10 ml) y se enfrió en un baño de hielo. Se añadió Et<sub>3</sub>N (0,180 ml, 1,29 mmol) seguido de PhCOCl (0,082 10 ml, 0,709 mmol). El baño de hielo se retiró después de 30 minutos y la mezcla se agitó a temperatura ambiente durante 20 horas, se añadió diclorometano (50 ml) y la solución se lavó con HCl al 10%, NaHCO<sub>3</sub> saturado y NaCl saturado. La fase orgánica se secó sobre sulfato de magnesio, se filtró 15 y el disolvente se retiró. Los disolventes se retiraron y el residuo se purificó por cromatografía en columna sobre gel de sílice, eluyendo con acetato de etilo en hexanos (0 a 45%). El compuesto del título se obtuvo en forma de un aceite transparente (0,319 g, 90%): CIMS *m/z* 548,2 (M+1).

## 20 Ejemplo 111

Ácido (S)-3-[4-({acetil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico (311).

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Este compuesto se preparó a partir del éster metílico del ácido (S)-3-[4-({acetil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico (310) siguiendo el Procedimiento General 97. La 5 purificación se realizó por cromatografía sobre gel de sílice, eluyendo con metanol en diclorometano (0 a 10%). El compuesto del título se obtuvo en forma de un sólido blanco con un rendimiento del 79%: p.f. 82-87°C; CIMS  $m/z$  472,2 (M+1). Análisis Calculado para  $C_{28}H_{29}N_3O_4 \cdot 0,4 H_2O$ : C, 70,25; H, 10 6,27; N, 8,78. Encontrado: C, 69,92; H, 6,16; N, 8,47.

El éster metílico del ácido (S)-3-[4-({acetil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico (310) se preparó de la siguiente forma.

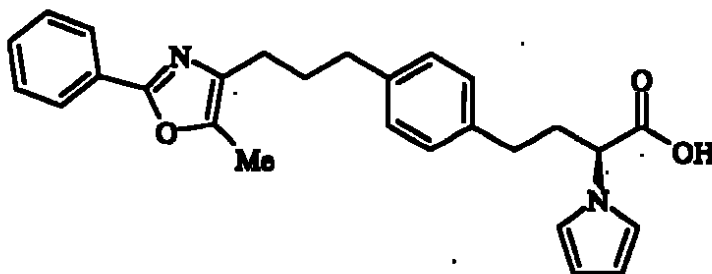
15 (a) Éster metílico del ácido (S)-3-[4-({acetil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico (310).

Se disolvió el éster metílico del ácido (S)-3-[4-([2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-metil)-fenil]-2- 20 pirrol-1-il-propiónico (303) (0,388 g, 0,875 mmol) en diclorometano (10 ml) y se enfrió en un baño de hielo. Se añadió piridina (0,177 ml, 2,187 mmol) seguido de  $Ac_2O$  (0,165 ml, 1,75 mmol). El baño de hielo se retiró después de 30 minutos y la mezcla se agitó a temperatura ambiente 25 durante 20 horas, se añadió diclorometano (50 ml) y la

solución se lavó con HCl al 10%, NaHCO<sub>3</sub> saturado y NaCl saturado. La fase orgánica se secó sobre sulfato de magnesio, se filtró y el disolvente se retiró. El residuo se purificó por cromatografía en columna sobre gel de 5 sílice, eluyendo con acetato de etilo en hexanos (0 a 40%). El compuesto del título se obtuvo en forma de un aceite amarillo pálido (0,376 g, 88%): CIMS  $m/z$  486,3 (M+1).

Ejemplo 112

Ácido 4-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-10 fenil}-2-pirrol-1-il-butírico (312).



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Se hidrolizó el éster metílico del ácido 4-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-butírico como en el Procedimiento General A, dando el ácido carboxílico 312 con un rendimiento del 90%. (δ) RMN (CHCl<sub>3</sub>) 7,86 (2H, m), 7,33 (3H, m), 7,03 (2H, d, J = 8,1 Hz), 6,97 (2H, d, J = 8,8 Hz), 6,68 (2H, m); 6,14 (2H, m), 4,46 (1H,



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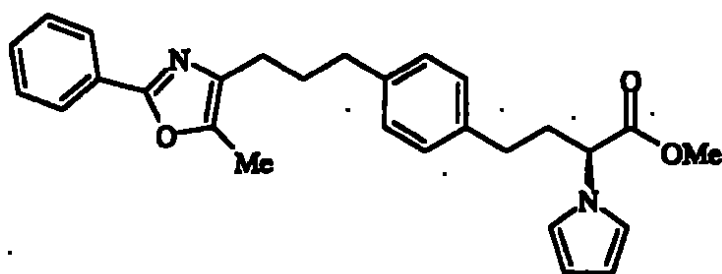
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m); 2,56 (3H, m), 2,44 (5H, m), 2,22 (3H, s), 1,88 (2H, m).  
CIMS  $m/z$  429,3 (M)<sup>+</sup>.

El éster metílico del ácido 4-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-butírico se preparó de la siguiente forma.

(a) Éster metílico del ácido 4-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-butírico (311).

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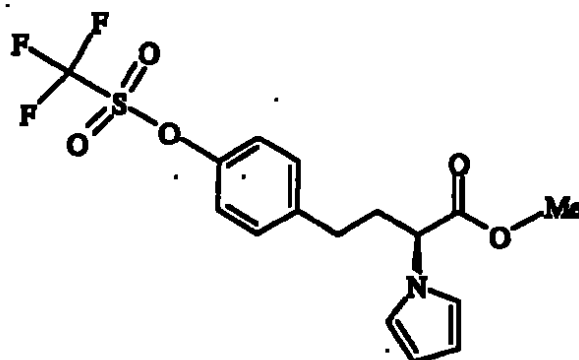
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El compuesto del título se preparó como en el procedimiento indicado para la preparación de los ésteres 120 a-d con un rendimiento del 38%. Se usó éster metílico 5 del ácido 2-pirrol-1-il-4-(4-trifluorometanosulfonil-fenil)-butírico como el componente triflato. (δ) RMN (CHCl<sub>3</sub>) 8,00 (2H, m), 7,47 (3H, m), 7,10 (2H, d, J = 7,6 Hz), 7,62 (2H, d, J = 7,6 Hz), 6,74 (2H, s), 6,21 (2H, s), 4,50 (1H, m), 3,69 (3H, s), 2,58 (6H, m), 2,37 (2H, s); 2,31 (3H, s), 1,99 (2H, m). CIMS m/z 44,3 (M)<sup>+</sup>.

Ejemplo 116

Éster metílico del ácido 2-pirrol-1-il-4-(4-trifluorometanosulfonil-fenil)-butírico (314).

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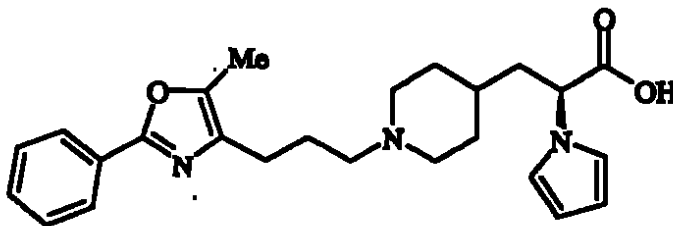
El compuesto del título se preparó como se describe en

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la síntesis del éster metílico del ácido (S)-2-pirrol-1-il-3-[(4-trifluorometanosulfonilo)fenil]-propiónico (119) a partir de homo-tirosina (CAS 141899-12-9) mediante la esterificación y condensación de pirrol como se describe en 5 la preparación del éster metílico de pirrolotirosina (1).  
(δ) RMN (CHCl<sub>3</sub>) 7,18 (4H, s), 6,71 (2H, s), 6,21 (2H, s), 4,51 (1H, m), 3,70 (3H, s), 2,45 (4H, s). CIMS m/z 391,9 (M)<sup>+</sup>.

Ejemplo 117

10      Ácido      3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-piperidin-4-il}-2-pirrol-1-il-propiónico (318).



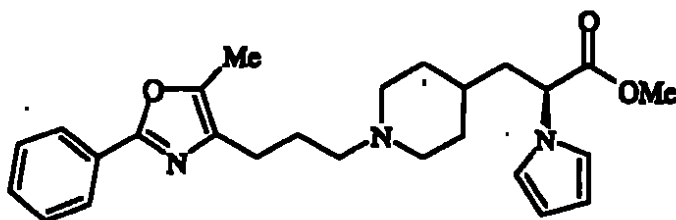
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El compuesto del título se preparó a partir del éster metílico del ácido 3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-5 propil]-piperidin-4-il}-2-pirrol-1-il-propiónico (317) mediante el Procedimiento General A con un rendimiento del 43%. RMN ( $\delta$ ,  $\text{CHCl}_3$ ); 7,9 (2H, m); 7,40 (3H, m), 6,65 (2H, s), 6,13 (2H, s), 6,01 (1H, m), 4,61 (1H, m), 3,50 (2H, m), 2,91 (2H, m), 2,59 (2H, m), 2,29 (3H, m), 2,27 (3H, s), 10 2,05 (3H, m), 1,85 (1H, m), 1,55 (1H, m). CIMS  $m/z$  422,3 (M)<sup>+</sup>.

El éster metílico del ácido 3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-piperidin-4-il}-2-pirrol-1-il-propiónico (317) se preparó de la siguiente forma.

15 (a) Éster metílico del ácido 3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-piperidin-4-il}-2-pirrol-1-il-propiónico (317).

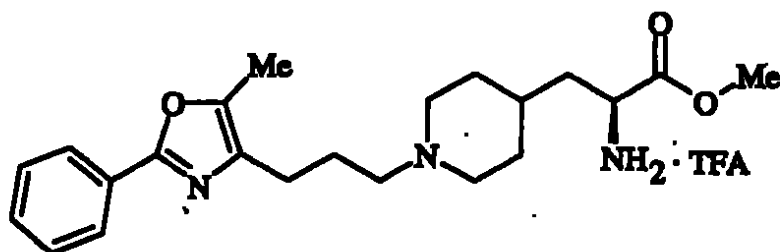


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El compuesto del título se preparó a partir de la sal TFA del éster amino (316) por la reacción de formación de pirrol como en el Ejemplo 1 con un rendimiento del 28%. RMN ( $\delta$ ;CHCl<sub>3</sub>); 7,95 (2H, m), 7,45 (3H, m), 6,70 (2H, s), 6,16 5 (2H, s), 4,66 (1H, m), 3,71 (3H, s), 2,52 (2H, m), 2,31 (3H, s), 2,03 (3H, m), 1,59 (3H, m), 1,21 (6H, m). CIMS m/z 436,3 (M)<sup>+</sup>.

(b) Sal del ácido trifluoroacético del éster metílico del ácido 2-amino-3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-10 propil]-piperidin-4-il}-propiónico (316)



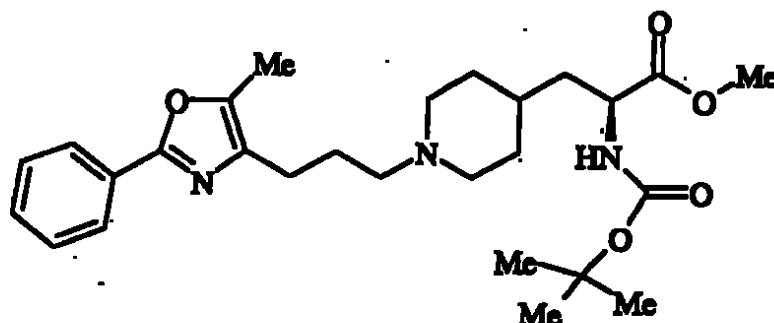
316

Preparado por tratamiento del éster metílico del ácido 2-terc-butoxicarbonilamino-3-{1-[3-(5-metil-2-fenil-oxazol-15 4-il)-propil]-piperidin-4-il}-propiónico (315) con 5 equivalentes de ácido trifluoroacético en diclorometano durante 24 horas a 23°C. La retirada del disolvente dio la sal del ácido trifluoroacético, que se usó sin purificación adicional.

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(c) Éster metílico del ácido 2-terc-butoxicarbonilamino-3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-piperidin-4-il]-propiónico



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El compuesto del título se preparó por combinación de 4-(3-bromo-propil)-5-metil-2-fenil-oxazol (1,21 g, 4,6 mmol), éster metílico del ácido 2-terc-butoxicarbonilamino-10 3-piperidin-4-il-propiónico (315,1 g, 3,67 mmol) y  $\text{Cs}_2\text{CO}_3$  (1,79 g, 5,5 mmol) en acetonitrilo (30 ml) a 23°C en una atmósfera de  $\text{N}_2$ . La mezcla se agitó vigorosamente durante 2 días después de lo cual la reacción se filtró y el disolvente se retiró al vacío. El residuo se cromatografió 15 ( $\text{SiO}_2$ ) con EtOAc/hexanos al 30% y dio 525 mg (rendimiento 30%) en forma de un aceite amarillo pálido. RMN ( $\delta$ ;  $\text{CHCl}_3$ ); 7,86 (2H, m), 7,43 (3H, m), 4,35 (1H, m), 3,72 (3H, s),

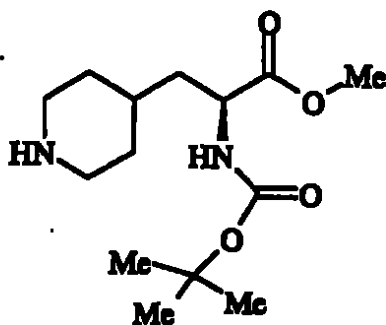
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2,51 (3H, m), 2,40 (4H, m), 2,32 (3H, s), 1,51 (5H, m), 1,40 (9H, s). CIMS  $m/z$  486,4 (M)<sup>+</sup>.

(d) Éster metílico del ácido 2-terc-butoxicarbonilamino-3-piperidin-4-il-propiónico (315, CAS 5 256925-70-9).

10

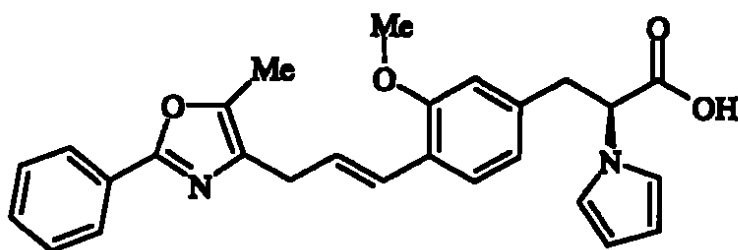


315

El compuesto del título se preparó como en la 15 esterificación de pirrolotirosina (1). Se usó sin purificación adicional.

#### Ejemplo 118

Ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil}-2-pirrol-1-il-propiónico (321).



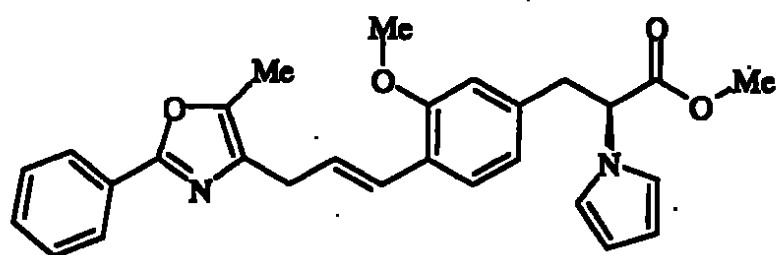
321

754

Preparado a partir del éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil}-2-pirrol-1-il-propiónico (320) utilizando el Procedimiento 5 de hidrólisis general A con un rendimiento del 57% en forma de una espuma beige. RMN ( $\delta$ ; CHCl<sub>3</sub>); 8,02 (2H, m), 7,41 (4H, m); 7,29 (1H, d, J = 7,8 Hz), 6,73 (1H, d, J = 16 Hz), 6,64 (2H, m), 6,60 (1H, d, J = 7,8 Hz), 6,32 (1H, m), 6,19 (1H, s), 6,14 (2H, s), 4,60 (1H, m), 3,63 (3H, s), 3,45 (2H, d, J = 6,8 Hz), 3,25 (2H, m), 2,03 (3H, s). CIMS m/z 441,3 (M)<sup>-</sup>.

El éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil}-2-pirrol-1-il-propiónico (320) se preparó de la siguiente forma.

15 (a) Éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil}-2-pirrol-1-il-propiónico (320).



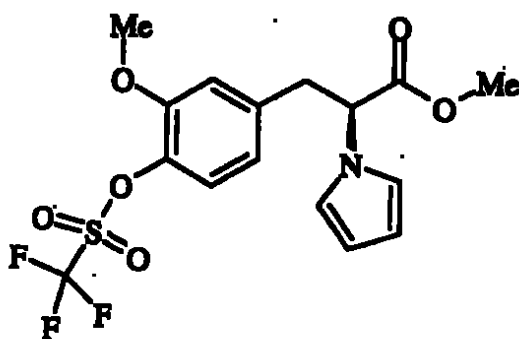
321



284  
755

El compuesto del título se preparó como en el procedimiento de acoplamiento de Pd usado para preparar los ésteres (120) a-d a partir del éster metílico del ácido 3-(3-metoxi-4-trifluorometanosulfonilo-fenil)-2-pirrol-1-il-propiónico y organo borano (117) con un rendimiento del 7% en forma de una espuma beige. RMN ( $\delta$ ;  $\text{CHCl}_3$ ); 8,00 (2H, d,  $J = 8,0$  Hz), 7,44 (3H, m), 7,23 (1H, d,  $J = 7,1$  Hz), 6,74 (1H, d,  $J = 16$  Hz), 6,69 (2H, m), 6,61 (1H, d,  $J = 7,8$  Hz), 6,30 (1H, m), 6,25 (1H, s), 6,14 (2H, m), 4,70 (1H, m), 3,75 (1H, m), 3,71 (3H, s), 3,66 (3H, s), 3,45 (2H, d,  $J = 6,6$  Hz), 3,25 (2H, m), 2,40 (3H, s). CIMS  $m/z$  457,3 (M)<sup>+</sup>.

(b) Éster metílico del ácido 3-(3-metoxi-4-trifluorometanosulfonilo-fenil)-2-pirrol-1-il-propiónico (319).

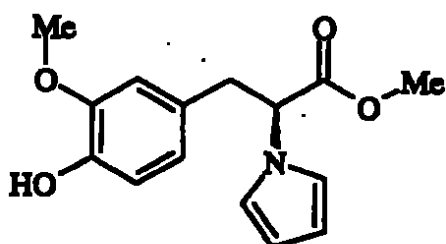


319

El compuesto del título se preparó usando el  
5 procedimiento general para la síntesis de triflato (119).  
El producto se obtuvo en forma de un aceite pardo claro con  
un rendimiento del 57% a partir del éster metílico del  
ácido 3-(4-hidroxi-3-metoxi-fenil)-2-pirrol-1-il-  
propiónico. Microanálisis CHN Teórico; C = 47,18; H = 3,96;  
10 N = 3,44; Observado: C = 47,19; H = 3,64; N = 3,42.

(c) Éster metílico del ácido 3-(4-hidroxi-3-metoxi-  
fenil)-2-pirrol-1-il-propiónico (CAS256925-70-9)

15

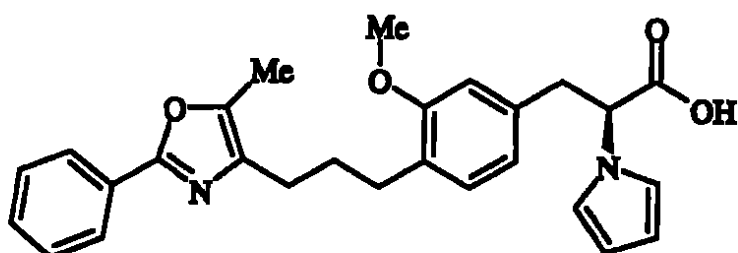


El compuesto del título se obtuvo a partir del éster  
20 metílico del ácido 2-amino-3-(4-hidroxi-3-metoxi-fenil)-  
propiónico como en la formación de pirrolotirosina (1) con  
un rendimiento del 69% en forma de un aceite amarillo. CIMS  
 $m/z$  276,1 (M)<sup>+</sup>.

#### Ejemplo 119

756  
757

413

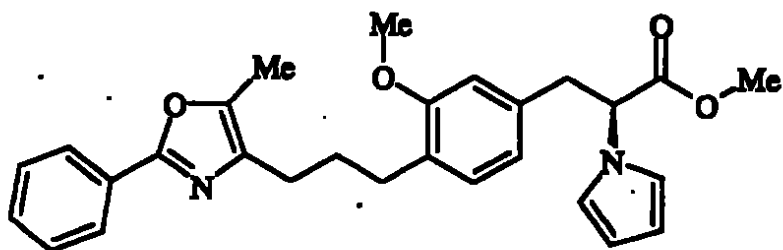


323

El compuesto del título se obtuvo con un rendimiento del 92% a partir del correspondiente éster metílico por el 5 procedimiento general A. Microanálisis CHN teórico; C = 72,95; H = 6,35; N = 6,30; Observado C = 72,94; H, 6,42; N = 6,00 P.f. 120-121°C.

El éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-10 propiónico (322) se obtuvo de la siguiente forma.

(a) Éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propiónico (322).



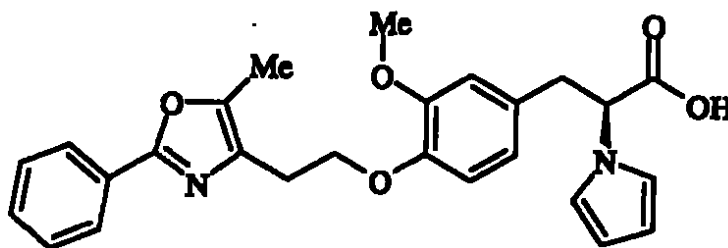
322

757  
758

El compuesto del título se obtuvo mediante el procedimiento de hidrogenación general usado para preparar los ésteres 130 a-c. Microanálisis CHN teórico C = 73,34; 5 H, 6,59; N = 6,11; Observado: C = 73,29; H, 6,53; N = 6,03.

Ejemplo 120

Ácido 3-{3-metoxi-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (325).



325

10

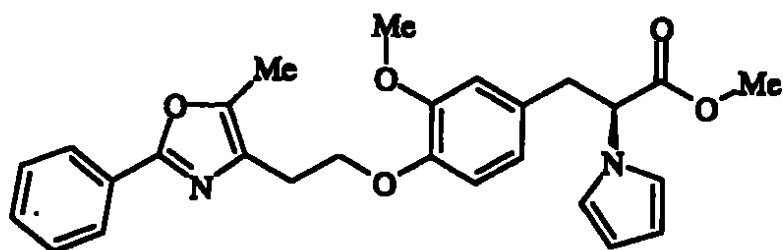
El compuesto del título se obtuvo a partir del éster metílico del ácido 3-{3-metoxi-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (324) mediante el procedimiento de hidrólisis general A con un 15 rendimiento del 86%. Microanálisis CHN teórico C = 69,94; H = 5,87, N = 6,27; Observado: C = 70,25; H ,5,75; N = 6,04; P.F = 142-143°C.

El éster metílico del ácido 3-{3-metoxi-4-[2-(5-metil-

~~758~~  
759

415

2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico  
(324) se obtuvo de la siguiente forma.



324

5

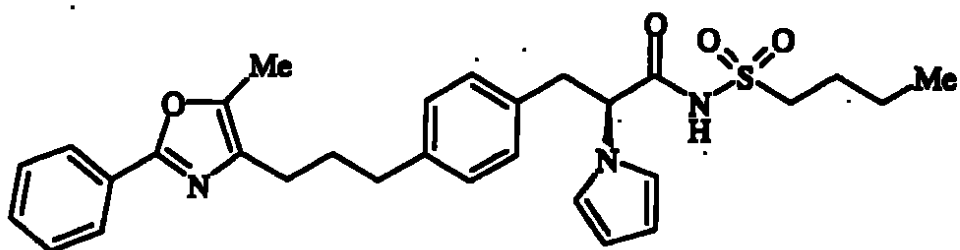
El compuesto del título se obtuvo a partir del éster metílico del ácido 3-(4-hidroxí-3-metoxi-fenil)-2-pirrol-1-il-propiónico mediante el procedimiento de acoplamiento general B con un rendimiento del 35%. Microanálisis CHN 10 teórico C = 70,42; H = 6,13, N = 6,08; Observado: C = 70,42; H = 6,03; N 6,04.

#### Ejemplo 121

(3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propionil)-amida del ácido butano-1-sulfónico  
15 (326).

788  
760

416



326

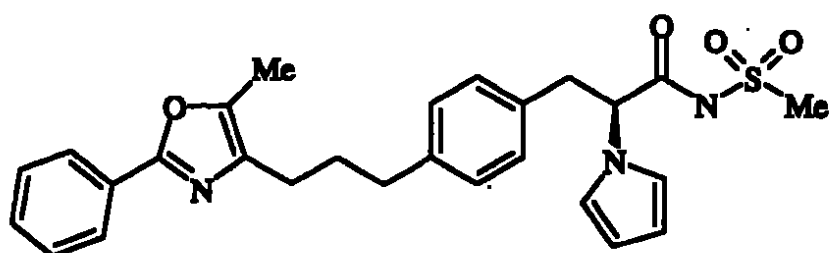
El compuesto del título se obtuvo a partir del ácido correspondiente con un rendimiento del 50% mediante el mismo procedimiento usado para obtener la acil sulfonamida (17). RMN ( $\delta$ ;  $\text{CHCl}_3$ ); 7,96 (2H, m), 7,43 (3H, m), 7,04 (2H, d,  $J = 8$  Hz), 6,88 (2H, d,  $J = 8,0$  Hz), 6,61 (2H, m), 6,22 (2H, m), 4,71 (1H, m), 3,35 (1H, m), 3,30 (2H, m), 3,20 (1H, m), 2,60 (2H, m), 2,45 (2H, m), 2,25 (3H, s), 1,95 10 (2H, m), 1,69 (2H, m), 1,45 (2H, m), 0,95 (3H, m). CIMS  $m/z$  543,3 (M)<sup>+</sup>.

#### Ejemplo 122

N-(3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propionil)-metanosulfonamida (327).

280  
761

417



327

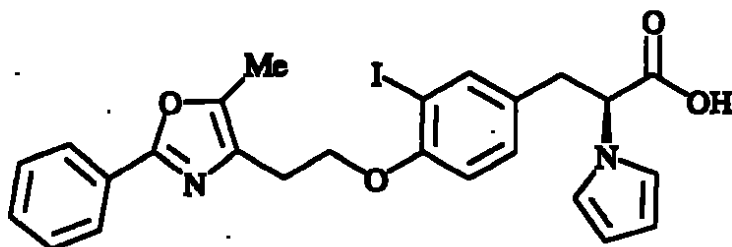
El compuesto del título se obtuvo en forma de un aceite pardo a partir del ácido correspondiente con un 5 rendimiento del 40% mediante el mismo procedimiento usado para obtener la acil sulfonamida (327). RMN ( $\delta$ ;  $\text{CHCl}_3$ ). 7,96 (2H, m), 7,40 (3H, m), 7,03 (2H, d,  $J = 1$  Hz), 6,89 (2H, d,  $J = 8,1$  Hz), 6,65 (1H, s), 6,14 (2H, s), 4,69 (2H, m), 3,49 (1H, m), 3,17 (1H, m), 3,08 (2H, m), 2,58 (2H, t,  $J = 7,3, 8,0$  Hz), 2,45 (2H, t,  $J = 7,3, 7,6$  Hz), 2,24 (3H, s), 1,85 (2H, m). CIMS  $m/z$  492,3 ( $M$ )<sup>+</sup>.

#### Ejemplo 123

Ácido 3-{3-yodo-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (330).

761  
762

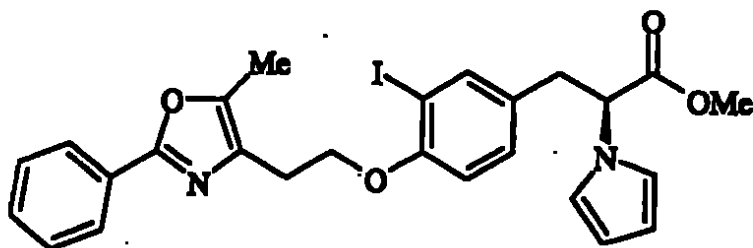
418



330

El compuesto del título se obtuvo a partir de la  
5 hidrólisis del correspondiente éster metílico del ácido 3-  
{3-yodo-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-  
pirrol-1-il-propiónico (329) mediante el procedimiento  
general A. Cristales blancos con un rendimiento del 68%.  
Microanálisis CHN Teórico C = 72,95, H, 6,35; N = 6,30;  
10 Observado: C = 72,71; H, 6,44; N = 6,29. P.F. = 202-203°C.

El éster metílico del ácido 3-{3-yodo-4-[2-(5-metil-2-  
fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico  
(329) se preparó de la siguiente forma.



329



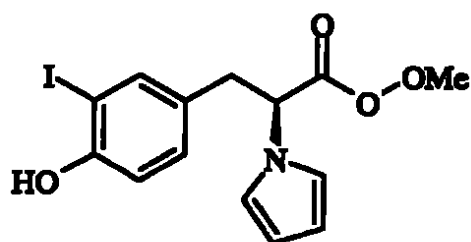
763

5

El compuesto del título se obtuvo mediante el procedimiento de acoplamiento general B a partir del éster metílico del ácido 3-(4-hidroxí-3-yodo-fenil)-2-pirrol-1-il-propiónico con un rendimiento del 63%. CIMS  $m/z$  557,1 (M)<sup>+</sup>.

(b) Éster metílico del ácido 3-(4-hidroxí-3-yodo-fenil)-2-pirrol-1-il-propiónico (328).

15



20

328

El compuesto del título se obtuvo con un rendimiento del 84% en dos etapas como en la síntesis del éster metílico de pirrolotirosina (1). CIMS  $m/z$  372,0 (M)<sup>+</sup>.

25 Ejemplo 124

CC#Cc1ccc(cc1)C[C@H](Cc2cnc(c2)c3ccccc3)C(=O)O[C@@H](C4=CC=CC=C4)N5C=CC=C5

10 El compuesto del título se obtuvo a partir del éster  
metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-3-prop-1-inil-fenil}-2-pirrol-1-il-propiónico (331,  
PD0333000-000) mediante el procedimiento de hidrólisis  
general A con un rendimiento del 66% en forma de cristales  
15 blancos a partir de acetato de etilo. P.F. = 155-156°C.  
Microanálisis CHN teórico: C = 73,99, H = 5,77; N = 6,16;  
Observado: C= 74,04; H = 5,72; H = 5,85.

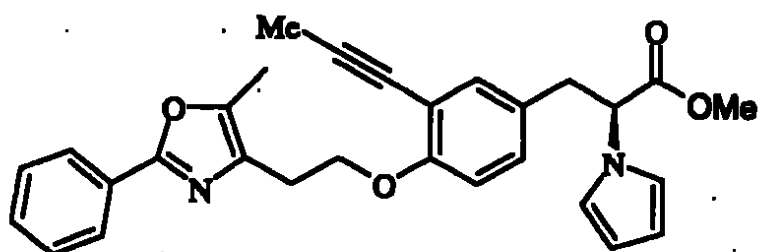
El éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-

764  
765

421

oxazol-4-il)-etoxi]-3-prop-1-inil-fenil)-2-pirrol-1-il-propiónico (331) se preparó de la siguiente forma.

(a) Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-3-prop-1-inil-fenil)-2-pirrol-1-il-5 propiónico (331).



331

10

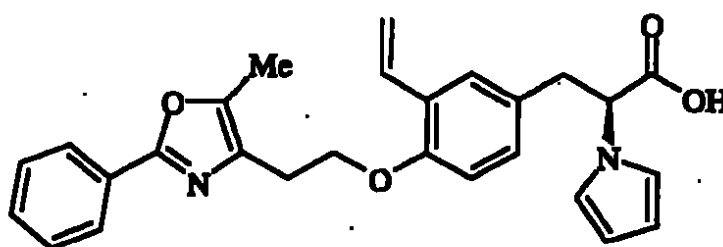
Se disolvió el compuesto del título (1,0 g, 1,8 mmol) en tolueno en una atmósfera de N<sub>2</sub> a 23°C. A esta solución se le añadió tributil-prop-1-inil-estannano (1,10 ml, 3,6 mmol) y Pd(Cl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>) (38 mg, 0,054 mmol) y el matraz se calentó a reflujo durante 18 horas. La reacción se lavó con KF acuoso (1 x 50 ml), agua (2 x 50 ml) y salmuera (1 x 50

765  
766

ml). La capa orgánica se secó sobre  $\text{Na}_2\text{SO}_4$  y el disolvente se retiró al vacío. El residuo se cromatografió con EtOAc/hexanos al 10-30%, dando 400 mg (rendimiento 47%) de producto en forma de una goma beige. CIMS  $m/z$  469,2 (M).

5 Ejemplo 125

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-3-vinil-fenil}-2-pirrol-1-il-propiónico (334).



334

10

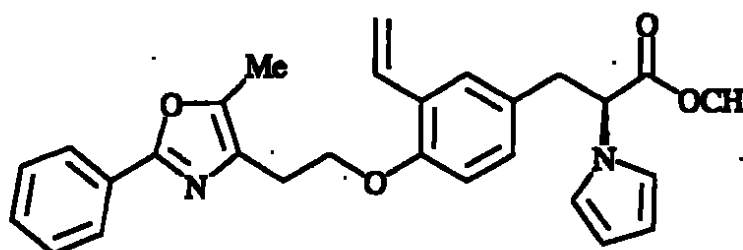
15

285  
767

El compuesto del título se obtuvo a partir del éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-3-vinil-fenil}-2-pirrol-1-il-propiónico (333) con un 5 rendimiento del 54% utilizando el procedimiento de hidrólisis A. RMN ( $\delta$ ,  $\text{CHCl}_3$ ): 7,96 (2H, m), 7,41 (3H, m), 6,99 (1H, s), 6,90 (2H, m), 6,71 (3H, m), 6,15 (2H, s), 5,58 (1H, d,  $J = 17$  Hz), 5,17 (1H, d,  $J = 11$  Hz); 4,72 (1H, m), 4,20 (2H, m), 3,36 (1H, m), 3,20 (1H, m), 2,99 (2H, m), 10 2,35 (3H, s). CIMS  $m/z$  443,1 ( $M$ )<sup>+</sup>.

El éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-3-vinil-fenil}-2-pirrol-1-il-propiónico (333) se obtuvo de la siguiente forma.

(a) Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-15 oxazol-4-il)-etoxi]-3-vinil-fenil}-2-pirrol-1-il-propiónico (333).



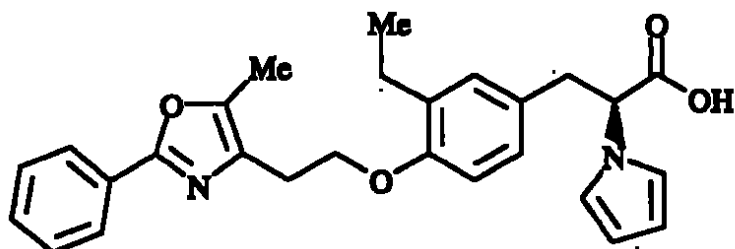
333

261  
768

El compuesto del título se obtuvo con un rendimiento del 61% utilizando vinil tributil estannano y un procedimiento similar al usado en la síntesis del Ejemplo 5 125. MICROANÁLISIS CHN teórico C = 73,66; H = 6,18, N = 6,14. Observado: C = 73,55; H = 5,92; N = 5,60 con 0,1 equivalente de EtOAc como impureza.

Ejemplo 126

Ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-10 etoxil]-fenil}-2-pirrol-1-il-propiónico (336).



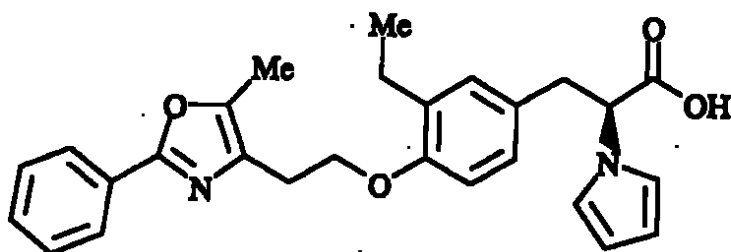
336

768  
769

El compuesto del título se obtuvo a partir del éster metílico del ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (335) con un rendimiento del 68% utilizando el procedimiento de 5 hidrólisis general A. Microanálisis CHN teórico C = 72,95; H = 6,35; N = 6,30; Observado: C = 72,71, H = 6,44; N = 6,29. P.F. = 164-165.

El éster metílico del ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico 10 (335) se preparó de la siguiente manera.

(a) Éster metílico del ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico (335).



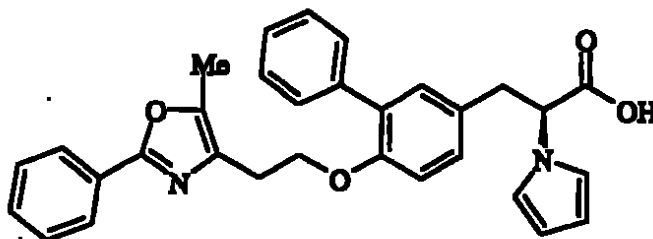
335

264  
790

El compuesto del título se obtuvo a partir del correspondiente derivado de vinil-fenilo mediante el 5 procedimiento de hidrogenación usado en la preparación de los ésteres 130 a-c con un rendimiento del 70% en forma de un polvo blanco. Microanálisis CHN teórico C = 73,34; H = 6,59; N = 6,11; Observado: C = 72,96; H = 6,60; N = 6,10.

Ejemplo 127

10      Ácido      3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bifenil-3-il}-2-pirrol-1-il-propiónico (338).



15

338

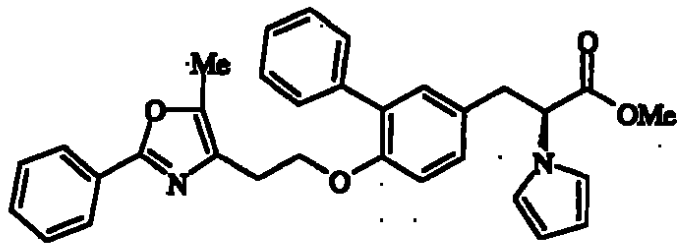
El compuesto del título se obtuvo a partir del éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)- 20 etoxi]-bifenil-3-il}-2-pirrol-1-il-propiónico (337) mediante le procedimiento de hidrólisis general A con un rendimiento del 56% en forma de cristales blancos. P.F. 163-164°C. Microanálisis CHN teórico C = 75,59, H = 5,73, N = 5,69; Observado: C = 75,39; H = 5,83, N = 5,43.

25      El éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-



720  
771

oxazol-4-il)-etoxi]-bifenil-3-il}-2-pirrol-1-il-propiónico  
(338) se preparó de la siguiente forma.



337

5 El compuesto del título se obtuvo con un rendimiento del 96% a partir del ácido fenil-borónico mediante un procedimiento catalizado con Pd de una forma similar a la usada para obtener el grupo vinil-fenilo.

CIMS  $m/z$  507,2 (M)<sup>+</sup>.

10 Ejemplo 128

A continuación se ilustran formas de dosificación farmacéuticas representativas, que contienen un compuesto de Fórmula I (Compuesto 4f) para uso terapéutico o profiláctico en los seres humanos.

| (i) Comprimido                | mg/comprimido |
|-------------------------------|---------------|
| Compuesto de la invención     | 25,0          |
| Lactosa                       | 50,0          |
| Almidón de maíz (para mezcla) | 10,0          |

771  
772

|                            |      |
|----------------------------|------|
| Almidón de maíz (pasta)    | 10,0 |
| Estearato de magnesio (1%) | 3,0  |
| 300,0                      |      |

La bifenilsulfonamida, la lactosa y el almidón de maíz (para la mezcla) se mezclan hasta la uniformidad. El almidón de maíz (pasta) se suspende en 200 ml de agua y se calienta con agitación para formar una pasta. La pasta se usa para granular los polvos mezclados. Los gránulos húmedos se pasan a través de un tamiz manual del No. 8 y se secan a 80°C. Los gránulos secos se lubrican con el estearato de magnesio al 1% y se prensan para formar comprimidos. Tales comprimidos pueden administrarse a un ser humano de una a cuatro veces al día para el tratamiento de infecciones producidas por bacterias patógenas.

| (ii) Cápsula                | mg/cápsula |
|-----------------------------|------------|
| Compuesto de la invención   | 10,0       |
| Dióxido de Silicio Coloidal | 1,5        |
| Lactosa                     | 465,5      |
| Almidón Pregelatinizado     | 120,0      |
| Estearato de Magnesio (1%)  | 3,0        |
| 600,0                       |            |

| (iii) Preparación para Solución Oral | Cantidad |
|--------------------------------------|----------|
| "Compuesto 4f"                       | 400 mg   |

772  
773

---

|                                 |        |
|---------------------------------|--------|
| Solución de sorbitol (70% N.F.) | 40 ml  |
| Benzoato Sódico                 |        |
| Sacarina                        | 20 mg  |
| Sabor de Cerezas                | 5 mg   |
| Agua destilada, c.s.            | 20 mg  |
|                                 | 100 ml |

La solución de sorbitol se añade a 40 ml de agua destilada y en esta solución se disuelve la bifenilsulfonamida. Se añaden la sacarina, el benzoato 5 sódico, el aromatizante y el colorante y se disuelven. El volumen se ajusta a 100 ml con agua destilada. Cada mililitro de jarabe contiene 4 mg del compuesto de la invención.

(iv) Solución Parenteral

- 10 En una solución de 700 ml de propilenglicol y 200 ml de agua para inyección, se suspenden 20 g de 2-amino-4-ciclopropil-7-fluoro-5-metil-6-[3-(1-metilamino-etil)-pirrolidin-1-il]-pirido[1,2-c]pirimidina-1,3-diona (Compuesto 4f). Después de completar la suspensión, el pH
- 15 se ajusta a 6,5 con ácido clorhídrico 1 N y el volumen se lleva a 1000 ml con agua para inyección. La formulación se esteriliza, se introduce en ampollas de 5,0 ml que contienen, cada una, 2,0 ml y se cierran herméticamente en una atmósfera de nitrógeno.

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|       |                                                              |                 |
|-------|--------------------------------------------------------------|-----------------|
| (v)   | Inyección 1 (1 mg/ml)                                        | Cantidad        |
|       | Compuesto de la Invención                                    | 1,0             |
|       | Fosfato Sódico Dibásico                                      | 12,0            |
|       | Fosfato Sódico Monobásico                                    | 0,7             |
|       | Cloruro Sódico                                               | 4,5             |
|       | Solución de hidróxido sódico N<br>(ajuste del pH a 7,0-7,5)  | c.s.            |
|       | Agua para inyección                                          | c.s. hasta 1 ml |
| (vi)  | Inyección 2 (10 mg/ml)                                       | Cantidad        |
|       | Compuesto de la Invención                                    | 10,0            |
|       | Fosfato Sódico Dibásico                                      | 1,1             |
|       | Fosfato Sódico Monobásico                                    | 0,3             |
|       | Polietilenglicol 400                                         | 200,0           |
|       | Solución de ácido clorhídrico N<br>(ajuste del pH a 7,0-7,5) | c.s.            |
|       | Agua para inyección                                          | c.s. hasta 1 ml |
| (vii) | Inyección 2 (10 mg/ml)                                       | Cantidad        |
|       | Compuesto de la Invención                                    | 20,0            |
|       | Ácido Oleico                                                 | 10,0            |
|       | Tricloromonofluorometano                                     | 5.000,0         |
|       | Diclorodifluorometano                                        | 10.000,0        |
|       | Diclorotetrafluoroetano                                      | 5.000,0         |

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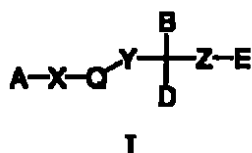
Todas las patentes y documentos de patente se incorporan en este documento como referencia, como si se incorporaran individualmente como referencia. La invención se ha descrito con referencia a diversas realizaciones y 5 técnicas específicas y preferidas. Sin embargo, debe entenderse que pueden realizarse muchas variaciones y modificaciones dentro del espíritu y alcance de la invención.

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Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

5 1. Un compuesto de fórmula (I)



10 o una sal farmacéuticamente aceptable del mismo, en la que:

A es arilo y arilo sustituido,

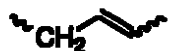
heteroarilo y heteroarilo sustituido,

heteroarilo condensado y heteroarilo condensado sustituido,

15 cicloalquilo (C<sub>3</sub>-C<sub>7</sub>) y cicloalquilo sustituido, o

heterocicloalquilo y heterocicloalquilo sustituido;

X es una cadena de 2 a 5 átomos de longitud seleccionada entre  $\sim\text{CH}_2\text{O}\sim$ ,  $\sim\text{CH}_2\text{CH}_2\text{O}\sim$ ,  $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$ ,  $\sim\text{CH}_2\equiv\sim$ , 509 o



510, indicando "∼" 511 un punto de unión;

20 Q es arilo o arilo sustituido;

heteroarilo o heteroarilo sustituido;

heteroarilo condensado o heteroarilo condensado sustituido; con la condición de que cuando q es un heteroarilo de cinco miembros, el punto de unión de X a Q

25 no está en el heteroátomo del heteroarilo;

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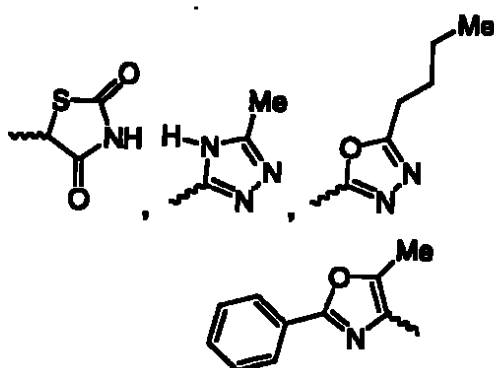
Y y Z, independientemente, están ausentes o son  $(CR_1R_2)_n$  y  $(CR_3R_4)_m$ , siendo cada uno de  $R_1-R_4$  independientemente H, halo, alquilo ( $C_1-C_6$ ), hidroxilo, alcoxi ( $C_1-C_6$ ), y siendo cada uno de m y n independientemente 1, 2 ó 3;

5 B es H, halo, alquilo ( $C_1-C_6$ ), haloalquilo ( $C_1-C_6$ ) o alcoxi ( $C_1-C_6$ );

D es H, H, -NH-arilo y -NH-arilo sustituido, alcanoílo ( $C_1-C_6$ ) y alcanoílo ( $C_1-C_6$ ) sustituido, benzoílo y benzoílo sustituido, arilo y arilo sustituido, heteroarilo y heteroarilo sustituido, cicloalquilo ( $C_3-C_7$ ) y cicloalquilo sustituido; o heterocicloalquilo y heterocicloalquilo sustituido;

E es  $COR_5$ , siendo  $R_5$  alquilo ( $C_1-C_6$ ), OH, alcoxi ( $C_1-C_6$ ),  $NR_6R_7$ , siendo cada uno de  $R_6$  y  $R_7$  independientemente H o alquilo ( $C_1-C_6$ ), o siendo uno de  $R_6$  y  $R_7$  H o alquilo ( $C_1-C_6$ ) y el otro  $SO_2R_8$ , siendo  $R_8$  H o alquilo ( $C_1-C_6$ ), o E es

heteroarilo sustituido o



; 512 con

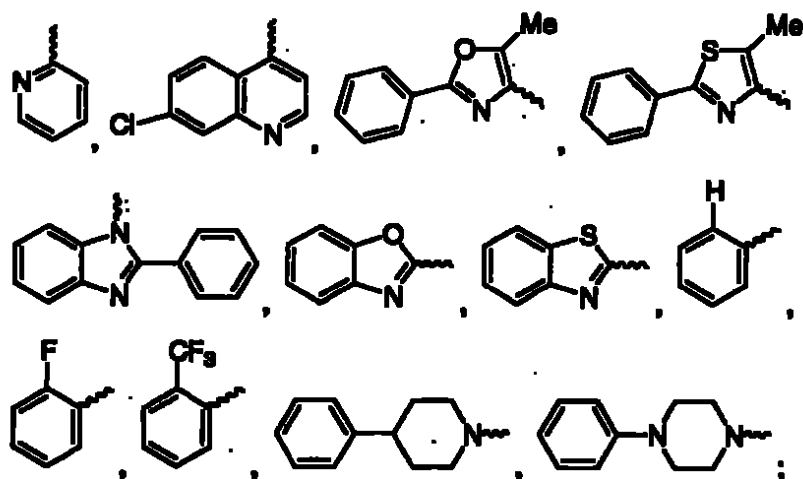
la condición de cuando A es '513 X es

20  $\sim CH_2-CH_2-O \sim$  514 Q es fenilo, Y y Z son  $CH_2$ , B es H, y E es

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778

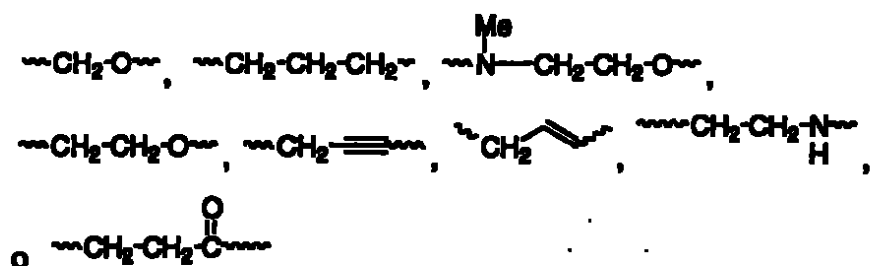
CO<sub>2</sub>H, D no sea pirrolilo.

2. El compuesto de la reivindicación 1, en el que  
A es



5

X es una cadena de 2 a 5 átomos de longitud seleccionada  
entre



10



778  
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Q es arilo o arilo sustituido;

heteroarilo o heteroarilo sustituido;

heteroarilo condensado o heteroarilo condensado  
5 sustituido; con la condición de que cuando q es un  
heteroarilo de cinco miembros, el punto de unión de X a Q  
no está en el heteroátomo del heteroarilo;

Y es CH<sub>2</sub>;

Z está ausente;

10 B es halo, alquilo (C<sub>1</sub>-C<sub>6</sub>), halo-alquilo (C<sub>1</sub>-C<sub>6</sub>) o alcoxi  
(C<sub>1</sub>-C<sub>6</sub>);

D es H, H, -NH-arilo y -NH-arilo sustituido,

alcanoílo (C<sub>1</sub>-C<sub>6</sub>) y alcanoílo (C<sub>1</sub>-C<sub>6</sub>) sustituido,

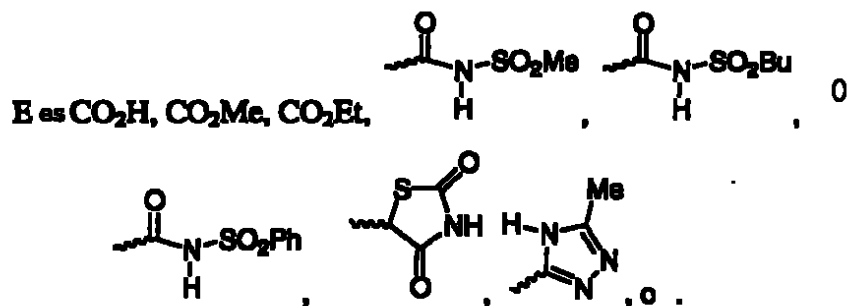
benzoílo y benzoílo sustituido,

15 arilo y arilo sustituido,

heteroarilo y heteroarilo sustituido,

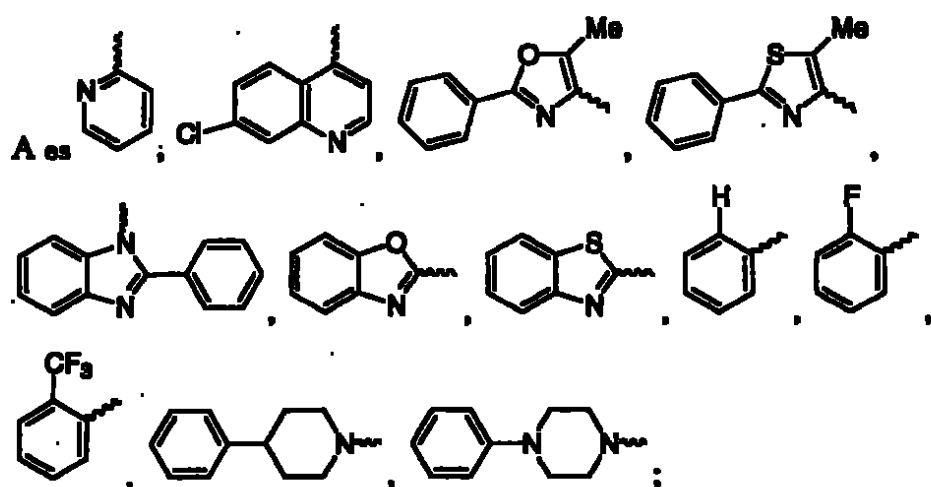
cicloalquilo (C<sub>3</sub>-C<sub>7</sub>) y cicloalquilo sustituido; o

heterocicloalquilo y heterocicloalquilo sustituido; y



~~274~~  
980

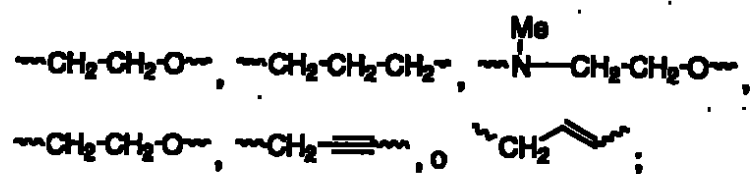
3. El compuesto de la reivindicación 1, en el que



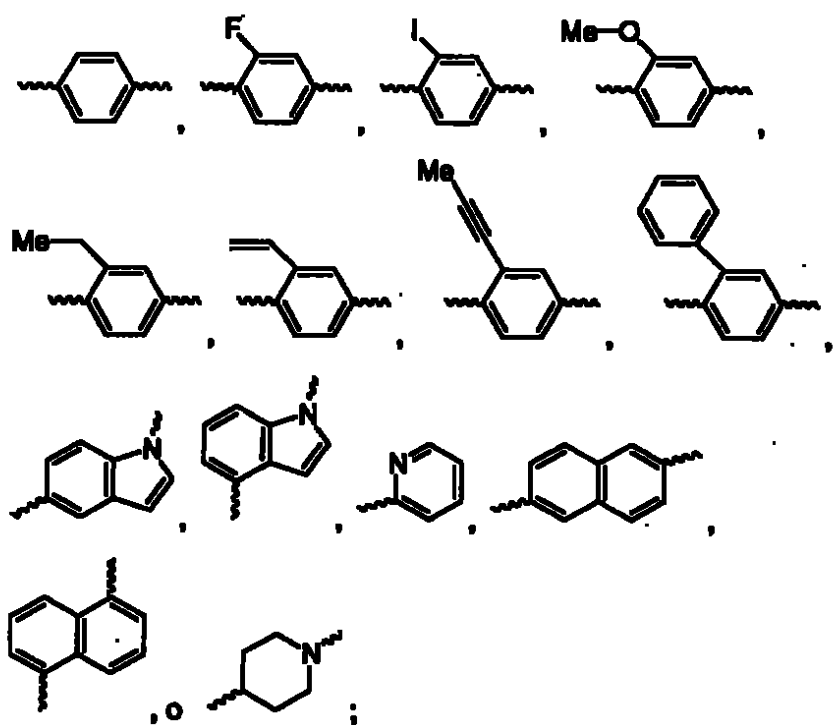
5

X es una cadena de 2 a 5 átomos de longitud seleccionada entre

781



Q 65



781  
782

Y es CH<sub>2</sub>;

Z está ausente;

B es H, halo, alquilo (C<sub>1</sub>-C<sub>6</sub>), halo-alquilo (C<sub>1</sub>-C<sub>6</sub>) o alcoxi (C<sub>1</sub>-C<sub>6</sub>);

5 D es H, H, -NH-arilo y -NH-arilo sustituido,

alcanoílo (C<sub>1</sub>-C<sub>6</sub>) y alcanoílo (C<sub>1</sub>-C<sub>6</sub>) sustituido,

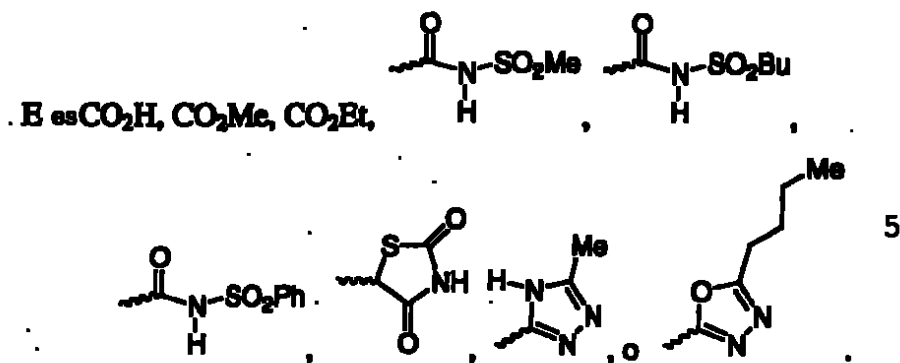
benzoílo y benzoílo sustituido,

arilo y arilo sustituido,

heteroarilo y heteroarilo sustituido,

10 cicloalquilo (C<sub>3</sub>-C<sub>7</sub>) y cicloalquilo sustituido; o

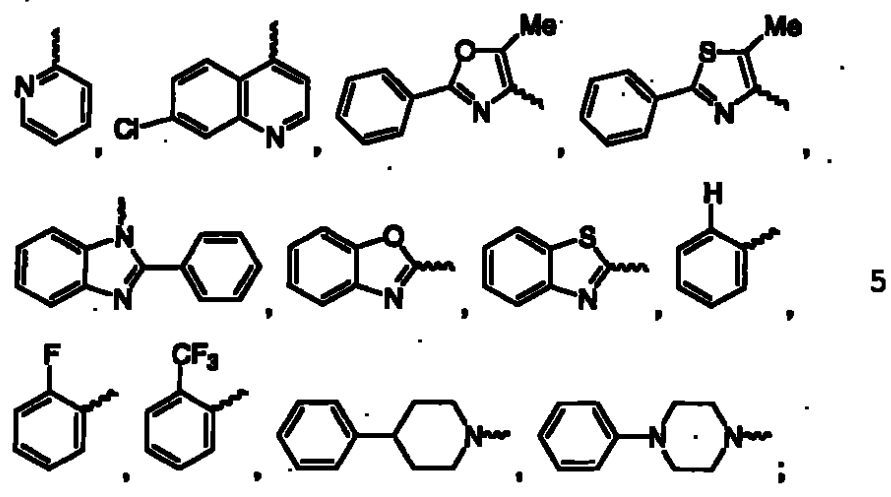
heterocicloalquilo y heterocicloalquilo sustituido; y



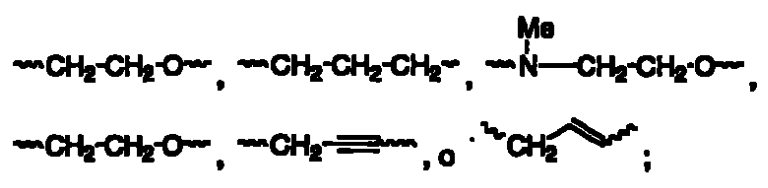
20 4. El compuesto de la reivindicación 1, en el que

A es

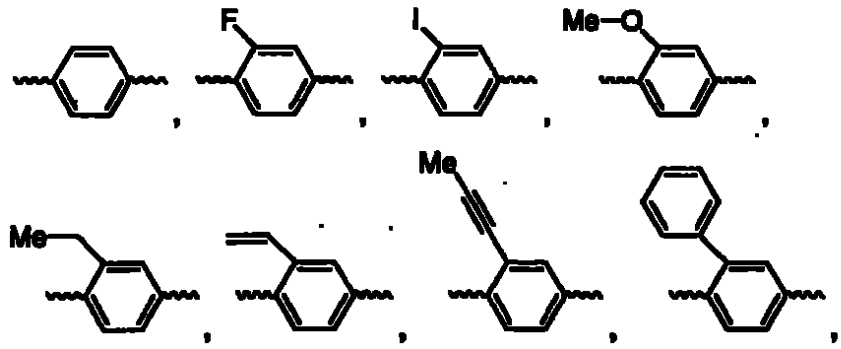
782  
783



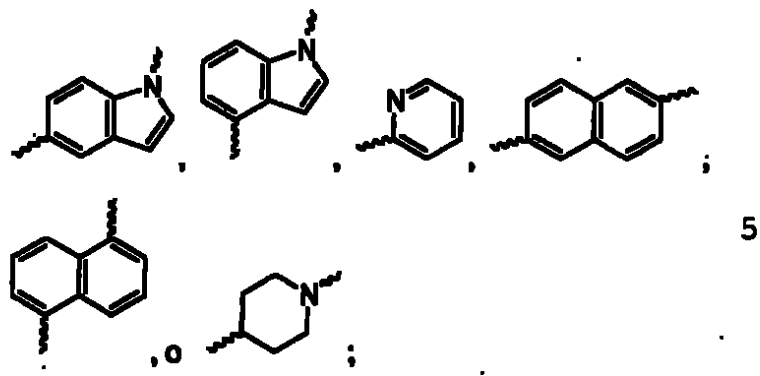
10 X es una cadena de 2 a 5 átomos de longitud seleccionada entre



Q es



283  
784



Y es CH<sub>2</sub>;

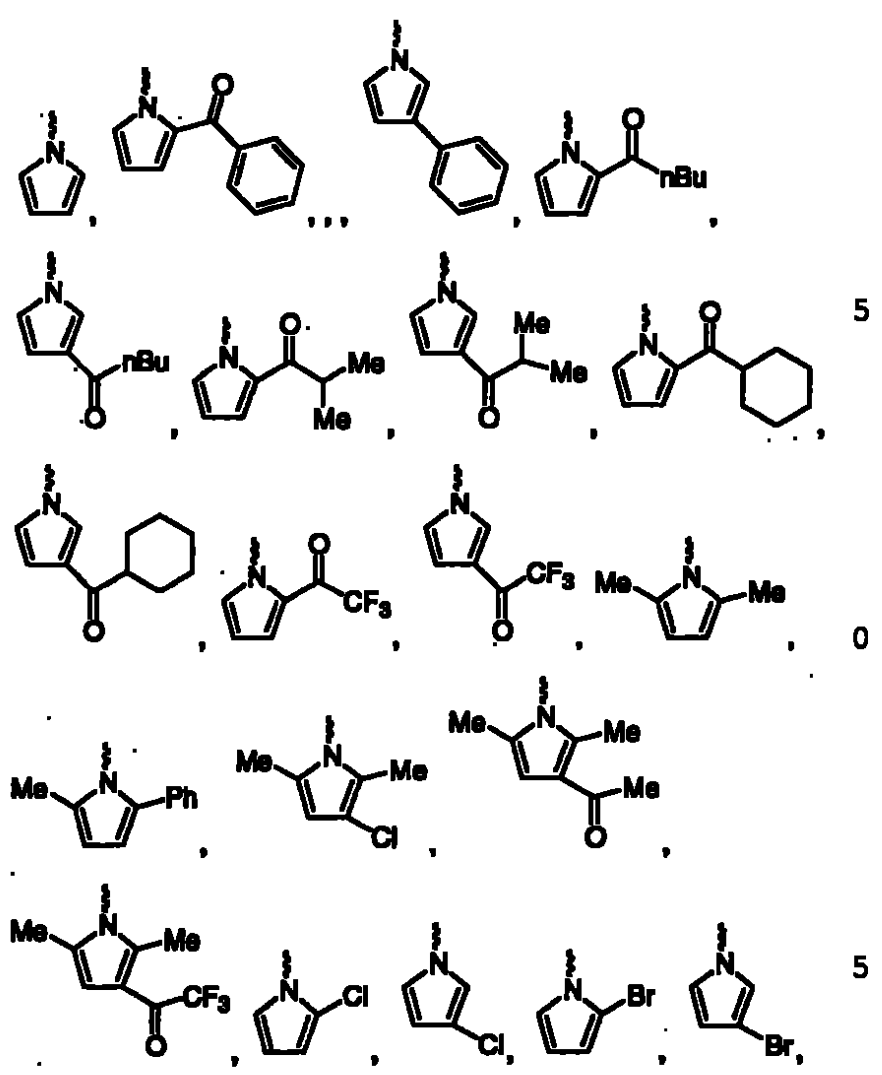
10 Z está ausente;

B es H, halo, alquilo (C<sub>1</sub>-C<sub>6</sub>), halo-alquilo (C<sub>1</sub>-C<sub>6</sub>) o alcoxi (C<sub>1</sub>-C<sub>6</sub>);

D es H, Me,

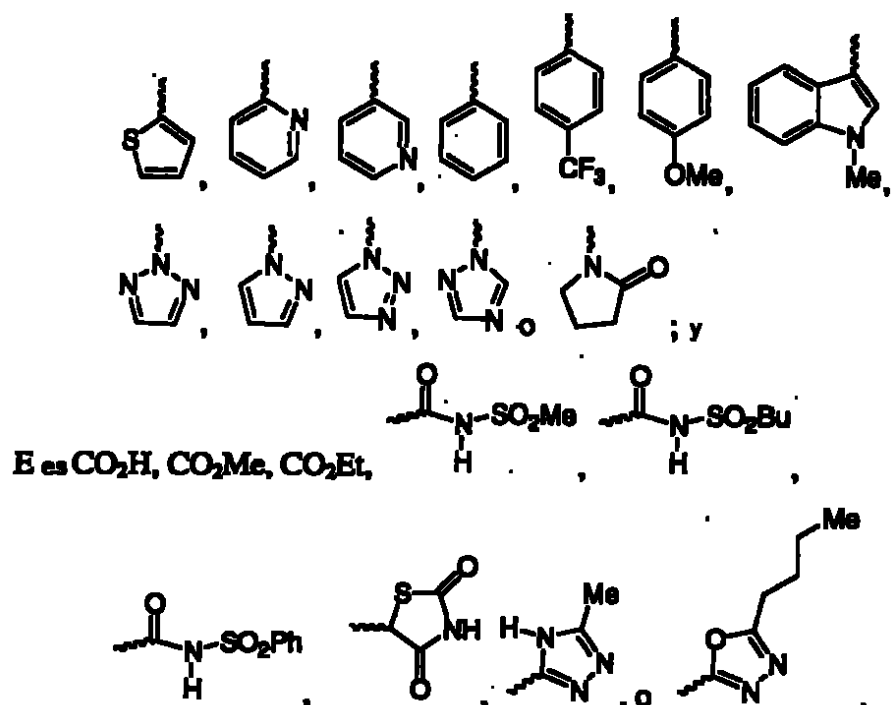
784  
785

441



786  
786

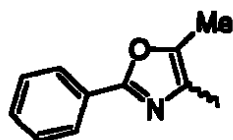
442



E es  $\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{Me}$ ,  $\text{CO}_2\text{Et}$ ,

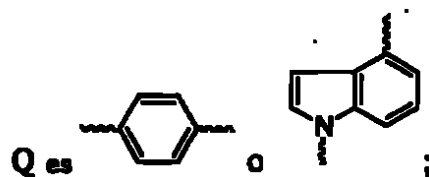
5. El compuesto de la reivindicación 1, en el que

A es



5

X es  $\text{---CH}_2\text{CH}_2\text{O---}$  o  $\text{---CH}_2\text{CH}_2\text{CH}_2\text{---}$ ;



0

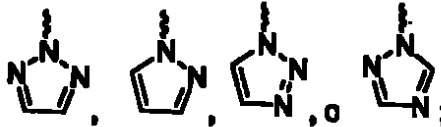
Y es  $\text{CH}_2$ ;



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987

Z está ausente;

B es H;

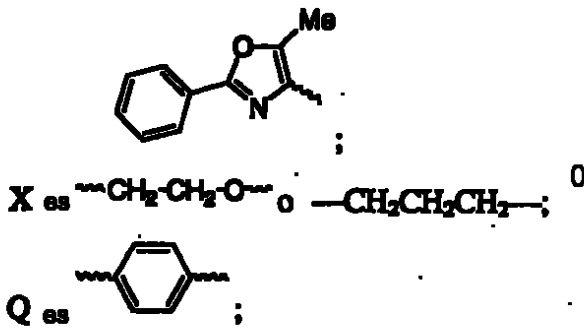
D es H, , 527; y

E es CO<sub>2</sub>H.

5

6. El compuesto de la reivindicación 1, en el que

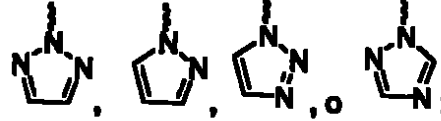
A es



Y es CH<sub>2</sub>;

15 Z está ausente;

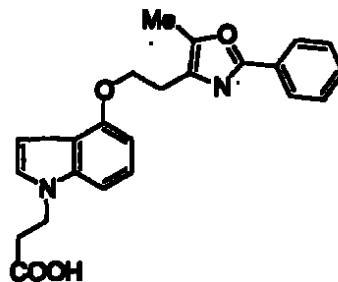
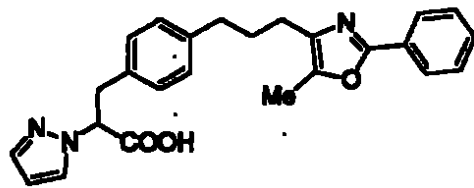
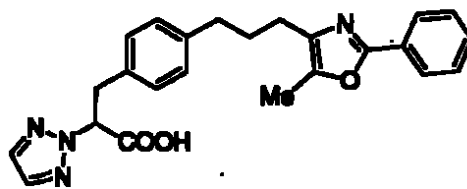
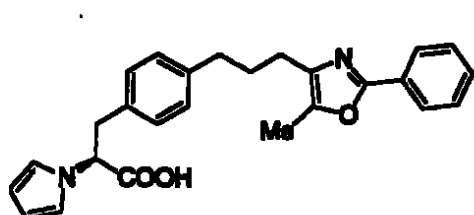
B es H;

D es H, , 529; y

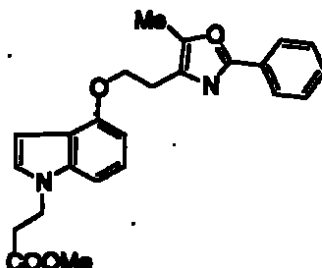
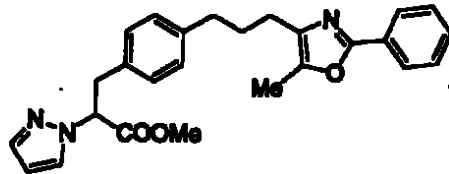
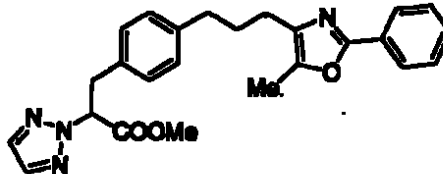
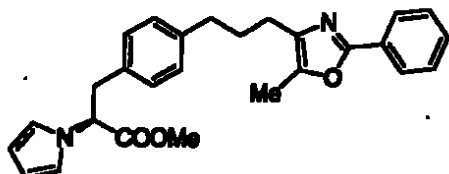
E es CO<sub>2</sub>H.

20 7. El compuesto que es:

444



8. El compuesto que es:



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9. El compuesto que es:

(R)-2-(2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-  
fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

(R)-2-Etil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
5 etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(R)-2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-  
fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

Ácido (R)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-  
il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

10 (R)-3-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;

Ácido (R)-2-(3-bromo-pirrol-1-il)-2-metil-3-{4-[2-(5-  
metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Ácido (S)-3,3,3-trifluoro-2-{4-[2-(5-metil-2-fenil-  
15 oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;

Ácido (R)-3,3,3-trifluoro-2-{4-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;

Ácido (R)-2-etil-3-{4-[2-(5-metil-2-fenil-oxazol-4-  
il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

20 Ácido (S)-2-etil-3-{4-[2-(5-metil-2-fenil-oxazol-4-  
il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido (R)-2-propil-3-{4-[2-(5-metil-2-fenil-oxazol-4-  
il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Ácido (S)-2-propil-3-{4-[2-(5-metil-2-fenil-oxazol-4-  
25 il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

281  
790

- Ácido (S)-3,3,3-trifluoroetil-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- Ácido (R)-3,3,3-trifluoroetil-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- 5 Ácido (R) 2-fluorometil-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- Ácido (S) 2-fluorometil-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- 10 Ácido (S)-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-2-fluorometil-2-pirrol-1-il-propiónico;
- Ácido (R)-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-2-fluorometil-2-pirrol-1-il-propiónico;
- (S)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;
- 15 (R)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;
- (S)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;
- (R)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;
- 20 (S)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;
- Ácido (R)-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- 25 Ácido (S)-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-fenil}-

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791

- 2-pirrol-1-il-propiónico;
- (R)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-(S)-  
pirrol-1-il-etil)-4H-1,2,4-triazol;
- (S)-3-{4-[2-(5-Etil-piridin-2-il)-etoxi]-fenil}-1-(S)-  
5 pirrol-1-il-etil)-4H-1,2,4-triazol;
- Ácido (R)-2-(3-bromo-pirrol-1-il)-3-{4-[2-(5-etil-  
piridin-2-il)-etoxi]-fenil}-propiónico;
- Ácido (S)-2-(3-bromo-pirrol-1-il)-3-{4-[2-(5-etil-  
piridin-2-il)-etoxi]-fenil}-propiónico;
- 10 Ácido (S)-3,3,3-trifluoro-3-{4-[2-(5-etil-piridin-2-  
il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (R)-3,3,3-trifluoro-3-{4-[2-(5-etil-piridin-2-  
il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (R)-2-etil-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-  
15 fenil}-2-pirrol-1-il-propiónico;
- Ácido (S)-2-etil-3-{4-[2-(5-etil-piridin-2-il)-etoxi]-  
fenil}-2-pirrol-1-il-propiónico;
- Ácido (R)-2-propil-3-{4-[2-(5-etil-piridin-2-il)-  
etoxi]-fenil}-2-pirrol-1-il-propiónico;
- 20 Ácido (S)-2-propil-3-{4-[2-(5-etil-piridin-2-il)-  
etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (S)-3,3,3-trifluoroetil-3-{4-[2-(5-etil-piridin-  
2-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (R)-3,3,3-trifluoroetil-3-{4-[2-(5-etil-piridin-  
25 2-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

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- Ácido (S)-2-pirrol-1-il-3-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-propiónico;
- Ácido (R)-2-pirrol-1-il-3-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-propiónico;
- 5 (R)-2-(2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil])-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;
- (S)-2-(2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil])-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;
- (R)-2-Etil-2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil])-1-pirrol-1-il-etil)-1,3,4-oxadiazol;
- 10 (S)-2-Etil-2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil])-1-pirrol-1-il-etil)-1,3,4-oxadiazol;
- (R)-2-2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-1-pirrol-1-il-etil)-1,3,4-oxadiazol;
- 15 (S)-2-2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-1-pirrol-1-il-etil)-1,3,4-oxadiazol;
- Ácido (R)-2-metil-3-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;
- Ácido (S)-2-metil-3-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;
- 20 (R)-3-Metil-5-(3-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;
- (S)-3-Metil-5-(3-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;
- 25 Ácido (R)-2-(3-bromo-pirrol-1-il)-3-[4-(4'-

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trifluorometil-bifenil-4-ilmetoxi)-fenil]-propiónico;

Ácido (R)-2-(3-bromo-pirrol-1-il)-3-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-propiónico;

Ácido (S)-3,3,3-trifluoro-2-[4-(4'-trifluorometil-  
5 bifenil-4-ilmetoxi)-bencil]-2-pirrol-1-il-propiónico;

Ácido (R)-3,3,3-trifluoro-2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-bencil]-2-pirrol-1-il-propiónico;

Ácido (R)-2-etil-3-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;

10 Ácido (S)-2-etil-3-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;

Ácido (R)-2-propil-3-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;

Ácido (S)-2-propil-3-[4-(4'-trifluorometil-bifenil-4-  
15 ilmetoxi)-fenil]-2-pirrol-1-il-propiónico;

Ácido (S)-3,3,3-trifluoroetil-2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-bencil]-2-pirrol-1-il-propiónico;

Ácido (R)-3,3,3-trifluoroetil-2-(4-(4'-trifluorometil-bifenil-4-ilmetoxi)-bencil)-2-pirrol-1-il-propiónico;

20 Ácido (R) 2-fluorometil-2-(4-(4'-trifluorometil-bifenil-4-ilmetoxi)-bencil)-2-pirrol-1-il-propiónico;

Ácido (S) 2-fluorometil-2-[4-(4'-trifluorometil-bifenil-4-ilmetoxi)-bencil]-2-pirrol-1-il-propiónico;

(S)-2-3-[4-[2-(Metil-piridin-2-il-amino)-etoxi]-  
25 fenil]-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

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- (R)-2-3-{4-[2-(Metil-piridin-2-il-amino)-etoxi]-  
fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;
- (S)-2-Etil-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-  
fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;
- 5 (R)-2-Etil-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-  
fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;
- (R)-2-2-{4-[2-(Metil-piridin-2-il-amino)-etoxi]-  
fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;
- (S)-2-2-{4-[2-(Metil-piridin-2-il-amino)-etoxi]-  
10 fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;
- Ácido (R)-2-metil-3-{4-[2-(metil-piridin-2-il-amino)-  
etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (S)-2-metil-3-{4-[2-(metil-piridin-2-il-amino)-  
etoxi]-fenil}-2-pirrol-1-il-propiónico;
- 15 (R)-3-Metil-5-(3-{4-[2-(metil-piridin-2-il-amino)-  
etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;
- (S)-3-Metil-5-(3-{4-[2-(metil-piridin-2-il-amino)-  
etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;
- Ácido (R)-2-(3-bromo-pirrol-1-il)-3-{4-[2-(metil-  
20 piridin-2-il-amino)-etoxi]-fenil}-propiónico;
- Ácido (S)-2-(3-bromo-pirrol-1-il)-3-{4-[2-(metil-  
piridin-2-il-amino)-etoxi]-fenil}-propiónico;
- Ácido (S)-3,3,3-trifluoro-2-{4-[2-(metil-piridin-2-il-  
amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- 25 Ácido (R)-3,3,3-trifluoro-2-{4-[2-(metil-piridin-2-il-



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- amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- Ácido (R)-2-etil-3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (S)-2-etil-3-{4-[2-(metil-piridin-2-il-amino)-5 etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (R)-2-propil-3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (S)-2-propil-3-{4-[2-(metil-piridin-2-il-amino)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- 10 Ácido (S)-3,3,3-trifluoroetil-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- Ácido (R)-3,3,3-trifluoroetil-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico;
- Ácido (R) 2-fluorometil-2-{4-[2-(metil-piridin-2-il-15 amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico; o
- Ácido (S) 2-fluorometil-2-{4-[2-(metil-piridin-2-il-amino)-etoxi]-bencil}-2-pirrol-1-il-propiónico.

10. El compuesto que es:
- 20 Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido (S)-2-(2-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido (S)-2-(3-benzoil-pirrol-1-il)-3-{4-[2-(5-metil-25 2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

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- Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-propiónico;
- Ácido (S)-3-{4-[2-(benzooxazol-2-il-metil-amino)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-propiónico;
- 5 N-(S)-(3-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propionil)-bencenosulfonamida;
- N-(S)-(3-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propionil)-metanosulfonamida;
- Ácido (S)-2-(3-isobutiril-pirrol-1-il)-3-{4-[2-(5-  
10 metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido (S)-2-(3-Ciclohexanocarbonil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido (S)-3-{4-[2-(benzooxazol-2-il-metil-amino)-etoxi]-fenil}-2-(3-ciclohexanocarbonil-pirrol-1-il)-  
15 propiónico;
- Ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-[4-(2-fluoro-benciloxi)-fenil]-propiónico;
- Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-  
20 propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-4-il-propiónico;
- 2-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-2H-tetrazol;
- 25 Ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-

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etoxi]-fenil)-2-tiofen-2-il-propiónico;

N-(2,2-Dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-fenil}-propionil)-metanosulfonamida;

N-(2-Fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
5 etoxi]-fenil)-2-fenil-propionil)-metanosulfonamida;

Ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[3-(5-  
metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;

Ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[2-(5-  
metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

10 Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-  
fenil)-2-fenil-propiónico;

Ácido (S)-2-(2-acetil-pirrol-1-il)-3-{4-[2-(5-metil-2-  
fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Ácido 3-{4-[2-(benzotiazol-2-ilsulfanil)-etoxi]-  
15 fenil)-2-pirrol-1-il-propiónico;

Ácido (S)-2-pirrol-1-il-3-{4-[2-(2-trifluorometil-  
fenil)-etoxi]-fenil}-propiónico;

Ácido (S)-3-{4-[2-(4-fenil-piperazin-1-il)-etoxi]-  
fenil)-2-pirrol-1-il-propiónico;

20 Ácido (S)-3-{4-[2-(5-metil-2-fenil-tiazol-4-il)-  
etoxi]-fenil)-2-pirrol-1-il-propiónico;

Ácido (S)-2-(3-cloro-2,5-dimetil-pirrol-1-il)-3-{4-[2-  
(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Ácido (S)-3-(4-{2-[(7-cloro-quinolin-4-il)-metil-  
25 amino]-etoxi]-fenil)-2-pirrol-1-il-propiónico;

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- Ácido (S)-2-(3-acetil-2,5-dimetil-pirrol-1-il)-3-{4-[2-(4-metil-2-fenil-oxazol-5-il)-etoxi]-fenil}-propiónico;
- Ácido (S)-2-[2,5-dimetil-3-(2,2,2-trifluoro-acetil)-pirrol-1-il]-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-5 fenil}-propiónico;
- Ácido 3-{4-[2-(2-bencil-bencimidazol-1-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido 2-(3-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- 10 Ácido 2-(2-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido 2-(2-cloro-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido (S)-2-(2-butiril-pirrol-1-il)-3-{4-[2-(5-metil-15 2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-[4-(2-fluoro-benciloxi)-fenil]-propiónico;
- Ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(2-metil-5-fenil-pirrol-1-il)-propiónico;
- 20 Ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-25 fenil}-2-tiofen-2-il-propiónico;

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- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-3-il-propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;
- 5 Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-trifluorofenil)-propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico; (R)
- Ácido 2-(4-metoxi-fenil)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- 10
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-fenil}-2-pirrol-1-il-propiónico;
- Ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;
- 15 Ácido 2,2-dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido 2-fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(2-oxo-pirrolidin-1-il)-propiónico;
- 20
- 2-Etil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-1,3,4-oxadiazol;
- Ácido 3-{4-[3-(5-Metil-2-fenil-oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico;
- 25 Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-

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fenil}-2-piridin-3-il-propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
fenil}-2-fenil-propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
5 fenil}-2-(3-trifluorofenil)-propiónico;

Ácido (R)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-fenil}-2-fenil-propiónico;

Ácido (S)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-  
il)-etoxi]-fenil}-2-pirrol-1-il-propiónico; éster metílico

10 Ácido 3-{5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
indol-1-il}-propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
indol-1-il}-propiónico;

(S)-2-(2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-  
15 fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

(S)-2-Etil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(S)-2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-  
fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

20 (S)-3-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;

Ácido 2-(3-bromo-pirrol-1-il)-2-metil-3-{4-[2-(5-  
metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Ácido 3,3,3-trifluoro-2-{4-[2-(5-metil-2-fenil-oxazol-  
25 4-il)-etoxi]-bencil}-2-pirrol-1-il-propiónico;

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Ácido 2-(4-benciloxi-indol-1-il)-propiónico;

Ácido 3-(1-(4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-bencil)-1H-pirrol-2-il)-propiónico;

Ácido (1-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-1H-5 indol-5-iloxi)-fenil-acético;

Ácido 2-(1-metil-1H-indol-3-il)-3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-propiónico;

Ácido 3-(4-[3-(5-metil-2-fenil-oxazol-4-il)-propoxi]-indol-1-il)-propiónico;

10 Ácido 2-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il)-propiónico;

Ácido 3-(4-[2-(2-trifluorometil-fenil)-etoxi]-indol-1-il)-propiónico;

Ácido (4-[3-(5-metil-2-fenil-oxazol-4-il)-propoxi]-15 indol-1-il)-acético;

Ácido 4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il)-acético;

Ácido 4-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il)-butírico;

20 Ácido 3-(3-fluoro-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-(S)-pirrol-1-il-propiónico;

Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-piridin-4-il-propiónico;

2-Metil-5-(2-(4-[2-(5-metil-2-fenil-oxazol-4-il)-25 etoxi]-fenil)-1-fenil-etil)-2H-tetrazol;

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- 1-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-fenil}-1-fenil-etil)-1H-tetrazol;
- Ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-fenil}-2-tiofen-2-il-propiónico;
- 5 Ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-fenil}-2-tiofen-3-il-propiónico;
- N-(2,2-dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-fenil}-propionil)-metanosulfonamida;
- N-(2-Fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
10 etoxi]-fenil}-2-fenil-propionil)-metanosulfonamida;
- Ácido 3-{3-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
isoxazol-5-il}-2-pirrol-1-il-propiónico;
- Ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[3-(5-  
metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;
- 15 Ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[2-(5-  
metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-  
fenil}-2-fenil-propiónico;
- Ácido 3-{4-[3-(5-metil-2-feniloxazol-4-il)-propil]-  
20 fenil}-2-fenilpropiónico;
- Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
piridin-3-il}-2-pirrol-1-il-propiónico;
- Ácido 3-{6-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-  
piridin-3-il}-2-fenilpropiónico;
- 25 Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-



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piridin-3-il)-2-fenilpropiónico;

Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
piridin-3-il)-2-tiofen-2-il-propiónico;

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
5 fenil}-2-fenil-acrílico;

Ácido {4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]bencilamino}fenilacético;

Éster metílico del ácido {4-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-bencilamino}-fenilacético;

10 Ácido metil-{4-[2-(5-metil-2-fenil-oxazol-4-il)-  
etoxi]-bencilamino}-fenilacético;

Ácido 6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
naftaleno-2-carboxílico;

Ácido 3-{5-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-  
15 naftalen-1-il)-2-pirrol-1-il-propiónico;

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-  
fenil}-2-1,2,3-triazol-1-il-propiónico; éster etílico;

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-  
fenil}-2-1,2,3-triazol-1-il-propiónico;

20 Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-  
fenil}-2-pirazol-1-il-propiónico;

Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-  
fenil}-2-1,2,4-triazol-1-il-propiónico;

5-metil-2-fenil-4-prop-2-eniloxazol;

25 Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-

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- inil]-fenil}-2-piridin-3-il-propiónico;
- Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-piridin-3-il-propiónico;
- Ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-5 fenil}-2-piridin-3-il-propiónico;
- Ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;
- Ácido 2-bifenil-4-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-propiónico;
- 10 Ácido 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-propiónico;
- Ácido 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;
- Ácido 2-(5-metil-isoxazol-3-il)-3-{4-[3-(5-metil-2-15 fenil-oxazol-4-il)-propil]-fenil}-propiónico;
- Ácido 2-(3-metil-isoxazol-5-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;
- Ácido (S)-3-(4-{[(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil}-fenil)-2-pirrol-1-il-propiónico;
- 20 Ácido (S)-3-(4-{[acetil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil}-fenil)-2-pirrol-1-il-propiónico;
- Ácido (S)-3-(4-{[metil-(5-metil-2-fenil-oxazol-4-ilmetil)-amino]-metil}-fenil)-2-pirrol-1-il-propiónico;
- Ácido (S)-3-(4-{[2-(5-metil-2-fenil-oxazol-4-il)-25 etilamino]-metil}-fenil)-2-pirrol-1-il-propiónico;

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- Ácido (S)-3-[4-({bencil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico;
- Ácido (S)-3-[4-({Benzoil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico;
- 5 Ácido (S)-3-[4-({acetil-[2-(5-metil-2-fenil-oxazol-4-il)-etil]-amino}-metil)-fenil]-2-pirrol-1-il-propiónico;
- Ácido 4-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-butírico;
- Ácido 3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-
- 10 piperidin-4-il}-2-pirrol-1-il-propiónico;
- Ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil}-2-pirrol-1-il-propiónico;
- Ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propiónico;
- 15 Ácido 3-{3-metoxi-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido butano-1-sulfónico; (3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propionil)-amida;
- N-(3-{4-[3-(5-Metil-2-fenil-oxazol-4-il)-propil]-
- 20 fenil}-2-pirrol-1-il-propionil)-metanosulfonamida;
- Ácido 3-{3-yodo-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-3-prop-1-inil-fenil}-2-pirrol-1-il-propiónico;
- 25 Ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-

- etoxi]-fenil)-2-pirrol-1-il-propiónico;
- Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bifenil-3-il}-2-pirrol-1-il-propiónico;
- Ácido 4-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-5 fenil}-2-pirrol-1-il-butírico;
- Ácido 2-pirrol-1-il-4-(4-trifluorometanosulfonil-fenil)-butírico; éster metílico
- Ácido 3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-piperidin-4-il}-2-pirrol-1-il-propiónico;
- 10 Ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil}-2-pirrol-1-il-propiónico;
- Ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propiónico;
- Ácido 3-{3-metoxi-4-[2-(5-metil-2-fenil-oxazol-4-il)-15 etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido butano-1-sulfónico; (3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propionil)-amida;
- N-(3-{4-[3-(5-Metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propionil)-metanosulfonamida;
- 20 Ácido 3-{3-yodo-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;
- Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-3-prop-1-inil-fenil}-2-pirrol-1-il-propiónico;
- Ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-25 etoxi]-fenil}-2-pirrol-1-il-propiónico;

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Ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
bifenil-3-il}-2-pirrol-1-il-propiónico.

11. El compuesto que es:

5 Éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido (S)-2-(2-benzoil-pirrol-1-  
il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
propiónico;

10 Éster metílico del ácido (S)-2-(3-benzoil-pirrol-1-  
il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
propiónico;

Éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-  
15 propiónico;

Éster metílico del ácido (S)-3-{4-[2-(benzooxazol-2-  
il-metil-amino)-etoxi]-fenil}-2-(3-fenil-pirrol-1-il)-  
propiónico;

N-(S)-(3-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-  
20 fenil}-2-pirrol-1-il-propionil)-bencenosulfonamida;

N-(S)-(3-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-  
fenil}-2-pirrol-1-il-propionil)-metanosulfonamida;

Éster metílico del ácido (S)-2-(3-isobutiril-pirrol-1-  
il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
25 propiónico;

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Éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido (S)-3-{4-[2-(Benzooxazol-2-il-5 metil-amino)-etoxi]-fenil}-2-(3-ciclohexanocarbonil-pirrol-1-il)-propiónico;

Éster metílico del ácido (S)-2-(3-ciclohexanocarbonil-pirrol-1-il)-3-[4-(2-fluoro-benciloxi)-fenil]-propiónico;

Éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-[2-(2,2,2-trifluoro-acetil)-pirrol-1-il]-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-4-il-propiónico;

2-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-2H-tetrazol;

Éster metílico del ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-2-il-propiónico;

N-(2,2-Dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propionil)-metanosulfonamida;

N-(2-Fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propionil)-metanosulfonamida;

Éster metílico del ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;

Éster metílico del ácido 2-(5-metil-2-fenil-oxazol-4-

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il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propil]-fenil}-2-fenil-propiónico;

5 Éster metílico del ácido (S)-2-(2-acetil-pirrol-1-il)-  
3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
propiónico;

Éster metílico del ácido 3-{4-[2-(benzotiazol-2-  
ilsulfanil)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

10 Éster metílico del ácido (S)-2-pirrol-1-il-3-{4-[2-(2-  
trifluorometil-fenil)-etoxi]-fenil}-propiónico;

Éster metílico del ácido (S)-3-{4-[2-(4-fenil-  
piperazin-1-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-  
15 tiazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido (S)-2-(3-cloro-2,5-dimetil-  
pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-  
fenil}-propiónico;

Éster metílico del ácido (S)-3-(4-{2-[(7-cloro-  
20 quinolin-4-il)-metil-amino]-etoxi}-fenil)-2-pirrol-1-il-  
propiónico;

Éster metílico del ácido (S)-2-(3-acetil-2,5-dimetil-  
pirrol-1-il)-3-{4-[2-(4-metil-2-fenil-oxazol-5-il)-etoxi]-  
fenil}-propiónico;

25 Éster metílico del ácido (S)-2-[2,5-dimetil-3-(2,2,2-

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trifluoro-acetil)-pirrol-1-il]-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido 3-{4-[2-(2-fenil-bencimidazol-1-il)-etoxi]-fenil}-2-pirrol-1-il-(5-

5 propiónico;

Éster metílico del ácido 2-(3-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido 2-(2-bromo-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

10 Éster metílico del ácido 2-(2-cloro-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido (S)-2-(2-butiril-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

15 Éster metílico del ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-[4-(2-fluoro-benciloxi)-fenil]-propiónico;

Éster metílico del ácido (S)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(2-metil-5-fenil-pirrol-1-il)-propiónico;

20 Éster metílico del ácido (S)-2-(2,5-dimetil-pirrol-1-il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico;

25 Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-



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- oxazol-4-il)-etoxi]-fenil}-2-tiofen-2-il-propiónico;
- Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-3-il-propiónico;
- Éster metílico del ácido 3-{4-(2-(5-metil-2-fenil-oxazol-4-il)-etoxi)-fenil}-2-fenil-propiónico;
- 5 oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;
- éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-trifluorofenil)-propiónico;
- éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico; (R)
- 10 Éster metílico del ácido 2-(4-metoxi-fenil)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etilamino]-fenil}-2-pirrol-1-il-propiónico;
- Éster metílico del ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;
- 15 fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;
- Éster metílico del ácido 2,2-dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico;
- Éster metílico del ácido 2-fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;
- 20 Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(2-oxo-pirrolidin-1-il)-propiónico;
- 2-Etil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-1,3,4-oxadiazol;
- 25 Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-

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oxazol-4-il)-propionil]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-3-il-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-(3-trifluorofenil)-propiónico;

Éster metílico del ácido (R)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propiónico;

10 Éster metílico del ácido (S)-2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-propiónico;

15 Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-indol-1-il}-propiónico;

(S)-2-(2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-5-propil-1,3,4-oxadiazol;

(S)-2-Etil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(S)-2-{4-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-pirrol-1-il-etil)-1,3,4-oxadiazol;

(S)-3-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-(S)-pirrol-1-il-etil)-4H-1,2,4-triazol;

25 Éster metílico del ácido 2-(3-bromo-pirrol-1-il)-2-

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metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
propiónico;

Éster metílico del ácido 3,3,3-trifluoro-2-{4-[2-(5-  
metil-2-fenil-oxazol-4-il)-etoxi]-bencil}-2-pirrol-1-il-

5 propiónico;

Éster metílico del ácido 2-(4-benciloxi-indol-1-il)-  
propiónico;

Éster metílico del ácido 3-(1-{4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propil]-bencil}-1H-pirrol-2-il)-propiónico;

10 Éster metílico del ácido (1-[2-(5-metil-2-fenil-  
oxazol-4-il)-etil]-1H-indol-5-iloxi)-fenil-acético;

Éster metílico del ácido 2-(1-metil-1H-indol-3-il)-3-  
{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
propiónico;

15 Éster metílico del ácido 3-(4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propoxi]-indol-1-il)-propiónico;

Éster metílico del ácido 2-(4-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-indol-1-il)-propiónico;

Éster metílico del ácido 3-(4-[2-(2-trifluorometil-  
20 fenil)-etoxi]-indol-1-il)-propiónico;

Éster metílico del ácido (4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propoxi]-indol-1-il)-acético;

Éster metílico del ácido 4-[2-(5-metil-2-fenil-oxazol-  
4-il)-etoxi]-indol-1-il)-acético;

25 Éster metílico del ácido 4-{4-[2-(5-metil-2-fenil-

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oxazol-4-il)-etoxi]-indol-1-il)-butírico;

Éster metílico del ácido 3-(3-fluoro-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-(S)-pirrol-1-il-propiónico;

5 Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-piridin-4-il-propiónico;

2-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-2H-tetrazol;

1-Metil-5-(2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-1-fenil-etil)-1H-tetrazol;

10 Éster metílico del ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-2-il-propiónico;

Éster metílico del ácido 2-metil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-tiofen-3-il-propiónico;

15 N-(2,2-Dimetil-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propionil)-metanosulfonamida;

N-(2-Fluoro-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-fenil-propionil)-metanosulfonamida;

Éster metílico del ácido 3-{3-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-isoxazol-5-il}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 2-(5-metil-2-fenil-oxazol-4-il)-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;

25 Éster metílico del ácido 2-(5-metil-2-fenil-oxazol-4-

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il)-3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-  
propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propil]-fenil}-2-fenil-propiónico;

5 Éster metílico del ácido 3-{4-[3-(5-metil-2-  
feniloxazol-4-il)-propil]-fenil}-2-fenilpropiónico;

Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-piridin-3-il}-2-pirrol-1-il-propiónico;

10 Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-piridin-3-il}-2-fenilpropiónico;

Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-piridin-3-il}-2-fenilpropiónico;

Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-piridin-3-il}-2-tiofen-2-il-propiónico;

15 Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-fenil}-2-fenil-acrílico;

Éster metílico del ácido {4-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-bencilamino}-fenilacético;

20 Éster metílico del ácido {4-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-bencilamino}-fenilacético;

Éster metílico del ácido metil-{4-[2-(5-metil-2-fenil-  
oxazol-4-il)-etoxi]-bencilamino}-fenilacético;

Éster metílico del ácido 6-[2-(5-metil-2-fenil-oxazol-  
4-il)-etoxi]-naftaleno-2-carboxílico;

25 Éster metílico del ácido 3-{5-[3-(5-metil-2-fenil-

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oxazol-4-il)-propil]-naftalen-1-il)-2-pirrol-1-il-  
propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propil]-fenil}-2-1,2,3-triazol-1-il-

5 propiónico; éster etílico

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propil]-fenil}-2-1,2,3-triazol-1-il-  
propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-  
10 oxazol-4-il)-propil]-fenil}-2-pirazol-1-il-propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propil]-fenil}-2-1,2,4-triazol-1-il-  
propiónico;

5-Metil-2-fenil-4-prop-2-eniloxazol;

15 Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-  
oxazol-4-il)-prop-1-inil]-fenil}-2-piridin-3-il-propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propil]-fenil}-2-piridin-3-il-propiónico;

Éster metílico del ácido 3-{4-[3-(5-metil-2-fenil-  
20 oxazol-4-il)-propil]-fenil}-2-piridin-3-il-propiónico;

Éster metílico del ácido 2-bifenil-4-il-3-{4-[3-(5-  
metil-2-fenil-oxazol-4-il)-propil]-fenil}-propiónico;

Éster metílico del ácido 2-bifenil-4-il-3-{4-[3-(5-  
metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil}-propiónico;

25 Éster metílico del ácido 2-bifenil-3-il-3-{4-[3-(5-

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metil-2-fenil-oxazol-4-il)-prop-1-inil]-fenil)-propiónico;

Éster metílico del ácido 2-bifenil-3-il-3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-propiónico;

Éster metílico del ácido 2-(5-metil-isoxazol-3-il)-3-  
5 {4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-  
propiónico;

Éster metílico del ácido 2-(3-metil-isoxazol-5-il)-3-  
{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-  
propiónico;

10 Éster metílico del ácido (S)-3-(4-[(5-metil-2-fenil-  
oxazol-4-ilmetil)-amino]-metil)-fenil)-2-pirrol-1-il-  
propiónico;

Éster metílico del ácido (S)-3-(4-([acetil-(5-metil-2-  
fenil-oxazol-4-ilmetil)-amino)-metil)-fenil)-2-pirrol-1-il-  
15 propiónico;

Éster metílico del ácido (S)-3-(4-([metil-(5-metil-2-  
fenil-oxazol-4-ilmetil)-amino)-metil)-fenil)-2-pirrol-1-il-  
propiónico;

Éster metílico del ácido (S)-3-(4-([2-(5-metil-2-  
20 fenil-oxazol-4-il)-etilamino)-metil)-fenil)-2-pirrol-1-il-  
propiónico;

Éster metílico del ácido (S)-3-[4-([bencil-[2-(5-  
metil-2-fenil-oxazol-4-il)-etil)-amino]-metil)-fenil)-2-  
pirrol-1-il-propiónico;

25 Éster metílico del ácido (S)-3-[4-([benzoil-[2-(5-

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metil-2-fenil-oxazol-4-il)-etil)-amino)-metil)-fenil-2-  
pirrol-1-il-propiónico;

Éster metílico del ácido (S)-3-[4-({acetil-[2-(5-  
metil-2-fenil-oxazol-4-il)-etil]-amino)-metil)-fenil)-2-  
5 pirrol-1-il-propiónico;

Éster metílico del ácido 4-{4-[3-(5-metil-2-fenil-  
oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-butírico;

Éster metílico del ácido 3-{1-[3-(5-metil-2-fenil-  
oxazol-4-il)-propil]-piperidin-4-il}-2-pirrol-1-il-  
10 propiónico;

Éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-  
fenil-oxazol-4-il)-propenil]-fenil}-2-pirrol-1-il-  
propiónico;

Éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-  
15 fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{3-metoxi-4-[2-(5-metil-2-  
fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido butano-1-sulfónico; (3-{4-[3-  
(5-metil-2-fenil-oxazol-4-il)-propil]-fenil}-2-pirrol-1-il-  
20 propionil)-amida;

N-(3-{4-[3-(5-Metil-2-fenil-oxazol-4-il)-propil]-  
fenil}-2-pirrol-1-il-propionil)-metanosulfonamida;

Éster metílico del ácido 3-{3-yodo-4-[2-(5-metil-2-  
fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

25 Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-



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oxazol-4-il)-etoxi]-3-prop-1-inil-fenil)-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-pirrol-1-il-propiónico;

5 Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bifenil-3-il)-2-pirrol-1-il-propiónico;

Éster metílico del ácido 4-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-2-pirrol-1-il-butírico;

Éster metílico del ácido 2-pirrol-1-il-4-(4-10 trifluorometanosulfonil-fenil)-butírico; éster metílico

Éster metílico del ácido 3-{1-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-piperidin-4-il)-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propenil]-fenil)-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{3-metoxi-4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{3-metoxi-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil)-2-pirrol-1-il-propiónico;

Éster metílico del ácido butano-1-sulfónico; (3-{4-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-fenil)-2-pirrol-1-il-propionil)-amida;

N-(3-{4-[3-(5-Metil-2-fenil-oxazol-4-il)-propil]-25 fenil)-2-pirrol-1-il-propionil)-metanosulfonamida;

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Éster metílico del ácido 3-{3-yodo-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-3-prop-1-inil-fenil}-2-pirrol-1-il-5 propiónico;

Éster metílico del ácido 3-{3-etil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-2-pirrol-1-il-propiónico;

Éster metílico del ácido 3-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-bifenil-3-il}-2-pirrol-1-il-propiónico.

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12. Una composición farmacéutica que comprende un compuesto de la reivindicación 1, mezclado con un vehículo, diluyente o excipiente.

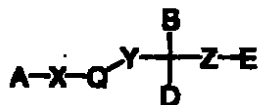
15 13. Un procedimiento para tratar, prevenir o controlar la diabetes mellitus no dependiente de insulina, la obesidad, la hiperglucemia, la hiperlipidemia, la hipercolesterolemia, la aterosclerosis, la hipertrigliceridemia, la hiperinsulinemia o el síndrome de  
20 resistencia a insulina en un mamífero, que comprende administrar al mamífero en necesidad del mismo una cantidad eficaz de un compuesto de la reivindicación 1.

14. Un procedimiento para modular la actividad de PPAR,  
25 reducir la glucosa en sangre o modular la diferenciación de

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adipocitos en un mamífero, que comprende administrar a un mamífero una cantidad eficaz de un modulador de PPAR de fórmula I, II o III.

- 5 15. un procedimiento para preparar un compuesto de fórmula I,



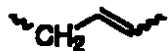
I

10 en la que:

A es arilo y arilo sustituido,  
heteroarilo y heteroarilo sustituido,  
heteroarilo condensado y heteroarilo condensado sustituido,

- 15 cicloalquilo (C<sub>3</sub>-C<sub>7</sub>) y cicloalquilo sustituido, o heterocicloalquilo y heterocicloalquilo sustituido;

X es una cadena de 2 a 5 átomos de longitud seleccionada entre  $\sim\text{CH}_2\text{O}\sim$ ,  $\sim\text{CH}_2\text{CH}_2\text{O}\sim$ ,  $\sim\text{CH}_2\text{CH}_2\text{CH}_2\sim$ ,  $\sim\text{CH}_2\equiv\sim$ , 533 o



534, indicando "535 un punto de unión;

- 20 Q es arilo o arilo sustituido;

heteroarilo o heteroarilo sustituido;  
heteroarilo condensado o heteroarilo condensado

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sustituido; con la condición de que cuando q es un heteroarilo de cinco miembros, el punto de unión de X a Q no está en el heteroátomo del heteroarilo;

Y y Z, independientemente, están ausentes o son  $(CR_1R_2)_n$  y  $5 (CR_3R_4)_m$ , siendo cada uno de  $R_1-R_4$  independientemente H, halo, alquilo ( $C_1-C_6$ ), hidroxilo, alcoxi ( $C_1-C_6$ ), y siendo cada uno de m y n independientemente 1, 2 ó 3;

B es halo, alquilo ( $C_1-C_6$ ), haloalquilo ( $C_1-C_6$ ) o alcoxi ( $C_1-C_6$ );

10 D es H, -NH-arilo y -NH-arilo sustituido,

alcanoílo ( $C_1-C_6$ ) y alcanoílo ( $C_1-C_6$ ) sustituido,

benzoílo y benzoílo sustituido,

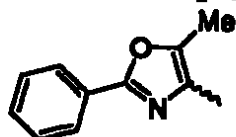
arilo y arilo sustituido,

heteroarilo y heteroarilo sustituido,

15 cicloalquilo ( $C_3-C_7$ ) y cicloalquilo sustituido; o

heterocicloalquilo y heterocicloalquilo sustituido;

E es  $CO_2H$ ; con la condición de que cuando A es



'536 X es  $\sim CH_2-CH_2-O \sim$  537 Q es fenilo, Y y Z son

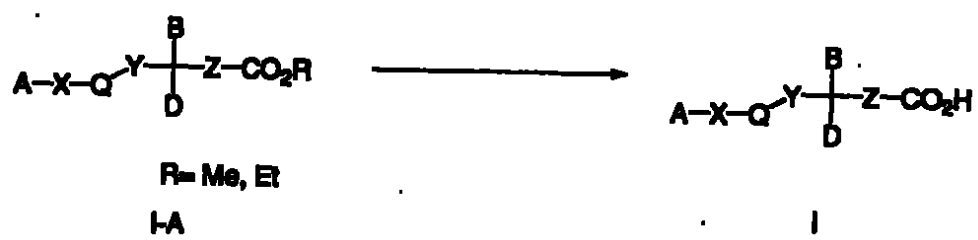
$CH_2$ , B es H, y E es  $CO_2H$ , D no sea pirrolilo.

20 que comprende:

(a) hidrolizar el resto éster del compuesto de fórmula I-A para obtener un resto ácido en condiciones básicas.

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RESUMEN

La presente invención proporciona compuestos de  
Fórmula (I):



en la que A, X, Q, Y, B, D, Z y E tienen cualquiera de  
los valores definidos en la memoria descriptiva, y sales  
10 farmacéuticamente aceptables de los mismos, que son útiles  
como agentes antidiabéticos. También se describen  
composiciones farmacéuticas que comprenden uno o más  
compuestos de Fórmula I, procedimientos para preparar  
compuestos de Fórmula I e intermedios útiles para preparar  
15 compuestos de Fórmula I.

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LUMB, J. Trevor  
Pfizer Inc.  
201 Tabor Road  
Morris Plains, New Jersey 07950  
ETATS-UNIS D'AMERIQUE

RECEIVED  
SEP 4 2002

**PCT**  
NOTIFICATION OF RECEIPT  
OF DEMAND BY COMPETENT INTERNATIONAL  
PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence  
and Administrative Instructions, Section 601(a))

Date of mailing  
(day/month/year)

28-08-2002

Applicant's or agent's file reference  
PC18324AHMB

IMPORTANT NOTIFICATION

International application No.

PCT/IB 02/ 02843

International filing date (day/month/year)

15/07/2002

Priority date (day/month/year)

29/08/2001

Applicant

WARNER-LAMBERT COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

19/08/2002

2. This date of receipt is:



the actual date of receipt of the demand by this Authority (Rule 61.1(b)).



the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).



the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide, Volume II*.



(If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. (+49-89) 2399-0, Tx: 523656 epmu d  
Fax: (+49-89) 2399-4465

Authorized officer

ALMALE MURILLO J

Tel. (+49-89) 2399-8059



# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

LUMB, J. Trevor  
Pfizer Inc.  
201 Tabor Road  
Morris Plains, New Jersey 07950  
ETATS-UNIS D'AMERIQUE

## NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing  
(day/month/year)

04/03/2003

Applicant's or agent's file reference

PC18324AHMB

### IMPORTANT NOTIFICATION

International application No.

PCT/IB 02/ 02843

International filing date (day/month/year)

15/07/2002

Priority date (day/month/year)

29/08/2001

Applicant

WARNER-LAMBERT COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**  
  
The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).  
  
Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.  
  
For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.  
  
The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. (+49-89) 2399-0, Tx: 523656 epmu d  
Fax: (+49-89) 2399-4465

Authorized officer

ALMALE MURILLO J  
Tel. (+49-89) 2399 2828





## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

|                                                                                                   |                                                                                                                        |                                                     |
|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| Applicant's or agent's file reference<br><b>PC18324AHMB</b>                                       | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |                                                     |
| International application No.<br><b>PCT/IB 02/ 02843</b>                                          | International filing date (day/month/year)<br><b>15/07/2002</b>                                                        | Priority date (day/month/year)<br><b>29/08/2001</b> |
| International Patent Classification (IPC) or national classification and IPC<br><b>C07D207/32</b> |                                                                                                                        |                                                     |
| Applicant<br><b>WARNER-LAMBERT COMPANY et al.</b>                                                 |                                                                                                                        |                                                     |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 2 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of \_\_\_\_\_ sheets.

3. This report contains indications relating to the following items:
- I ☒ Basis of the report
  - II ☐ Priority
  - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

|                                                                                                                                                                                                                                             |                                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Date of submission of the demand<br><b>19/08/2002</b>                                                                                                                                                                                       | Date of completion of this report<br><b>27/02/2003</b>                    |
| Name and mailing address of the IPEA/<br> European Patent Office<br>D-80298 Munich<br>Tel. (+49-89) 2399-0, Tx: 523656 epmu d<br>Fax: (+49-89) 2399-4465 | Authorized officer<br><b>TZSCHOPPE D A</b><br><br>Tel. (+49-89) 2399 2828 |

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/IB 02/02843

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B28

**I. Basis of the report**

The basis of this international preliminary examination is the application as originally filed.

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

**V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability**

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

## INTERNATIONAL SEARCH REPORT

Int. Application No.  
PCT/IB 02/02843886  
829

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D207/32 C07D263/32 C07D413/12 C07D403/12 C07D401/12

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)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                       | Relevant to claim No. |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | WO 00 23425 A (NOVONORDISK AS ;REDDY RESEARCH FOUNDATION (IN))<br>27 April 2000 (2000-04-27)<br>page 1, line 5 - line 10; claim 1;<br>examples 1-6                                       | 1-15                  |
| X          | WO 00 66572 A (GURRAM RANGA MADHAVAN ;LOHRAY BRAJ BHUSHAN (IN); RAJAGOPALAN RAMAN) 9 November 2000 (2000-11-09)<br>page 8, line 10 -page 9, line 24; claim 1;<br>examples 2,5,6,32,33,43 | 1-15                  |
| X          | EP 1 067 109 A (ONO PHARMACEUTICAL CO)<br>10 January 2001 (2001-01-10)<br>claim 1; tables 1-20                                                                                           | 1-15                  |
|            | -/-                                                                                                                                                                                      |                       |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claims) 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 underlain 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, each combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

27 September 2002

Date of mailing of the international search report

08/10/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5518 Patenthaus 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax. (+31-70) 340-8515

Authorized officer

Seemann, I

## INTERNATIONAL SEARCH REPORT

Inventor's Application No.  
PCT/IB 02/02843820  
B30

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                       | Relevant to claim No. |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | US 6 274 608 B1 (BURY PAUL STANLEY ET AL)<br>14 August 2001 (2001-08-14)<br>column 1, line 15 - line 25; claim 1                                                         | 1-15                  |
| X          | WO 99 08501 A (REDDY RESEARCH FOUNDATION<br>;REDDY CHEMINOR INC (US))<br>25 February 1999 (1999-02-25)<br>page 4, line 11 -page 5, line 4; claim 1;<br>examples 27,28,32 | 1-15                  |
| X          | WO 01 17994 A (GLAXO GROUP LTD ;COBB<br>JEFFREY EDMOND (US); LAMBERT MILLARD HURST<br>I) 15 March 2001 (2001-03-15)<br>page 6, line 28 -page 8, line 12; claim 1         | 1-15                  |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 02/02843

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:  
see FURTHER INFORMATION sheet PCT/ISA/210
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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## Continuation of Box I.2

The present claims relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, it was intended to be carried out the search for those parts of the claims which appear to be supported and disclosed, namely those parts which represent a reasonable generalisation of the compounds as disclosed in Table 1. However, even for compounds with  $X = -CH_2-CH_2-O-$ ,  $Q = \text{phenylene}$ ,  $Y = -CH_2-$ ,  $Z = -CH_2-$  or absent and  $E = -CO-R$  ( $R = \text{any substituent}$ ) the initial phase of the search revealed such a large number of documents relevant to the issue of novelty that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). Therefore, the cited documents represent only a small and arbitrary selection out of the relevant prior art.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/IB 02/02843

833

| Patent document<br>cited in search report |    | Publication<br>date | Patent family<br>member(s)                                                                                                          | Publication<br>date                                                                                          |
|-------------------------------------------|----|---------------------|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| WO 0023425                                | A  | 27-04-2000          | AU 6190299 A<br>WO 0023425 A1<br>EP 1123279 A1<br>US 2002111344 A1<br>US 2002103188 A1<br>US 2002115657 A1                          | 08-05-2000<br>27-04-2000<br>16-08-2001<br>15-08-2002<br>01-08-2002<br>22-08-2002                             |
| WO 0066572                                | A  | 09-11-2000          | AU 3983100 A<br>BG 106146 A<br>CN 1353699 T<br>CZ 20013832 A3<br>EP 1175412 A1<br>WO 0066572 A1<br>NO 20015259 A<br>TR 200103848 T2 | 17-11-2000<br>31-05-2002<br>12-06-2002<br>17-04-2002<br>30-01-2002<br>09-11-2000<br>15-11-2001<br>22-04-2002 |
| EP 1067109                                | A  | 10-01-2001          | AU 3275999 A<br>EP 1067109 A1<br>WO 9946232 A1                                                                                      | 27-09-1999<br>10-01-2001<br>16-09-1999                                                                       |
| US 6274608                                | B1 | 14-08-2001          | AU 3958200 A<br>WO 0063196 A1                                                                                                       | 02-11-2000<br>26-10-2000                                                                                     |
| WO 9908501                                | A  | 25-02-1999          | AU 1120599 A<br>CN 1280571 T<br>EP 1073643 A2<br>US 2002103215 A1<br>WO 9908501 A2<br>US 6369067 B1<br>US 6444816 B1                | 08-03-1999<br>17-01-2001<br>07-02-2001<br>01-08-2002<br>25-02-1999<br>09-04-2002<br>03-09-2002               |
| WO 0117994                                | A  | 15-03-2001          | AU 7115300 A<br>EP 1210345 A1<br>WO 0117994 A1                                                                                      | 10-04-2001<br>05-06-2002<br>15-03-2001                                                                       |

## REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

|                                                                                         | USUARIO               | RADICADOR |
|-----------------------------------------------------------------------------------------|-----------------------|-----------|
| <b>PATENTE DE INVENCION</b> ✓                                                           | ( )                   | ✓         |
| <b>MODELO DE UTILIDAD</b>                                                               | ( )                   | ✓         |
| - 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.                                                     | ( )                   | ( )       |
| - Comprobante de Pago de las tasas establecidas.                                        | ( )                   | ( )       |
| <b>COMPLETA</b> ( )                                                                     | <b>INCOMPLETA</b> ( ) | ( )       |

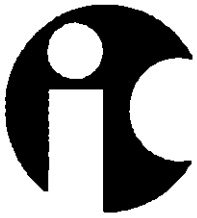
|                                                                                                              |                       |     |
|--------------------------------------------------------------------------------------------------------------|-----------------------|-----|
| <b>DISEÑO INDUSTRIAL</b> ( )                                                                                 |                       |     |
| - Indicación de que se solicita el registro de Diseño Industrial                                             | ( )                   | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta la solicitud.                         | ( )                   | ( ) |
| - Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño. | ( )                   | ( ) |
| - Comprobante de pago de las tasas establecidas                                                              | ( )                   | ( ) |
| <b>COMPLETA</b> ( )                                                                                          | <b>INCOMPLETA</b> ( ) | ( ) |

|                                                                                      |                       |     |
|--------------------------------------------------------------------------------------|-----------------------|-----|
| <b>ESQUEMA DE TRAZADO</b> ( )                                                        |                       |     |
| - Indicación de que solicita el registro de un Esquema de trazado.                   | ( )                   | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta La solicitud. | ( )                   | ( ) |
| - Representación gráfica del esquema de trazado.                                     | ( )                   | ( ) |
| - Comprobante de pago de las tasas establecidas.                                     | ( )                   | ( ) |
| <b>COMPLETA</b> ( )                                                                  | <b>INCOMPLETA</b> ( ) | ( ) |

Firma Responsable:

Fecha:





835

Folio ~~884~~

2020  
Bogotá DC

Doctor  
**CARLOS R. OLARTE**  
Apoderado  
**WARNER-LAMBERT COMPANY LLC.**

|                    |                                   |                         |
|--------------------|-----------------------------------|-------------------------|
| <b>REFERENCIA:</b> | <b>Radicación No.</b>             | <b>04 16880</b>         |
|                    | <b>Solicitud Internacional</b>    | <b>PCT/IB2002/02843</b> |
|                    | <b>Fecha inicio fase nacional</b> | <b>29/03/2004</b>       |
|                    | <b>Trámite</b>                    | <b>011</b>              |
|                    | <b>Evento</b>                     | <b>379</b>              |
|                    | <b>Actuación</b>                  | <b>416</b>              |
|                    | <b>Oficio No.</b>                 | <b>651</b>              |
|                    | <b>Folios</b>                     | <b>001</b>              |

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase  
Dado en Bogotá DC,

12 MAYO 2004

  
**ALIX CARMENZA CÉSPEDES DE VERGEL**  
Jefe de la División de Nuevas Creaciones

202057

**DIVISION DE NUEVAS CREACIONES**

**RADICACIÓN EXPEDIENTE No 04-018880**

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION**

**PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 542**

**DE FECHA 30 DE JULIO DEL 2004 EL TERMINO HABIL SEÑALADO POR LA**

**LEY EXPIRA EL 26 DE OCTUBRE DEL 2004**

**NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.**

**SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.**

**SI**          

**NO**       **X**       

**Bogotá D.C, AGOSTO DE 2006**

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

837

RADICACIÓN: 4-16680

EDICTO No. 13889

**LA SECRETARÍA GENERAL AD-HOC  
HACE SABER:**

Que esta Superintendencia profirió Resolución No. 23305 de 31-AGO-2006. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

**RESUELVE**

**ARTICULO PRIMERO:** Declarar abandonada la solicitud de privilegio de patente de invención que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT), de acuerdo con las razones expuestas en la parte considerativa de la presente resolución.

**ARTICULO SEGUNDO:** Notificar personalmente el contenido de la presente resolución al

doctor Carlos Reinaldo Olarte García, o a quien haga sus veces, en su calidad de apoderado de Warner - Lambert Company L.L.C., entregándole copia de la misma, advirtiéndole que contra ella proceda el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

**NOTIFÍQUESE Y CUMPLASE**

Dada en Bogotá, D.C., a los

31 AGO 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

  
JAIME EMILIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 18-SEP-2006  
Secretaría General Ad-Hoc  
EDICTO No. 13889

Este edicto se desliza hoy 28-SEP-2006 a las cinco (5:00 p.m.)