03 / 107405

Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No** 03-107405

54 **TITULO** MODULADORES DE RECEPTORES ACTIVADOS POR EL PROLIFERADOR DE PEROXISOMAS

51 **CLASIFICACIÓN INTERNACIONAL**

71 **SOLICITANTE** Eli Lilly Company

DOMICILIO

74 **APODERADO** CARLOS R OLARTE

22 **BOGOTA, D C,** DICIEMBRE 05 / 2003

Industria y Comercio
SUPERINTENDENCIA

03 107405 00

SUPERINTENDENCIA Y COMERCIO
Radicacion : 0410/MD 00000000 Folios: 1864
Fecha (MM/D: 2003-12-MD 16:36:21
Tramite : 411 PCT-ENTRADA FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS SOLICITUDES

cación

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

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

(2) SOLICITANTE (71)

Nombre: ELI LILLY AND COMPANY.
Dirección: Indianapolis, Indiana 46285. Estados Unidos de America.
Nacionalidad o Domicilio:
Lugar de Constitución: Indianapolis, Estados Unidos de América.
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@olarteruisbeck.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/US02/15143 Fecha Mayo 24, 2002
Publicación Internacional No. WO 02/100403 Fecha Diciembre 19, 2002

(6) Título (54) MODULADORES DE RECEPTORES ACTIVADOS POR EL PROLIFERADOR DE PEROXISOMAS.

(7) Clasificación Internacional (51) A61K31/42

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Junio 7, 2001	60/296,701

(9) Comprobante de pago No. 82,748 **Fecha** 03-12-11

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

(10) ANEXOS

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

(11) FIGURA CARATERISTICA

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 14.782.747 de Btá T.P. 74.295

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

LISTA DE INVENTORES

Lynn Stacy GOSSETT
7345 Donegal Drive
Indianapolis, Indiana 46217
Estados Unidos de América
Nacionalidad: Estadounidense

Jonathan Edward GREEN
1019 East 96th Street, Apartment D
Indianapolis, Indiana 46240
Estados Unidos de América
Nacionalidad: Estadounidense

James Robert HENRY
7307 Elm Ridge Drive
Indianapolis, Indiana 46236
Estados Unidos de América
Nacionalidad: Estadounidense

Winton Dennis JONES, Junior
1227 East 126th Street
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United States of América
Nacionalidad: Estadounidense

Donald Paul MATTHEWS
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Estados Unidos de América
Nacionalidad: Estadounidense

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Nacionalidad: China

Daryl Lynn SMITH
7656 Madden Lane
Fishers, Indiana 46038
Estados Unidos de América
Nacionalidad: Estadounidense

Jennifer Ann VANCE
132 El Bosque
San Diego, California 95134
Estados Unidos de América
Nacionalidad: Estadounidense

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13828 Springmill Ponds Circle
Carmel, Indiana 46032
Estados Unidos de América
Nacionalidad: Estadounidense

Maria Rosario Gonzalez-García
Avenida de la Industría 30
28108 Alcobendas (Madrid)
España.
Nacionalidad: Española

A

5

SUPERINTENDENCIA Y COMERCIO

Radicacion : 0410/403 00000000 Folios: 1064

Fecha (AMD): 2003-12-05 16:58:21

Tramite : 011 PCI-PRIMI S/V PASE: NRC1 411 PRESENCIAL

Dependencia: 2000 DIVISION DE NUEVAS EMPRESAS

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 82,746

FECHA : NOVIEMBRE 12 DE 2003

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JORGE LUIS GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	11025952	12/11/2003	80,420,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL : $	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

ELI LILLY AND COMPANY

Bilingüe inglés- español otorgado en Indianapolis, Indiana, Estados Unidos el 17 de julio de 2003 y firmado por Peter G. Stringer, Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company.

Todd Rokita — Secretario de Estado

Secretario de Estado de Indiana — Estado de Indiana

APOSTILLA

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

1. País: Estados Unidos de América- Este documento Público
2. ha sido firmado por Catherine Michel
3. Quien ejerce funciones de Secretario de la Corte del Circuito en y para el condado Johnson
4. Lleva el sello del Secretario de la Corte del Circuito en y para el estado de Indiana

CERTIFICADO

5. En Indianapolis, Indiana — 6. El 22 de julio de 2003
7. Por el Secretario de Estado de Indiana — 8. No. A2003- 11279
9. Gran Sello del Estado de Indiana
10. Firma legible de Todd Rokita- Secretario de Estado de Indiana

* Vigente desde el 1 mayo de 2003, todas las apostillas del Secretario de Estado de Indiana tienen el sello impreso electrónicamente.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, fax (317) 233-3283

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 17 de julio de 2003 el suscrito notario Catherine Michel certifica que Peter G. Stringer, domiciliado en 7620 Castleton Farms, West Drive, Indianapolis, Indiana - 46256 Estados Unidos ejercía funciones de Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company, con sede en Indianapolis, Indiana, Estados Unidos.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
inglés - Español - Inglés
Resolución No 2117 del 7 Oct 1987

DESPACHO NOTARIAL ONCE DE ESTE CIRCULO HACE CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE TENDIO A LA VISTA.

10 NOV 2003

BOGOTA D.C. - COLOMBIA
ANA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

El otorgante fundamenta sus certificaciones en este documento: Delegación de Autoridad concerniente a Ciertas Materias de Patentes, suscrito el 20 de enero de 2003: conforme al poder otorgado al Asesor General de la Compañia por el Comité ejecutivo de la Junta Directiva de Eli Lilly and Company.

Firma del notario público Catherine Michel certifica

Sus funciones vencen el 21 de octubre de 2008 - residente en el condado Johnson

Sello de notario público de Indiana

--

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 28 de julio-2003.

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

...ENO NOTARIAL DE ESTE
...CULO HAGO CONSTAR QUE ESTA
...TOCOPIA COINCIDE CON EL
...GINAL QUE HE TENIDO A LA VISTA.
10 NOV 2003
BOGOTA, D.C. - COLOMBIA
...A NAVARRO DE BAUTISTA
ONCE (11)

OLARTERAISBECK

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

Power of Attorney

The undersigned,

ELI LILLY AND COMPANY

domiciled in

Lilly Corporate Center, Indianapolis, Indiana 46285 US

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck 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.

Poder

El suscrito,

ELI LILLY AND COMPANY

domiciliado en

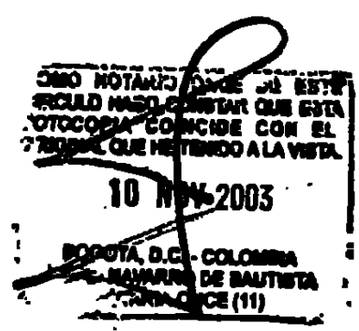
Lilly Corporate Center, Indianapolis, Indiana 46285 US

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck 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: 17 July 2003

City,Country/Ciudad,País: Indianapolis, Indiana, United States of America



SECRETARY OF STATE
STATE OF INDIANA

Todd Rokita
Secretary of State

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1. **Country: United States of America**

2. **This public document has been signed by** *Catherine Michel*

3. **acting in the capacity of circuit court clerk in & for** *Johnson* **County**

4. **and bears the seal/stamp of circuit court clerk in & for the State of Indiana**

Certified

5. **at Indianapolis, Indiana**

6. **this** *Twenty-second* **day of** *July, 2003*

7. **by Secretary of State of Indiana**

8. **No. A2003-** *11279*

9. **Seal/Stamp:**

10. **Signature:**

Todd Rokita

Indiana Secretary of State

*Effective May 1, 2003 all apostilles from the Indiana Secretary of State will have an electronically printed seal.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, Fax (317) 233-3283

NOV 2003

BOGOTA D.C. - COLOMBIA

ONCE (11)

OLARTERAISBECK

OLARTE RAISBECK & FRIEDL, LTDA.
LEGAL & PROFESSIONAL SERVICES

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TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

On this date,
17 July 2003
The undersigned Notary Public certifies:

1. That
Peter G. Stringer
of legal age and domiciled in
7620 Castleton Farms, West Drive, Indianapolis, Indiana 46256 US
signed the foregoing document.

2. That the grantor has executed the foregoing document as Executive Director, International Patents
of ELI LILLY AND COMPANY

3. That ELI LILLY AND COMPANY
having its principal place of business located in
Indianapolis, Indiana, United States of America
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):
Delegation of Authority Concerning Certain Patent Matters, executed January 20, 2003; pursuant to the authority granted to the General Counsel of the Company by the executive Committee of the Board of Directors of Eli Lilly and Company

NOTARY PUBLIC (Signature):



Catherine Michel
My Commission Expires October 21, 2008
Resident of Johnson County

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
mayor de edad y domiciliado
suscribió el documento que antecede.

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

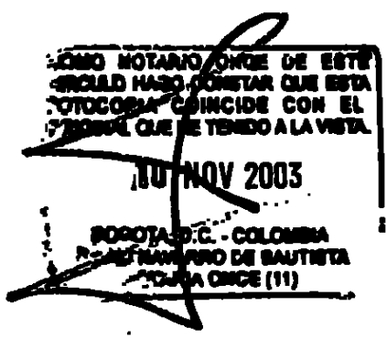
de

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):



PATENT COOPERATION TREATY

Received

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

JANG, Soonhee
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
United States of America

CPM

Date of mailing (day/month/year)	
09 December 2002 (09.12.02)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
X-14528	
International application No.	**International filing date (day/month/year)**
PCT/US02/15143	24 May 2002 (24.05.02)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
GONZALEZ-GARCIA, Maria Rosario Pensamiento 5,1°C 28020 Madrid Spain	ES	ES
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [X] the nationality [X] the residence

Name and Address	State of Nationality	State of Residence
GONZALEZ-GARCIA, Maria, Rosario Pensamiento 5,1°C 28020 Madrid Spain	ES	ES
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

Added applicant/inventor for the purpose of United States only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Kiwa MPAY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

005328118

Date 21 May 2002

PCT INTERNATIONAL APPLICATION COVER LETTER

Regarding the International Application of:

Docket or Reference Number: Docket No. X-14528

Applicant(s): ELI LILLY AND COMPANY, GOSSETT, Lynn, et. al.

Entitled: MODULATORS OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS

To the United States Receiving Office (RO/US):

Accompanying this cover letter is the above-identified International application, including a completed Request form PCT/RO/101 and Fee Sheet. Please process the application according to the provisions of the Patent Cooperation Treaty.

The following requests are made of the RO/US:

1. ☒ PREPARATION AND TRANSMITTAL OF CERTIFIED COPY OF PRIORITY DOCUMENTS

Please prepare and transmit to the International Bureau a certified copy of the United States origin priority documents identified in Box VI of the Request form (37 CFR 1.19 1.451).

To cover the cost of copy preparation and certification (37 CFR 1.19(a)(3) and (b)(1).

☐ a (check) (money order) in the amount of $_____ is attached to this transmittal letter.

☒ the RO/US is hereby authorized to charge the following deposit account no.:05-0840

The appropriate Search fee for the above-named Authority is indicated on the Fee Calculation Sheet (PCT/RO/101 Annex).

2. ☐ SUPPLEMENTAL SEARCH FEES (ONLY WHEN ISA/US CONDUCTS THE INTERNATIONAL SEARCH --Please charge any Supplemental Search fees that may be required by the United States International Searching Authority (ISA/US) to deposit account no.:05-0840

NOTE: SUPPLEMENTAL SEARCH FEES FOR ISA/EP ARE PAYABLE DIRECTLY TO THE EUROPEAN PATENT OFFICE

3. ☐ REQUEST FOR FOREIGN TRANSMITTAL LICENSE -- According to the provisions of 35 U.S.C. 184 and 37CFR 5.11, a license to transmit the accompanying International application to foreign agencies or authorities is hereby requested.

Very truly yours,

Soonhee Jang
Patent Attorney
Reg. No. 44,802

PCT REQUEST X-14528

Original (for SUBMISSION) - printed on 21.05.2002 01:50:33 PM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2002)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	X-14528
I	Title of invention	MODULATORS OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	ELI LILLY AND COMPANY
II-5	Address:	Lilly Corporate Center Indianapolis, IN 46285 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	317.651.3571
II-9	Facsimile No.	317.276.3861
III-1	Applicant and/or Inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	GOSSETT, Lynn, Stacy
III-1-5	Address:	7345 Donegal Drive Indianapolis, IN 46217 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	GREEN, Jonathan, Edward
III-2-5	Address:	1019 East 96th Street, Apartment D Indianapolis, IN 46240 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	HENRY, James, Robert
III-3-5	Address:	7307 Elm Ridge Drive Indianapolis, IN 46236 United States of America
III-3-6	State of nationality	US
III-3-7	State of residence	US
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	JONES, Winton, Dennis, Junior
III-4-5	Address:	1227 East 126th Street Carmel, IN 46033 United States of America
III-4-6	State of nationality	US
III-4-7	State of residence	US
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	MATTHEWS, Donald, Paul
III-5-5	Address:	7736 Wawasee Drive Indianapolis, IN 46250 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US
III-6	Applicant and/or inventor	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	SHEN, Quan, Rong
III-6-5	Address:	10565 Harlowe Drive Fishers, IN 46038 United States of America
III-6-6	State of nationality	CN
III-6-7	State of residence	US

PCT REQUEST

X-14528

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III-7	Applicant and/or inventor	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	SMITH, Daryl, Lynn
III-7-5	Address:	7656 Madden Lane Fishers, IN 46038 United States of America
III-7-6	State of nationality	US
III-7-7	State of residence	US
III-8	Applicant and/or inventor	
III-8-1	This person is:	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	VANCE, Jennifer, Ann
III-8-5	Address:	132 El Bosque San Diego, CA 95134 United States of America
III-8-6	State of nationality	US
III-8-7	State of residence	US
III-9	Applicant and/or inventor	
III-9-1	This person is:	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	WARSHAWSKY, Alan, M.
III-9-5	Address:	13828 Springmill Ponds Circle Carmel, IN 46032 United States of America
III-9-6	State of nationality	US
III-9-7	State of residence	US
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	JANG, Soonhee
IV-1-2	Address:	ELI LILLY AND COMPANY P. O. Box 6288 Indianapolis, IN 46206-6288 United States of America
IV-1-3	Telephone No.	317.651.3571
IV-1-4	Facsimile No.	317.276.3861
IV-1-5	Agent's registration No.	44,802
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	CORNEGLIO, Donald, L.(30,741)

PCT REQUEST X-14528

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V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT (patent and utility model) AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ (patent and utility model) DE (patent and utility model) DK (patent and utility model) DM DZ EC EE (patent and utility model) ES FI (patent and utility model) GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK (patent and utility model) SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
V-3	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-8 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-8	Exclusion(s) from precautionary designations	NONE

PCT REQUEST X-14528

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VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	07 June 2001 (07.06.2001)	
VI-1-2	Number	60/296,701	
VI-1-3	Country	US	
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	1	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	1	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name:	in relation to this international application ELI LILLY AND COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1 (ii)		ELI LILLY AND COMPANY is entitled as employer of the inventor, GOSSETT, Lynn, Stacy
VIII-2-1 (ii)		ELI LILLY AND COMPANY is entitled as employer of the inventor, GREEN, Jonathan, Edward
VIII-2-1 (ii)		ELI LILLY AND COMPANY is entitled as employer of the inventor, HENRY, James, Robert
VIII-2-1 (ii)		ELI LILLY AND COMPANY is entitled as employer of the inventor, JONES, Winton, Dennis, Junior
VIII-2-1 (ii)		ELI LILLY AND COMPANY is entitled as employer of the inventor, MATTHEWS, Donald, Paul
VIII-2-1 (ii)		ELI LILLY AND COMPANY is entitled as employer of the inventor, SHEN, Quan, Rong
VIII-2-1 (ii)		ELI LILLY AND COMPANY is entitled as employer of the inventor, SMITH, Daryl, Lynn
VIII-2-1 (ii)		ELI LILLY AND COMPANY was entitled as employer of the inventor, VANCE, Jennifer, Ann
VIII-2-1 (ii)		ELI LILLY AND COMPANY is entitled as employer of the inventor, WARSHAWSKY, Alan, M.
VIII-2-1 (bi)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)): Name:	in relation to this international application ELI LILLY AND COMPANY is entitled to claim priority of earlier application No. 60/296,701 by virtue of the following:
VIII-3-1 (M)		an assignment from GOSSETT, Lynn, Stacy to ELI LILLY AND COMPANY, dated 06 November 2001 (06.11.2001)
VIII-3-1 (M)		an assignment from GREEN, Jonathan, Edward to ELI LILLY AND COMPANY, dated 06 November 2001 (06.11.2001)
VIII-3-1 (M)		an assignment from HENRY, James, Robert to ELI LILLY AND COMPANY, dated 06 November 2001 (06.11.2001)
VIII-3-1 (M)		an assignment from JONES, Winton, Dennis, Junior to ELI LILLY AND COMPANY, dated 06 November 2001 (06.11.2001)
VIII-3-1 (M)		an assignment from MATTHEWS, Donald, Paul to ELI LILLY AND COMPANY, dated 06 November 2001 (06.11.2001)
VIII-3-1 (M)		an assignment from SHEN, Quan, Rong to ELI LILLY AND COMPANY, dated 06 November 2001 (06.11.2001)
VIII-3-1 (M)		an assignment from SMITH, Daryl, Lynn to ELI LILLY AND COMPANY, dated 06 November 2001 (06.11.2001)
VIII-3-1 (M)		an assignment from VANCE, Jennifer, Ann to ELI LILLY AND COMPANY, dated 13 November 2001 (13.11.2001)
VIII-3-1 (M)		an assignment from WARSHAWSKY, Alan, M. to ELI LILLY AND COMPANY, dated 06 November 2001 (06.11.2001)

VIII-3-1 (b)	This declaration is made for the purposes of:	AP: (GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

PCT REQUEST X-14528

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IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	10	-
IX-2	Description	406	-
IX-3	Claims	27	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	444	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Other (specified):	Return Receipt Postcard	-
IX-18	Other (specified):	Delegation of Authority	-
IX-18	Other (specified):	PCT International Application Cover Letter	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	Soonhee Jang	
X-1-1	Name	ELI LILLY AND COMPANY	
X-1-2	Name of signatory	Soonhee Jang	
X-1-3	Capacity	Patent Attorney	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

PCT REQUEST X-14528

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FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PCT (ANNEX - FEE CALCULATION SHEET) X-14528

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(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	

0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet				
0-4-1	Prepared using		PCT-EASY Version 2.92 (updated 01.01.2002)		
0-9	Applicant's or agent's file reference		X-14528		
2	Applicant		ELI LILLY AND COMPANY, et al.		
12	Calculation of prescribed fees		fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee	T	⇨	240	
12-2-1	Search fee	S	⇨	866	
12-2-2	International search to be carried out by		EP		
12-3	International fee				
	Basic fee				
	(first 30 sheets)	b1	407		
12-4	Remaining sheets		414		
12-5	Additional amount	(X)	9		
12-6	Total additional amount	b2	3,726		
12-7	b1 + b2 =	B	4,133		
12-8	Designation fees				
	Number of designations contained in international application		93		
12-9	Number of designation fees payable (maximum 5)		5		
12-10	Amount of designation fee	(X)	88		
12-11	Total designation fees	D	440		
12-12	PCT-EASY fee reduction	R	-125		
12-13	Total international fee (B+D-R)	I	⇨	4,448	
12-14	Fee for priority document				
	Number of priority documents requested		1		
12-15	Fee per document	(X)	15		
12-16	Total priority document fee	P	⇨	15	
12-17	TOTAL FEES PAYABLE (T+S+I+P)		⇨	5,569	
12-19	Mode of payment		authorization to charge deposit account		
12-20	Deposit account instructions				
	The receiving Office:		United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	Authorization to charge the total fees indicated above.		✓		

PCT (ANNEX - FEE CALCULATI N SHEET) X-14528

Original (for SUBMISSION) - printed on 21.05.2002 01:50:33 PM

12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	05-0840
12-22	Date	21 May 2002 (21.05.2002)
12-23	Name and signature	Soonhee Jang

VALIDATION LOG AND REMARKS

13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
		Green? Reference number for attached copy of general power of attorney not indicated.
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

ABSTRACT OF THE DISCLOSURE

52

MODULATORS OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS

The present invention is directed to a compound of formula I,

and pharmaceutically acceptable salts, solvates, hydrates or stereoisomer thereof, which are useful in treating Syndrome X, Type II diabetes, hyperglycemia, hyperlipidemia, obesity, coagaulopathy, hypertension, arteriosclerosis, and other disorders related to Syndrome X as well as cardiovascular diseases.

X-14528 (PCT)

Delegation of Authority Concerning Certain Patent Matters

Pursuant to the authority granted to the General Counsel of the Company by the Executive Committee of the Board of Directors of Eli Lilly and Company ("Company") at its meeting held on August 29, 1986, I delegate to Robert A. Armitage, Vice President and General Patent Counsel, Lilly Research Laboratories (a division of the Company):

> **Authority to approve and execute for and on behalf of the Company, documents in connection with patent matters relating to:**
>
> **(i) the institution, prosecution, and completion of proceedings directed towards the issuance of patents;**
>
> **(ii) the amendment, restriction, renewal, reissue, revival, maintenance, restoration, cancellation, extension, and abandonment of patents and of applications for patents;**
>
> **(iii) the institution, prosecution, and termination of proceedings of interference, opposition, revocation, and nullification, including the filing of preliminary statements, concessions of priority, disclaimers, abandonments of the contents, and abandonments of the invention;**
>
> **(iv) the settlement of patent proceedings of interference, opposition, revocation, and nullification, subject to prior approval by the Senior Vice President and General Counsel of the Company;**
>
> **(v) the filing of statutory disclaimers;**
>
> **(vi) the institution, prosecution, and termination of appellate proceedings; and**
>
> **(vii) the granting and the revocation of powers of attorney in connection with any of the foregoing.**

Dated: 2/13/01

Rebecca O. Kendall

Rebecca O. Kendall
Senior Vice President and General Counsel

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person:

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

hereby appoints as its agents the following persons registered to practice at the United States Patent and Trademark Office (USPTO):

Name	Reg.	Name	Reg.
ANDERSON, Arvie J.	45,263	KELEHER, Gerald P.	43,707
APELGREN, Lynn D.	45,341	KELLEY, James J	41,888
ARMITAGE, Robert A.	27,417	KOIVUNIEMI, Paul J.	31,533
BARRETT, Brian P	39,597	LAGRANDEUR, Thomas	51,026
BATES, Michael T.	34,121	LEE, Kirby W.	47,744
BENJAMIN, Roger S	27,025	LEEDS, James P.	35,241
BIRCH, Gary M.	48,881	LENTZ, Nelsen L	38,537
BOUDREAUX, William R.	35,796	MCGRAW, Elizabeth A.	44,646
CALTRIDER, Steven P	36,467	NORMAN, Douglas K.	33,267
CANTRELL, Paul R.	36,470	PALMBERG, Arleen	40,422
CLEVELAND, John A . Jr	50,697	PLANT, Thomas G	35,784
COHEN, Charles E.	34,565	PREIN, Edward J	37,212
CORNEGLIO, Donald L.	30,741	REED, Grant E.	41,264
COX, Gregory A.	47,504	SALES, James J.	33,773
DAVIS, Paula K.	47,517	SAYLES, Michael J.	32,295
DEMETER, John C.	30,167	STEMERICK, David M.	40,187
DESAI, Manisha A.	43,585	STEWART, Mark J.	43,936
FEENEY, Joanne L.	35,134	TITUS, Robert D.	40,206
GAYLO, Paul J.	36,808	TUCKER, R. Craig	45,165
GINAH, Francis O.	44,712	TUCKER, Tina M.	47,145
GONGOLA, Janet A	41,436	VORNDRAN-JONES, MaCharri	36,711
HAMILTON, Amy E.	33,894	VOY, Gilbert T.	43,972
HOFFMANN, James A.	50,221	WEBSTER, Thomas D.	39,872
HUNTER, Frederick D.	26,915	WELCH, Lawrence T.	29,487
JACKSON, Thomas E	33,064	WILSON, Alexander	45,782
JANG, Soonbee	44,802	WISKERCHEN, Mary Ann	45,511
JOYNER, Charles T.	30,466	WOOD, Dan L.	48,613

all of whom having a business address of

ELI LILLY AND COMPANY
Lilly Corporate Center
Drop Code 1104
Indianapolis, Indiana 46285
United States of America

and the following persons registered to practice before the European Patent Office (EPO):

BURNSIDE, Ivan, Reg. No GA307
PRITCHARD, Judith, Reg. No. GA307
TAPPING, Kenneth G., Reg. No. GA307
VAUGHAN, Jennifer A., Reg. No. GA307

all of whom having a business address of.

ELI LILLY AND COMPANY LIMITED
European Patent Operations
Kingsclere Road
Basingstoke Hampshire
RG21 2XA
United Kingdom

to represent the undersigned before all the competent International Authorities in which they are legally qualified in connection with any and all international applications filed by the undersigned with my office as receiving Office, to make or receive payments on behalf of the undersigned, and to appoint additional attorneys to represent Eli Lilly and Company before the competent authorities during preliminary examination.

Signature _____ Date: 17 Apr 2002
(Day/ Month/ Year)

Robert A. Armitage, Vice President and General Patent Counsel, Lilly Research Laboratories
Eli Lilly and Company

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

JONES, Winton Dennis

hereby appoints (appoint) the following person as: ☐ agent ☒ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

to represent the undersigned before ☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

In connection with any and all international applications filed by the undersigned with the following Office United States Patent and Trademark Office (USPTO) as receiving Office and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):*

Winton Dennis Jones

Date: 15 / 07 / 2000
Day / Month / Year

Form PCT/Model of general power of attorney (for several international applications) (July 1992)

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

SMITH, Daryl Lynn

hereby appoints (appoint) the following person as: ☐ **agent** ☒ **common representative**

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

to represent the undersigned before

☒ **all the competent International Authorities**

☐ **the International Searching Authority only**

☐ **the International Preliminary Examining Authority only**

in connection with any and all international applications filed by the undersigned with the following Office

any competent office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature(s) ***(where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power)***

Daryl L Smith

Daryl Lynn Smith

Date: 10 / 7 / 01
Day/ Month/ /Year

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GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a legal entity, full official designation.)

VANCE, Jennifer Ann

hereby appoints (appoint) the following person as: ☐ agent ☒ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with any competent office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power)*:

Jennifer Ann Vance

JENNIFER ANN VANCE

Date: 17TH May 2002
Day/ Month/ /Year

Form PCT/Model of general power of attorney (for several international applications) (July 1992)

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GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

WARSHAWSKY, Alan M.

hereby appoints (appoint) the following person as: ☐ agent ☒ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation.)

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

to represent the undersigned before ☐ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with any competent office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature(s) (*where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power*):

Alan M Warshawsky

Alan M. Warshawsky

Date: 15/5/2002
Day/ Month/ /Year

Form PCT/Model of general power of attorney (for several international applications) (July 1992)

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

GOSSETT, Lynn Stacy

hereby appoints (appoint) the following person as: ☐ agent ☒ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation.)

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

to represent the undersigned before ☐ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with any competent office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature(s) (*where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power*):

Lynn Stacy Gossett
Lynn Stacy Gossett

Date: 23 May 2002
Day/ Month/ Year

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PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a legal entity, full official designation.)

GREEN, Jonathan Edward

hereby appoints (appoint) the following person as: ☐ agent ☒ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

to represent the undersigned before ☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with any competent office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):*

Jonathan Edward Green

Date: 23 May 2002
Day/ Month/ /Year

Form PCT/Model of general power of attorney (for several international applications) (July 1992)

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a legal entity, full official designation.)

MATTHEWS, Donald Paul

hereby appoints (appoint) the following person as: ☐ agent ☒ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

to represent the undersigned before ☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with any competent office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power)*

Donald Paul Matthews

Donald Paul Matthews

Date: 23 / May / 2002
Day/ Month/ /Year

Form PCT/Model of general power of attorney (for several international applications) (July 1992)

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a legal entity, full official designation.)

HENRY, James Robert

hereby appoints (appoint) the following person as: ☐ agent ☒ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

to represent the undersigned before ☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with any competent office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power)*:

James Robert Henry

Date: 23 May 2002
Day/ Month/ /Year

Form PCT/Model of general power of attorney (for several international applications) (July 1992)

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a legal entity, full official designation.)

SHEN, Quan Rong

hereby appoints (appoint) the following person as: ☐ agent ☒ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

to represent the undersigned before ☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with any competent office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power)*

Quan Rong Shen

Quan Rong Shen

Date: 23 May 2002
Day/ Month/ /Year

Form PCT/Model of general power of attorney (for several international applications) (July 1992)

VIA FACSIMILE: 703.305.3230

IN THE UNITED STATES RECEIVING OFFICE (USRO) UNDER THE PCT

Applicant Docket:	X-14528
International Application No.:	PCT/US 02/15143
Applicant(s):	ELI LILLY AND COMPANY
Earliest Priority Date:	June 7, 2001 (07.06.01)
International Filing Date:	24 May 2002 (24.05.02)
Title:	MODULATORS OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS

REQUEST FOR RECORDING OF A CHANGE UNDER RULE 92 *BIS*

Box PCT
Assistant Commissioner for Patents
Arlington, VA 22202
Attn: RO/US

Dear Sir/Madam:

Applicant requests for the recording of a change under PCT Rule 92 *bis* to add the name of Applicant/Inventor who was inadvertently omitted in the PCT Request filed on May 24, 2002.

Please add "GONZALEZ-GARCIA, Maria Rosario" as Applicant US only and Inventor for the above identified application.

The PCT Power of Attorney signed by the new applicant, GONZALEZ-GARCIA, Maria Rosario, is enclosed.

Respectfully submitted,

Soonhee Jang
Attorney for Applicant
Registration No. 44,802
Phone: 317-651-3571

Eli Lilly and Company
Patent Division/SJ
P.O. Box 6288
Indianapolis, Indiana 46206-6288

7/9/02

Docket No. X-14528 (PCT)

ASSIGNMENT

WHEREAS we, **LYNN STACY GOSSETT, JONATHAN EDWARD GREEN, JAMES ROBERT HENRY, WINTON DENNIS JONES, DONALD PAUL MATTHEWS, QUAN RONG SHEN, DARYL LYNN SMITH, JENNIFER ANN VANCE,** and **ALAN M. WARSHAWSKY,** have made an invention which is the subject of an international application under the Patent Cooperation Treaty ("PCT") patent application entitled **PHARMACEUTICAL COMPOUNDS,** containing 434 pages, and which is to be filed in the United States Patent and Trademark Office acting as PCT Receiving Office ("Application"); and we hereby authorize and direct our common representative to insert below the filing date and application number when they become known: PCT/US 02/15143, filed 24 MAY 2002; and

WHEREAS ELI LILLY AND COMPANY, an Indiana corporation having its principal place of business at Lilly Corporate Center, Indianapolis, Indiana 46285, wishes to acquire the entire interest in all inventions disclosed in such Application;

NOW, THEREFORE, in consideration of good and valuable consideration, the receipt of which is hereby acknowledged, we hereby sell, assign, transfer and set over unto Eli Lilly and Company, its successors and assigns (collectively "Lilly") our entire right, title and interest in, to and under the Application, including all priority rights for other countries arising therefrom, all inventions therein disclosed, and any and all present or future patent applications to such inventions that may be filed in the United States or any foreign country, inclusive of, but not limited to, continuations, continuations-in-part, divisions, substitutions, reexaminations, reissues, international applications under the Patent Cooperation Treaty ("PCT"), United States provisional patent applications, certificates of addition, utility models, petty patents, as well as all other intellectual property related to the Application, inclusive of, but not limited to, supplementary protection certificates, copyrights, trademarks, and data package exclusivity rights; and any and all Letters Patent of the United States and of all foreign countries and all related patent term extensions which may be granted for Letters Patent with respect to the Application; all of the above to be held and enjoyed by Lilly for its own use and enjoyment to the full end of the term or terms for which such Letters Patent and related intellectual property rights may be granted, as fully and entirely as the same would have been held and enjoyed by us had this Assignment and sale to Lilly not been made.

For ourselves and for our heirs, successors and legal representatives, we covenant that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this Assignment.

For ourselves and for our heirs, successors and legal representatives, we further covenant and agree with Lilly that upon request we and they will, without further consideration than that now paid, but at the expense of Lilly: (i) execute original, provisional, substitute, continuation, divisional, continuation-in-part, reexamined, or reissued applications, amended specifications, or rightful declarations or oaths for such application; (ii) communicate to Lilly any facts known to us or them relating to such inventions or the history thereof; (iii) execute preliminary statements and testify in any

interference proceedings, litigation discovery proceedings and depositions, oppositions, cancellation proceedings, priority contests, public use proceedings, administrative agency proceedings, litigation and other court actions and the like; (iv) execute and deliver any application papers, affidavits, declarations, assignments, or other instruments; and (v) do all other acts which, in the opinion of counsel for Lilly, may be necessary or desirable to secure the grant of Letters Patent and related intellectual property to Lilly or its nominees, in the United States and in all other countries where Lilly may desire to have such inventions, or any of them, patented, with specifications and claims in such form as shall be approved by counsel for Lilly and to vest and confirm in Lilly or its nominees the full and complete legal and equitable title to all such Letters Patent and related intellectual property.

IN WITNESS WHEREOF we have executed this assignment on the date indicated below.

5/23/02
Date

Lynn Stacy Gossett
LYNN STACY GOSSETT

UNITED STATES OF AMERICA

STATE OF INDIANA)
) SS:
COUNTY OF MARION)

May 23, 2002

Before me, a Notary Public for Marion County, State of Indiana, personally appeared LYNN STACY GOSSETT and acknowledged the execution of the foregoing instrument this 23rd day of May, 2002.

Michelle D. Hall
Notary Public

Michelle D. Hall
Notary Public
State of Indiana
County of Marion
Commission Expires: 10/29/08

IN WITNESS WHEREOF we have executed this assignment on the date indicated below.

5/23/02
Date

JONATHAN EDWARD GREEN

UNITED STATES OF AMERICA

STATE OF INDIANA)
) SS: May 23, 2002
COUNTY OF MARION)

Before me, a Notary Public for Marion County, State of Indiana, personally appeared JONATHAN EDWARD GREEN and acknowledged the execution of the foregoing instrument this 23rd day of May, 2002.

Notary Public

Michelle D. Hall
Notary Public
State of Indiana
County of Marion
Commission Expires: 10/22/08

IN WITNESS WHEREOF we have executed this assignment on the date indicated below.

5/23/02
Date

JAMES ROBERT HENRY

UNITED STATES OF AMERICA

STATE OF INDIANA)
) SS:
COUNTY OF MARION)

May 23, 2002

Before me, a Notary Public for Marion County, State of Indiana, personally appeared **JAMES ROBERT HENRY** and acknowledged the execution of the foregoing instrument this 23rd day of May, 2002.

Notary Public

Michelle D. Hall
Notary Public
State of Indiana
County of Marion
Commission Expires: 10/29/08

IN WITNESS WHEREOF we have executed this assignment on the date indicated below.

5/22/02
Date

Winton Dennis Jones
WINTON DENNIS JONES

UNITED STATES OF AMERICA

STATE OF INDIANA)
) SS:
COUNTY OF MARION)

May 23, 2002

Before me, a Notary Public for Marion County, State of Indiana, personally appeared WINTON DENNIS JONES and acknowledged the execution of the foregoing instrument this 23rd day of May, 2002.

Michelle D. Hall
Notary Public

Michelle D. Hall
Notary Public
State of Indiana
County of Marion
Commission Expires: 10/22/08

IN WITNESS WHEREOF we have executed this assignment on the date indicated below.

5/23/2002
Date

Donald Paul Matthews
DONALD PAUL MATTHEWS

UNITED STATES OF AMERICA

STATE OF INDIANA)
) SS:
COUNTY OF MARION)

May 23, 2002

Before me, a Notary Public for Marion County, State of Indiana, personally appeared **DONALD PAUL MATTHEWS** and acknowledged the execution of the foregoing instrument this 23rd day of May, 2002.

Michelle D. Hall
Notary Public

Michelle D. Hall
Notary Public
State of Indiana
County of Marion
Commission Expires: 10/22/08

IN WITNESS WHEREOF we have executed this assignment on the date indicated below.

5/23/2002
Date

Quan Rong Shen
QUAN RONG SHEN

UNITED STATES OF AMERICA

STATE OF INDIANA)
) SS:
COUNTY OF MARION)

May 23, 2002

Before me, a Notary Public for Marion County, State of Indiana, personally appeared **QUAN RONG SHEN** and acknowledged the execution of the foregoing instrument this 23rd day of May, 2002.

Michelle D. Hall
Notary Public

Michelle D. Hall
Notary Public
State of Indiana
County of Marion
Commission Expires: 10/23/08

IN WITNESS WHEREOF we have executed this assignment on the date indicated below.

23 May 2002
Date

Daryl Lynn Smith
DARYL LYNN SMITH

UNITED STATES OF AMERICA

STATE OF INDIANA)
) SS:
COUNTY OF MARION)

May 23, 2002

Before me, a Notary Public for Marion County, State of Indiana, personally appeared DARYL LYNN SMITH and acknowledged the execution of the foregoing instrument this 23rd day of May, 2002.

Michelle D. Hall
Notary Public

Michelle D. Hall
Notary Public
State of Indiana
County of Marion
Commission Expires: 10/22/08

IN WITNESS WHEREOF we have executed this assignment on the date indicated below.

May 17, 2002
Date

JENNIFER ANN VANCE

UNITED STATES OF AMERICA

STATE OF CALIFORNIA)
) SS: MAY 17th, 2002
COUNTY OF SANTA CLARA)

Before me, a Notary Public for SANTA CLARA County, State of California, personally appeared **JENNIFER ANN VANCE** and acknowledged the execution of the foregoing instrument this 17th day of MAY, 2002.

Notary Public

My Commission Expires:

4/10/06

ALBERT SIU TOUNG
COMM. #1347264
NOTARY PUBLIC - CALIFORNIA
SANTA CLARA COUNTY
My Comm. Expires Apr. 10, 2006

IN WITNESS WHEREOF we have executed this assignment on the date indicated below.

5/15/2002
Date

Alan M Warshawsky
ALAN M. WARSHAWSKY

UNITED STATES OF AMERICA

STATE OF INDIANA)
) **SS:** May 15, 2002
COUNTY OF MARION)

Before me, a Notary Public for Marion County, State of Indiana, personally appeared ALAN M. WARSHAWSKY and acknowledged the execution of the foregoing instrument this 15th **day of** May, **2002.**

Michelle D Hall
Notary Public

Michelle D. Hall
Notary Public
State of Indiana
County of Marion
Commission Expires: 10/23/08

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number
WO 02/100403 A1

(51) International Patent Classification[7]: A61K 31/42, C07D 263/32, A61P 3/10, C07D 231/12, A61K 31/422, 31/426, 31/427, C07D 233/58, 277/24, 277/24, 277/38, C07C 271/24, 271/22, 233/87, 233/63, C07D 413/12, 417/12, 413/14, 413/04, 413/10, 417/14, 417/04, 213/81, 307/83

(21) International Application Number: PCT/US02/15143

(22) International Filing Date: 24 May 2002 (24.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/296,701 7 June 2001 (07.06.2001) US

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: GOSSETT, Lynn, Stacy [US/US]; 7345 Donegal Drive, Indianapolis, IN 46217 (US). GREEN, Jonathan, Edward [US/US]; 1019 East 96th Street, Apartment D, Indianapolis, IN 46240 (US). HENRY, James, Robert [US/US]; 7307 Elm Ridge Drive, Indianapolis, IN 46236 (US). JONES, Winton, Dennis, Junior [US/US]; 1227 East 126th Street, Carmel, IN 46033 (US). MATTHEWS, Donald, Paul [US/US]; 7736 Wawasee Drive, Indianapolis, IN 46250 (US). SHEN, Quan, Rong [CN/US]; 10565 Harlow Drive, Fishers, IN 46038 (US). SMITH, Daryl, Lynn [US/US]; 7656 Madden Lane, Fishers, IN 46038 (US). VANCE, Jennifer, Ann [US/US]; 132 El Bosque, San Diego, CA 95134 (US). WARSHAWSKY, Alan, M. [US/US]; 13828 Spring Mill Ponds Circle, Carmel, IN 46032 (US).

(74) Agents: JANG, Soonbee et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

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

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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

WO 02/100403 A1

(54) Title: MODULATORS OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS (PPAR)

(57) Abstract: The present invention is directed to a compound of formula I, and pharmaceutically acceptable salts, solvates, hydrates or stereoisomer thereof, which are useful in treating Syndrome X, Type II diabetes, hyperglycemia, hyperlipidemia, obesity, coagulopathy, hypertension, arteriosclerosis, and other disorders related to Syndrome X as well as cardiovascular diseases.

MODULATORS OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS (PPAR)

FIELD OF THE INVENTION

The present invention relates to a compound of peroxisome proliferator activated receptor (PPAR) agonists, which are useful for the treatment and/or prevention of disorders modulated by a PPAR.

BACKGROUND OF THE INVENTION

The peroxisome proliferator activated receptors (PPARs) are members of the nuclear receptor gene family that are activated by fatty acids and fatty acid metabolites. The PPARs belong to the subset of nuclear receptors that function as heterodimers with the 9-*cis* retinoic acid receptor (RXR). Three subtypes, designated PPARα, PPARγand PPARδ, are found in species ranging from *Xenopus* to humans.

PPARα is the main subtype in the liver and has facilitated analysis of the mechanism by which peroxisome proliferators exert their pleiotropic effects. PPARα is activated by a number of medium and long-chain fatty acids, and it is involved in stimulating β-oxidation of fatty acids. PPARα is also involved with the activity of fibrates and fatty acids in rodents and humans. Fibric acid derivatives such as clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, produce a substantial reduction in plasma triglycerides along with moderate reduction in low-density lipoprotein (LDL) cholesterol, and they are used particularly for the treatment of hypertriglyceridemia.

PPARγ is the main subtype in adipose tissue and involved in activating the program of adipocyte differentiation. PPARγ is not involved in stimulating peroxisome proliferation in the liver. There are two isomers of PPARγ: PPARγ1 and PPARγ2, which differ only in that PPARγ2 contains an additional 28 amino acids present at the amino terminus. The DNA sequences for the PPARγ receptors are described in Elbrecht, et al., BBRC 224;431-437 (1996). Although peroxisome proliferators, including the fibrates and fatty acids, activate the transcriptional activity of PPAR's, only prostaglandin J_2 derivatives have been identified as natural ligands for PPARγ, which also binds the anti-diabetic agents thiazolidinediones with high affinity. The physiological functions of

PPARα and PPARγ in lipid and carbohydrate metabolism were uncovered once it was recognized that they were the receptors for the fibrate and glitazone drugs, repectively.

PPARα and PPARγ receptors have been implicated in diabetes mellitus, cardiovascular disease, obesity, and gastrointestinal disease, such as inflammatory bowel disease and other inflammation related illnesses. Such inflammation related illnesses include, but are not limited to Alzheimer's disease, Crohn's disease, rheumatoid arthritis, psoriasis, and ischemia reprofusion injury.

By contrast, PPARδ (also referred to as PPARβ and NUC1) is not reported to be receptor for any known class of drug molecules, and its role in mammalian physiology has remained undefined. The human nuclear receptor gene PPARδ (hPPARδ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., *Molecular Endocrinology*, 6:1634-1641 (1992).

Diabetes is a disease in which a mammal's ability to regulate glucose levels in the blood is impaired because the mammal has a reduced ability to convert glucose to glycogen for storage in muscle and liver cells. In Type I diabetes, this reduced ability to store glucose is caused by reduced insulin production. "Type II Diabetes" or "non-insulin dependent diabetes mellitus" (NIDDM) is the form of diabetes, which is due to a profound resistance to insulin stimulating or regulatory effect on glucose and lipid metabolism in the main insulin-sensitive tissues, muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. When these cells become desensitized to insulin, the body tries to compensate by producing abnormally high levels of insulin and hyperinsulemia results. Hyperinsulemia is associated with hypertension and elevated body weight. Since insulin is involved in promoting the cellular uptake of glucose, amino acids and triglycerides from the blood by insulin sensitive cells, insulin insensitivity can result in elevated levels of triglycerides and LDL (known as the "bad" cholesterol) which are risk factors in cardiovascular diseases. The constellation of symptoms which includes hyperinsulemia combined with hypertension, elevated body weight, elevated triglycerides and elevated LDL is known as Syndrome X.

Hyperlipidemia is a condition which is characterized by an abnormal increase in serum lipids, such as cholesterol, triglycerides and phospholipids. These lipids

do not circulate freely in solution in plasma, but are bound to proteins and transported as macromolecular complexes called lipoproteins. One form of hyperlipidemia is hypercholesterolemia, characterized by the existence of elevated LDL cholesterol levels. The initial treatment for hypercholesterolemia is often a diet low in fat and cholesterol coupled with appropriate physical exercise. Drug intervention is initiated if LDL-lowering goals are not met by diet and exercise alone. It is desirable to lower elevated levels of LDL cholesterol and increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CHD). See Gordon, et al., *Am. J. Med.*, 62, 707-714 (1977); Stampfer, et al., *N. England J. Med.*, 325, 373- 381 (1991); and Kannel, et al., *Ann. Internal Med.*, 90, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, but the quantities needed to achieve HDL elevation are associated with undesirable effects, such as flushing.

There are several treatments currently available for treating diabetes mellitus but these treatments still remain unsatisfactory and have limitations. While physical exercise and reduction in dietary intake of calories will improve the diabetic condition, compliance with this approach can be poor because of sedentary lifestyles and excess food consumption, in particular high fat-containing food. Therefore, treatment with hypoglycemics, such as sulfonylureas (e.g., chlorpropamide, tolbutamide, tolazamide and acetohexamide) and biguanides (e.g. phenformin and metformin) are often necessary as the disease progresses. Sulfonylureas stimulate the β cells of the pancreas to secrete more insulin as the disease progresses. However, the response of the β cells eventually fails and treatment with insulin injections is necessary. In addition, both sulfonylurea treatment and insulin injection have the life threatening side effect of hypoglycemic coma, and thus patients using these treatments must carefully control dosage.

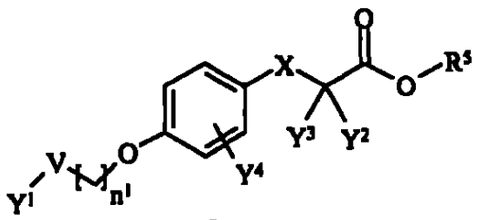
It has been well established that improved glycemic control in patients with diabetes (Type I and Type II) is accompanied by decreased microvasclular complications (DCCT and UKPDS). Due to difficulty in maintaining adequate glycemic control over time in patients with Type II diabetes, the use of insulin sensitizers in the therapy of Type II diabetes is growing. There is also a growing body of evidence that PPARγ agonist, insulin sensitizer, may have benefits in the treatment of Type II diabetes beyond their effects in improving glycemic control.

In the last decade a class of compounds known as thiazolidinediones (e.g. U.S. Pat. Nos. 5,089,514; 4,342,771; 4,367,234; 4,340,605; and 5,306,726) have emerged as effective anidiabetic agents that have been shown to increase the sensitivity of insulin sensitive tissues, such as skeletal muscle, liver and adipose, to insulin. Increasing insulin sensitivity rather than the amount of insulin in the blood reduces the likelihood of hypoglycemic coma. Although thiazolidinediones have been shown to increase insulin sensitivity by binding to PPARγ receptors, this treatment also produces unwanted side effects such as weight gain and, for troglitazone, liver toxicity.

In view of the above, there exists a need for new pharmaceutical agents which modulate these receptors to prevent, treat and/or alleviate these diseases or conditions while ameliorating side effects of current treatments.

SUMMARY OF THE INVENTION

The present invention relates to compound of novel peroxisome proliferator activated receptor agonists having a structural formula I,



I

and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof, wherein:

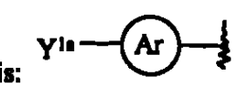
n^1 is 2, 3, 4 or 5;

V is a bond or O;

X is CH_2 or O;

p is 0 or 1;

m is 1-4;

Y^1 is:  wherein,

 is: aryl or heteroaryl,

wherein aryl and heteroaryl are optionally substituted with one or more groups independently selected from the group consisting of:

hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, haloalkyl and haloalkyloxy;

Y^{1a} is: hydrogen,
$(C_0$-$C_3)$alkyl-aryl,
C(O)-aryl,
heteroaryl,
cycloalkyl,
heterocycloalkyl,
aryloxy,
$NR^5(CH_2)_mOR^5$,
aryl-Z-aryl,
aryl-Z-heteroaryl,
aryl-Z-cycloalkyl,
aryl-Z-heterocycloalkyl,
heteroaryl-Z-aryl,
heteroaryl-Z-heterocycloalkyl or
heterocycloalkyl-Z-aryl,
wherein aryl, cycloalkyl, aryloxy, heteroaryl, and heterocycloalkyl are optionally substituted with one or more substituents independently selected from the group consisting of:
halo,
hydroxyl,
nitro,
cyano,
C_1-C_6 alkyl,
C_1-C_6 alkoxy optionally substituted with $N(R^5)_2$,
haloalkyl,
$N(R^5)_2$,
$N[C(O)R^5]_2$,

$N[S(O)_2R^5]_2$,
$NR^5S(O)_2R^5$,
$NR^5C(O)R^5$,
$NR^5C(O)OR^5$,
$C(O)N(R^5)_2$,
$C(O)OR^5$ and
$C(O)R^5$;

Z is: a bond,
-oxygen-
$-C(O)NR^5-$
$-NR^5C(O)-$,
$-NR^5C(O)O-$,
-C(O)-,
$-NR^5-$,
$-[O]_p(CH_2)_m-$,
$-(CH_2)_m[O]_p-$,
$-NR^5(CH_2)_m-$ or
$-(CH_2)_mNR^5-$;

Y^2 and Y^3 are each independently:
hydrogen,
C_1-C_6 alkyl or
C_1-C_6 alkoxy;

Y^4 is: $(C_1–C_3)$alkyl-$NR^5C(O)$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(O)$-$(C_2$-$C_5)$alkenyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(O)$-$(C_2$-$C_5)$alkynyl-Y^7;
$(C_1–C_3)$alkyl-$NR^5C(O)O$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(O)NR^5$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(S)NR^5$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_0–C_3)$alkyl-$C(O)NR^5$-$(C_0$-$C_5)$alkyl-Y^7,

$(C_1–C_3)$alkyl-$OC(O)NY^{10}Y^{11}$,
(C_1-C_3)alkyl-$NY^{10}Y^{11}$,
$(C_1–C_3)$alkyl-O-(C_0-C_5)alkyl-Y^7,
$(C_1–C_3)$alkyl-S-(C_0-C_5)alkyl-Y^7 or
CN;

Y^7 is: hydrogen,
aryl,
heteroaryl,
C_1-C_{12} alkyl,
C_1-C_6 alkoxy,
cycloalkyl,
heterocycloalkyl,
aryloxy,
C(O)-heteroaryl or
SR^6,
wherein alkyl, aryl, aryloxy, alkoxy, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more groups independently selected from R^7:

Y^{10} and Y^{11} are each independently:
hydrogen,
aryl,
heteroaryl,
C_1-C_{10} alkyl,
cycloalkyl,
$SO_2(R^6)$; or
Y^{10} and Y^{11} together are a 5- to 10-membered heterocycloalkyl ring or heterocycloalkyl ring fused with aryl, and the heterocycloalkyl ring optionally containing one or more heteroatoms selected from N, O or S; and wherein,

aryl, heteroaryl, heterocycloalkyl and alkyl are optionally substituted with one or more substituents independently selected from R^7;

R^5 is: hydrogen or C_1-C_6 alkyl;

R^6 is: hydrogen,
C_1-C_{10} alkyl,
cycloalkyl,
aryl, or
heteroaryl,
wherein alkyl, cycloalkyl, aryl and heteroaryl are optionally substituted with one or more substituents independently selected from R^7;

R^7 is: halo,
nitro,
oxo,
cyano,
hydroxyl,
benzyl,
phenyl,
phenoxy,
heteroaryl,
$C(O)R^6$,
C_1-C_{10} alkyl,
C_1-C_6 alkoxy,
C_1-C_6 haloalkyl,
C_1-C_6 haloalkyloxy,
$O(CH_2)_m$-phenyl,
$(CH_2)_mOC(O)$-aryl,
$C(O)OR^5$,
$S(O)_2R^5$,
$S(O)_2N(R^5)_2$,

SR^5 or

$N(R^5)_2$,

wherein phenyl and phenoxy are optionally substituted with one or more groups independently selected from halo or trifluoromethyl.

The compounds of the present invention are useful in the treatment or prevention of diseases or condition relates to hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component.

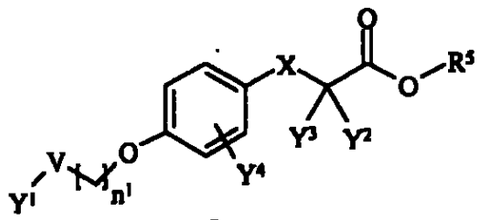
In one embodiment, the present invention also relates to pharmaceutical compositions which comprising at least one compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate thereof and a pharmaceutically acceptable carrier. Within the scope of this invention also include a pharmaceutical composition containing additional therapeutic agent as well as at least one compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate thereof and a pharmaceutically acceptable carrier.

In another embodiment, the present invention relates to a method of modulating a peroxisome proliferator activated receptor by contacting the receptor with at least one compound of Formula I, and pharmaceutically acceptable salts, solvates and hydrates thereof.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are directed to peroxisome proliferator activated receptor (PPAR) agonists, which are useful for the treatment and/or prevention of disorders modulated by a PPAR.

An embodiment of the present invention is a compound of structural formula I:



I

and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof, wherein:

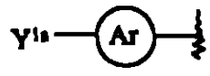
n^1 is 2, 3, 4 or 5;

V is a bond or O;

X is CH_2 or O;

p is 0 or 1;

m is 1-4;

Y^1 is:  wherein,

 is: aryl or heteroaryl,

wherein aryl and heteroaryl are optionally substituted with one or more groups independently selected from the group consisting of:

hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, haloalkyl and haloalkyloxy;

Y^{1a} is: hydrogen,

$(C_0$-$C_3)$alkyl-aryl,

C(O)-aryl,

heteroaryl,

cycloalkyl,
heterocycloalkyl,
aryloxy,
$NR^5(CH_2)_mOR^5$,
aryl-Z-aryl,
aryl-Z-heteroaryl,
aryl-Z-cycloalkyl,
aryl-Z-heterocycloalkyl,
heteroaryl-Z-aryl,
heteroaryl-Z-heterocycloalkyl or
heterocycloalkyl-Z-aryl,

wherein aryl, cycloalkyl, aryloxy, heteroaryl, and heterocycloalkyl are optionally substituted with one or more substituents independently selected from the group consisting of:

halo,
hydroxyl,
nitro,
cyano,
C_1-C_6 alkyl,
C_1-C_6 alkoxy optionally substituted with $N(R^5)_2$,
haloalkyl,
$N(R^5)_2$,
$N[C(O)R^5]_2$,
$N[S(O)_2R^5]_2$,
$NR^5S(O)_2R^5$,
$NR^5C(O)R^5$,
$NR^5C(O)OR^5$,
$C(O)N(R^5)_2$,
$C(O)OR^5$ and
$C(O)R^5$;

Z is: a bond,
-oxygen-
$-C(O)NR^5-$
$-NR^5C(O)-$,
$-NR^5C(O)O-$,
$-C(O)-$,
$-NR^5-$,
$-[O]_p(CH_2)_m-$,
$-(CH_2)_m[O]_p-$,
$-NR^5(CH_2)_m-$ or
$-(CH_2)_mNR^5-$;

Y^2 and Y^3 are each independently:
hydrogen,
C_1-C_6 alkyl or
C_1-C_6 alkoxy;

Y^4 is: $(C_1–C_3)$alkyl-$NR^5C(O)$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(O)$-$(C_2$-$C_5)$alkenyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(O)$-$(C_2$-$C_5)$alkynyl-Y^7;
$(C_1–C_3)$alkyl-$NR^5C(O)O$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(O)NR^5$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(S)NR^5$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_0–C_3)$alkyl-$C(O)NR^5$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-$OC(O)NY^{10}Y^{11}$,
$(C_1$-$C_3)$alkyl-$NY^{10}Y^{11}$,
$(C_1–C_3)$alkyl-O-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-S-$(C_0$-$C_5)$alkyl-Y^7 or
CN;

Y^7 is: hydrogen,
aryl,
heteroaryl,
C_1-C_{12} alkyl,
C_1-C_6 alkoxy,
cycloalkyl,
heterocycloalkyl,
aryloxy,
C(O)-heteroaryl or
SR^6,
wherein alkyl, aryl, aryloxy, alkoxy, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more groups independently selected from R^7:

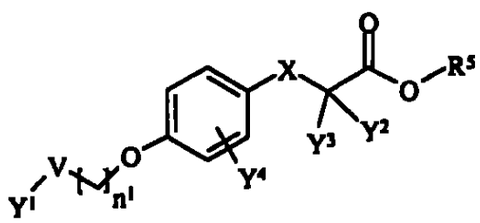
Y^{10} and Y^{11} are each independently:
hydrogen,
aryl,
heteroaryl,
C_1-C_{10} alkyl,
cycloalkyl,
$SO_2(R^6)$; or
Y^{10} and Y^{11} together are a 5- to 10-membered heterocycloalkyl ring or heterocycloalkyl ring fused with aryl, and the heterocycloalkyl ring optionally containing one or more heteroatoms selected from N, O or S; and wherein, aryl, heteroaryl, heterocycloalkyl and alkyl are optionally substituted with one or more substituents independently selected from R^7;

R^5 is: hydrogen or C_1-C_6 alkyl;

R^6 is: hydrogen,
C_1-C_{10} alkyl,
cycloalkyl,
aryl, or
heteroaryl,
wherein alkyl, cycloalkyl, aryl and heteroaryl are optionally substituted with one or more substituents independently selected from R^7;

R^7 is: halo,
nitro,
oxo,
cyano,
hydroxyl,
benzyl,
phenyl,
phenoxy,
heteroaryl,
$C(O)R^6$,
C_1-C_{10} alkyl,
C_1-C_6 alkoxy,
C_1-C_6 haloalkyl,
C_1-C_6 haloalkyloxy,
$O(CH_2)_m$-phenyl,
$(CH_2)_mOC(O)$-aryl,
$C(O)OR^5$,
$S(O)_2R^5$,
$S(O)_2N(R^5)_2$,
SR^5 or
$N(R^5)_2$,
wherein phenyl and phenoxy are optionally substituted with one or more groups independently selected from halo or trifluoromethyl.

An embodiment of the present invention also include a compound represented by the structural Formula Ia:



Ia

or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein:

Y^1 is an unsubstituted or substituted group selected from the group consisting of: aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aryl-C_1-C_4 alkyl, heteroaryl-C_1-C_4 alkyl, cycloalkyl-C_1-C_4 alkyl, and t-butyl;

Y^2 is selected from the group consisting of:

H, C_1-C_{10} alkyl, cycloalkyl,(C_1-C_{10} alkyl)-Y^5 , O-Y^6;

Y^5 is selected from the group consisting of:

an aryl, substituted aryl group, -COR^4, -$COOR^4$, -$CONR^6R^7$,-CSR^4 , and -$C(S)NR^6R^7$;

Y^6 is selected from the group consisting of:

an aliphatic group, a substituted aliphatic group, an aryl, substituted aryl group, -COR^4, -$COOR^4$, -$CONR^6R^7$, -CSR^4, and -$C(S)NR^6R^7$;

R^4, R^6 and R^7 are each independently selected from the group consisting of: H, an aliphatic group, a substituted aliphatic group, an aryl group and a substituted aryl group;

Y^3 is selected from the group consisting of:

H, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and (C_1-C_{10} alkyl)-R^8; R^8 is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

R^5 is selected from the group consisting of:

H, aliphatic group, a substituted aliphatic group, heteroaryl, substituted heteroaryl, an aryl, a substituted aryl, and (C_1-C_{10} alkyl)-R^9;

R^9 is selected from the group consisting of:

aryl, substituted aryl, heteroaryl, and substituted heteroaryl, aminoalkyl, and cycloalkyl;

V is a bond or O;

X is CH_2 or O;

Y^4 is selected from the group consisting of:

$-(C_1-C_3)$alkyl-O-W-Y^7, $-C(O)NY^8Y^9$, $-(C_1-C_3)$alkyl-$NY^{10}Y^{11}$, and

$-(C_1-C_3)$alkyl$N(Y^{13})W-(C_0-C_5)$alkyl-Y^{14} ;

W is selected from the group consisting of:
a bond, $-CONY^{12}$, -C(O)-, $-OCH_2-$, C_1-C_6 alkyl, $-CO_2-$, $-CHOY^{15}-$, $-CSNY^{16}$ and

$-SO_2-$;

Y^7 is selected from the group consisting of:

aryl, substituted aryl, heteroaryl, substituted heteroaryl, aliphatic, branched aliphatic and substituted (C_1-C_{10}) alkyl;

Y^8, Y^9, Y^{10}, Y^{11}, Y^{12}, Y^{13}, Y^{14}, Y^{15}, and Y^{16} are each independently selected from the group consisting of:

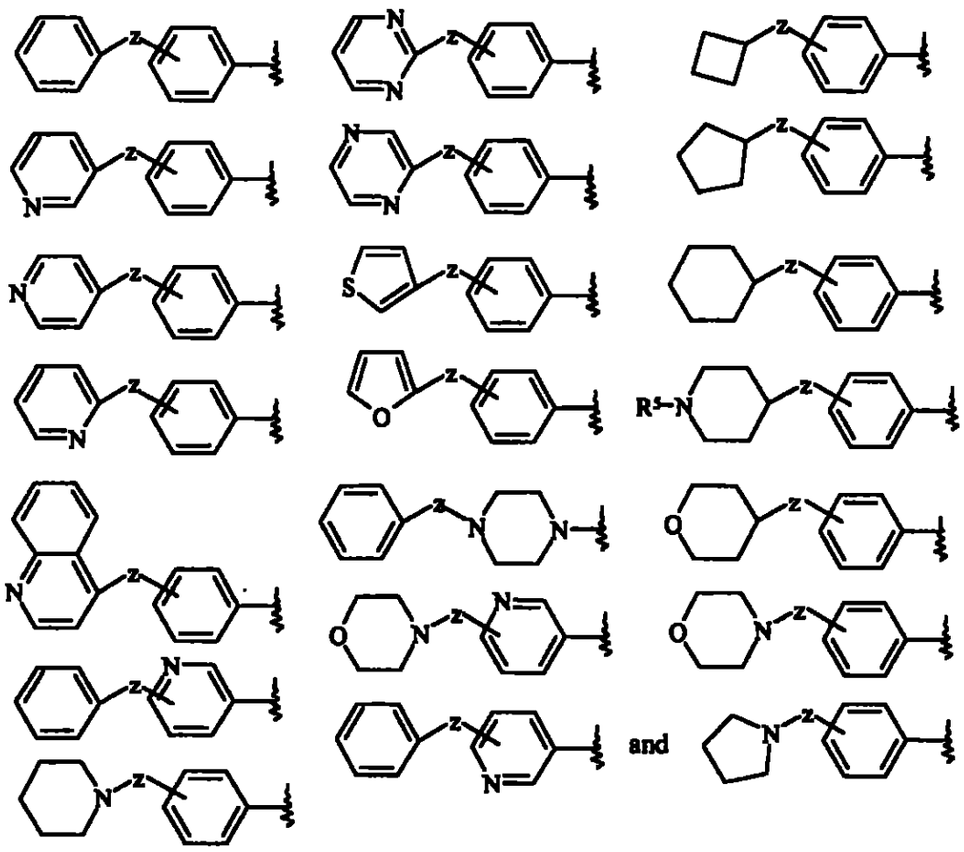
aryl, substituted aryl, heteroaryl, substituted heteroaryl, aliphatic, branched aliphatic and substituted (C_1-C_{10}) alkyl; and n^1 are 2, 3, 4 or 5.

The substituent Y^1 of the compound represented by a formula Ia includes

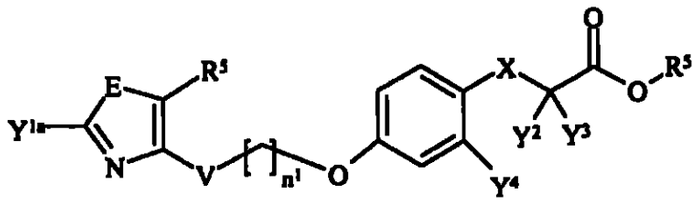


where Y^{1a} and  are defined above in formula I, and substituted group includes the substituents recited above and as defined in the embodiment.

The compound of present invention as recited above, wherein Y^{1a} is selected from the group consisting of: aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aryloxy,

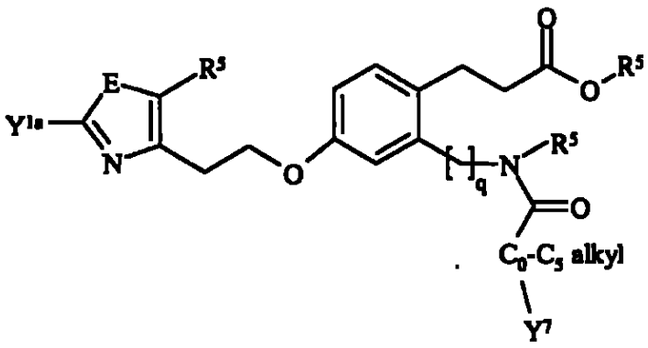


A preferred embodiment of the present invention is a compound represented by the following structural formula,



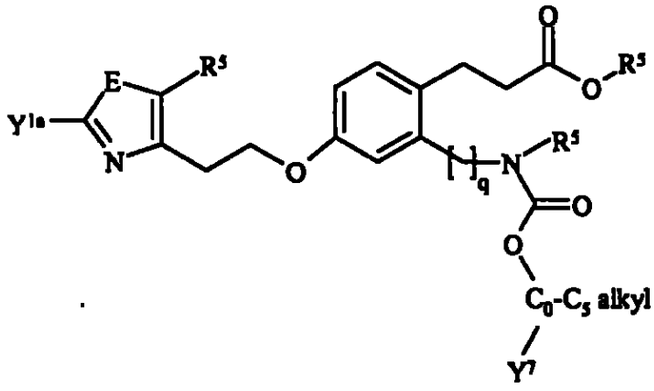
wherein E is O or S.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



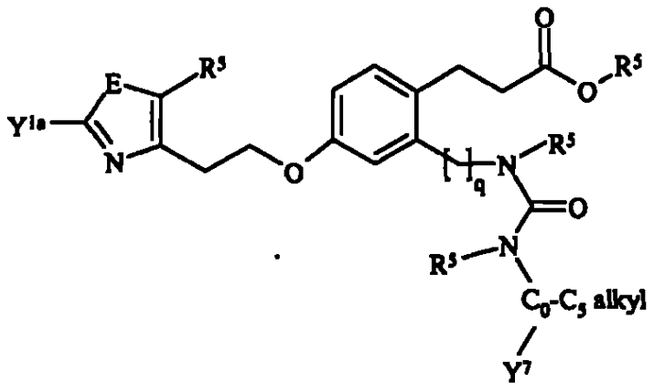
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



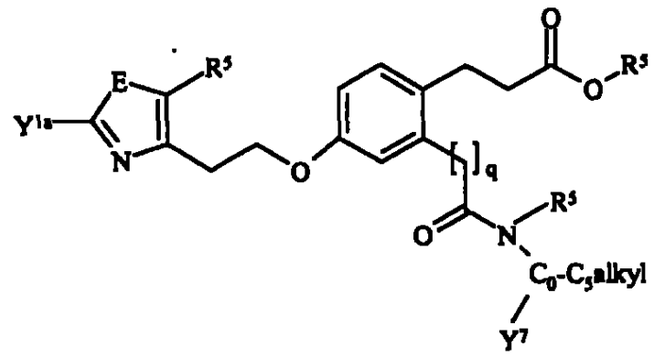
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



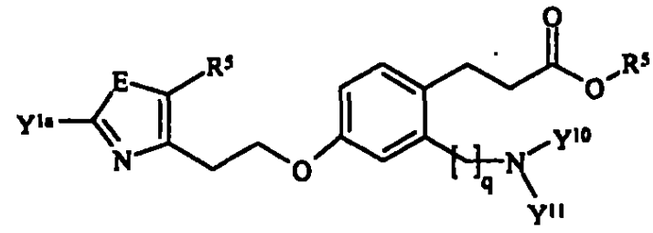
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



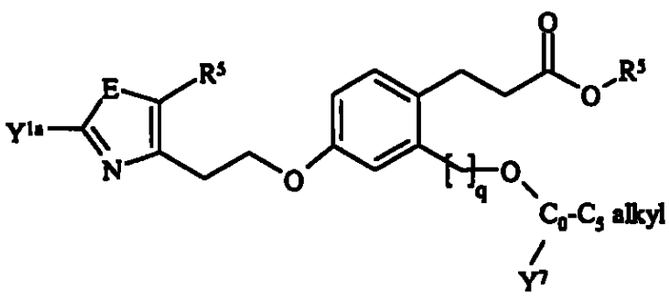
wherein q is 0 or 1; and each R^5 is independently hydrogen or methyl.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



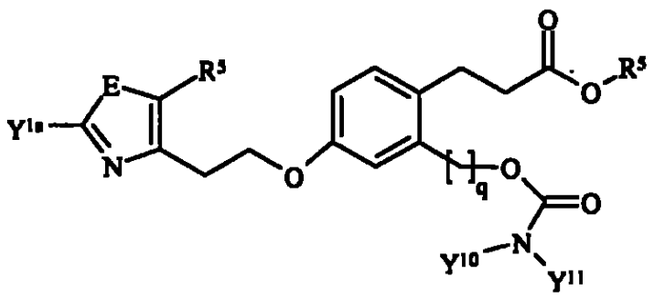
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



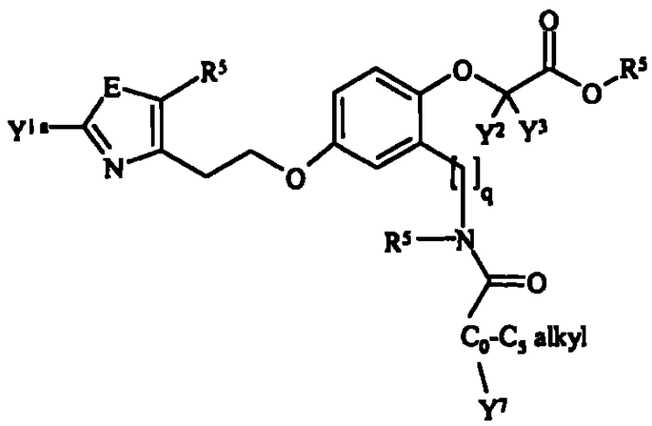
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



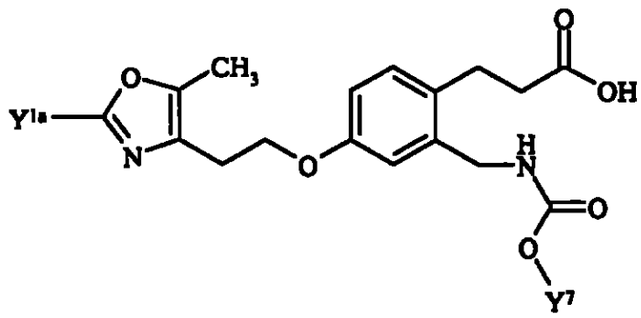
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,

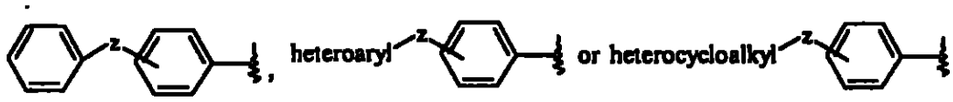


wherein q is 1 or 2; and each R^5, Y^2 and Y^3 are independently hydrogen or methyl.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,

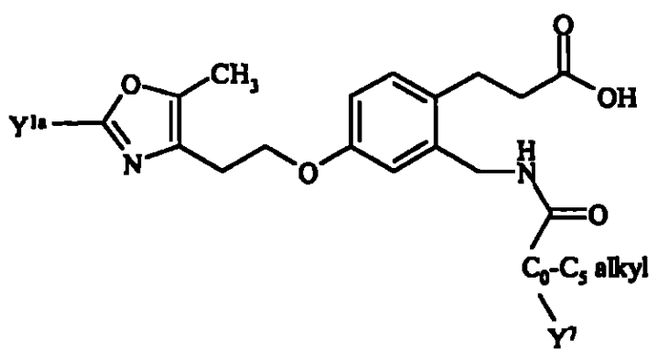


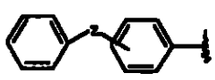
wherein Y^{1a} is optionally substituted phenyl, naphthyl,



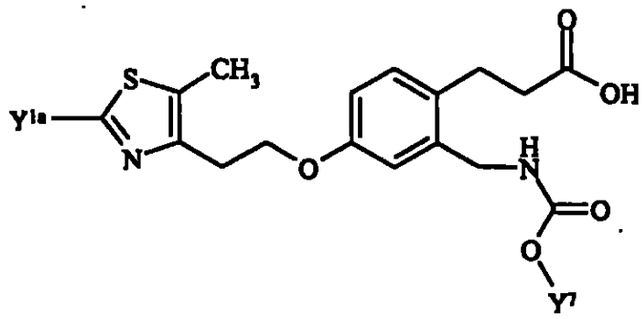
and Z is a bond, oxygen, -NH-, -N(CH_3)-, -NHC(O)- or -C(O)NH-.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



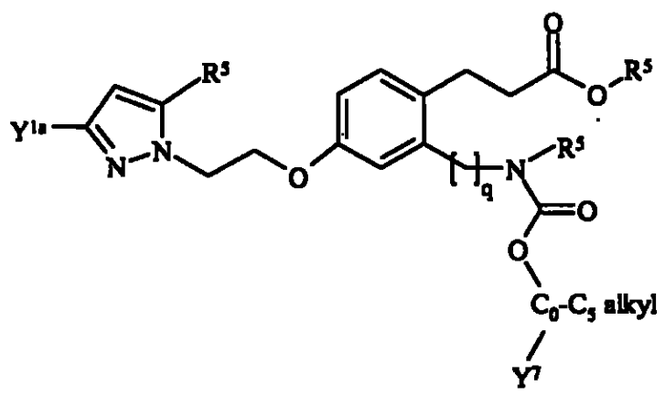
wherein Y^{1a} is optionally substituted phenyl, naphthyl or  and Z is a bond, oxygen, -NH-, -N(CH_3)-, -NHC(O)- or -C(O)NH-.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



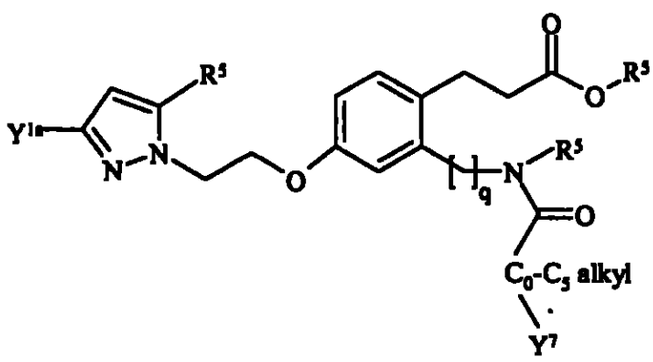
wherein Y^{1a} is optionally substituted aryl, heteroaryl, heterocycloalkyl, heteroaryl-Z-heterocycloalkyl or heteroaryl-Z-aryl.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



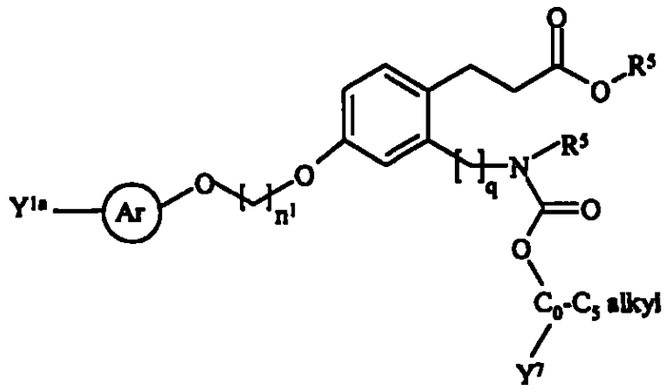
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



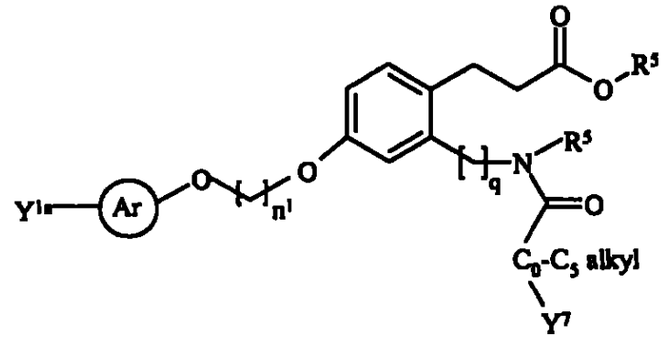
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,



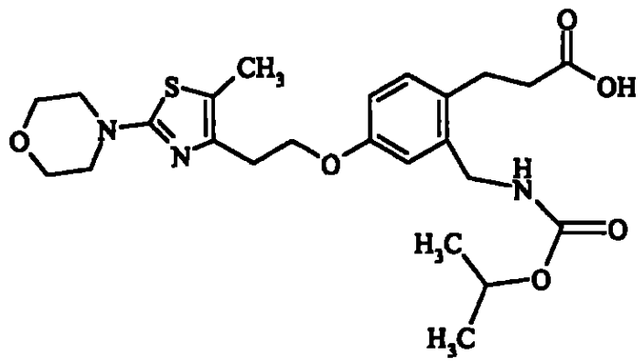
wherein, Y^{1a} is hydrogen, aryl, heteroaryl, or aryloxy; q is 1 or 2; and n^1 is 2, 3, or 4.

Another preferred embodiment of the present invention is a compound represented by the following structural formula,

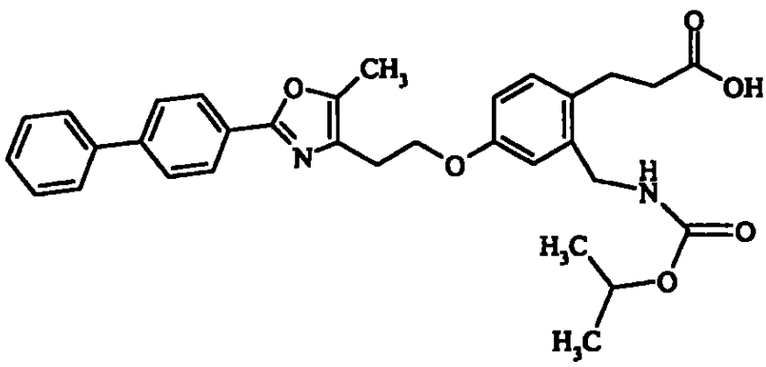


wherein, Y^{1a} is hydrogen, aryl, heteroaryl or aryloxy; q is 1 or 2; and n^1 is 2, 3, or 4.

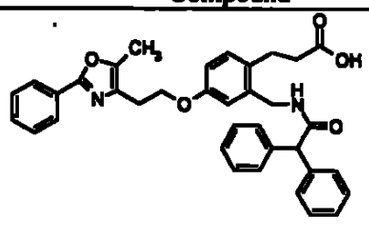
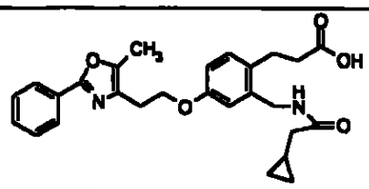
A preferred compound is a compound represented by the following structural formula,

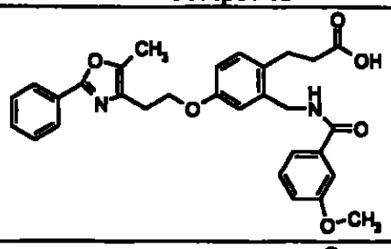
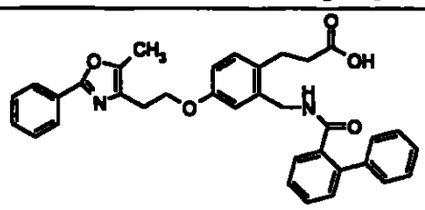
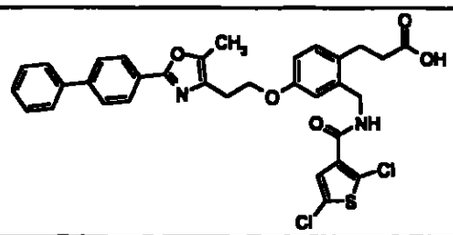
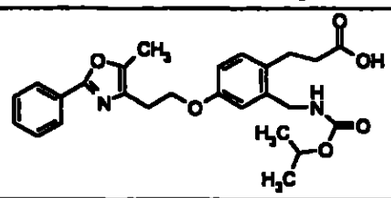
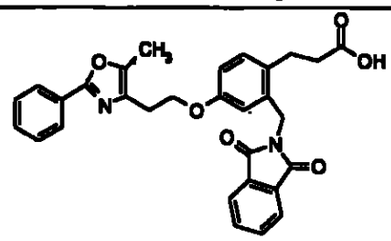
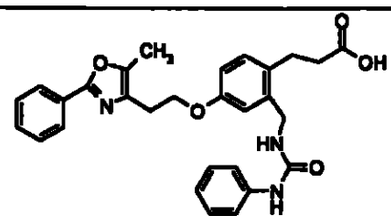


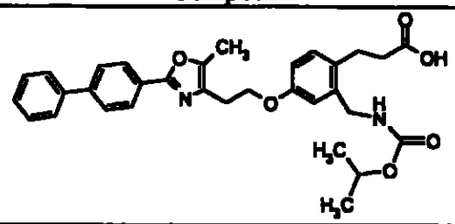
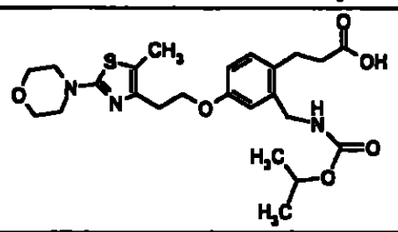
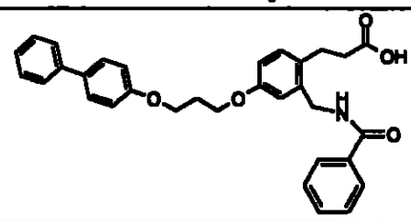
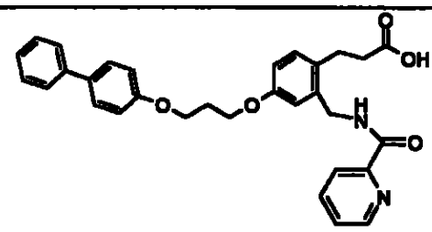
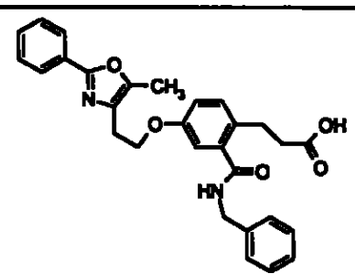
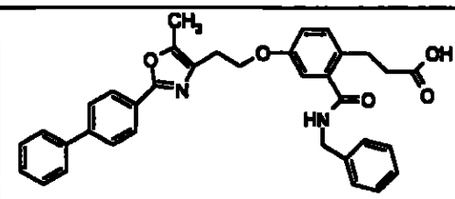
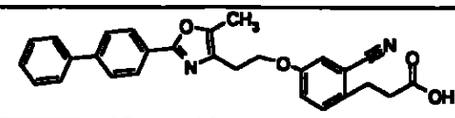
A preferred compound is a compound represented by the following structural formula,

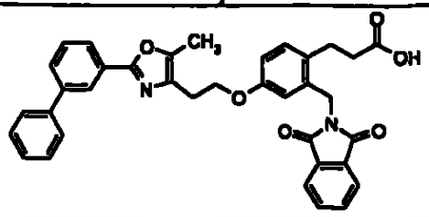
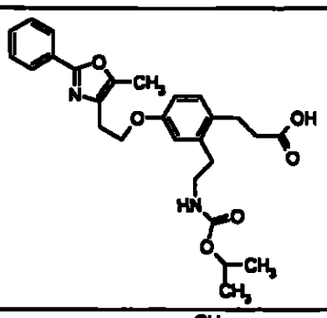
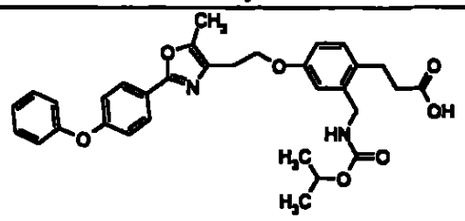
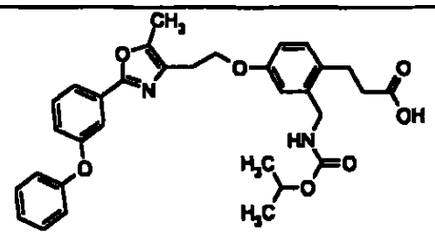
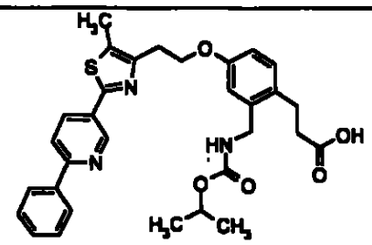


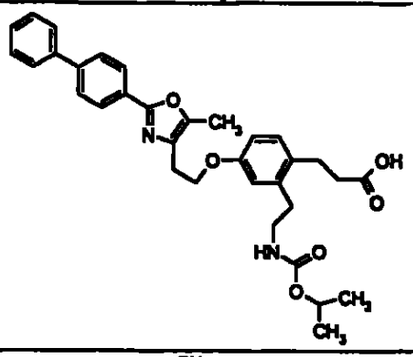
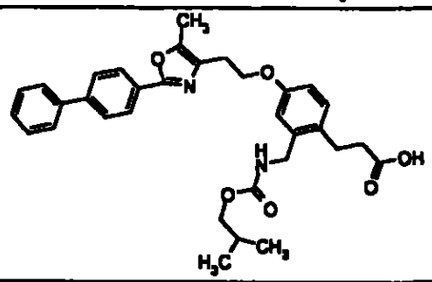
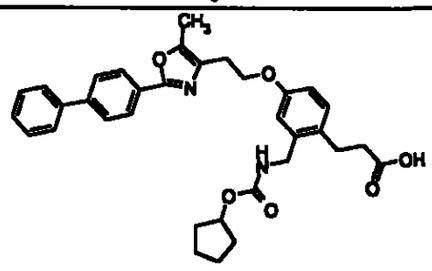
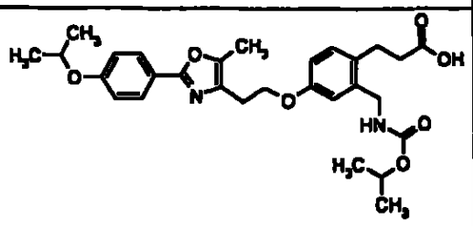
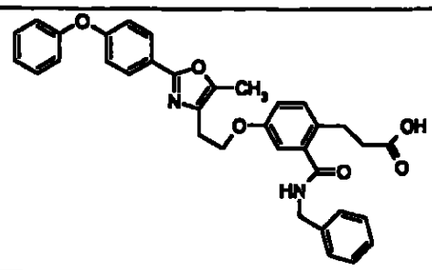
More preferred compounds of the present invention are listed below:

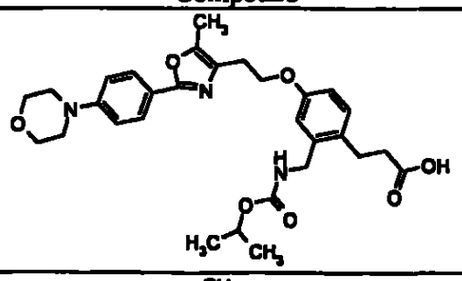
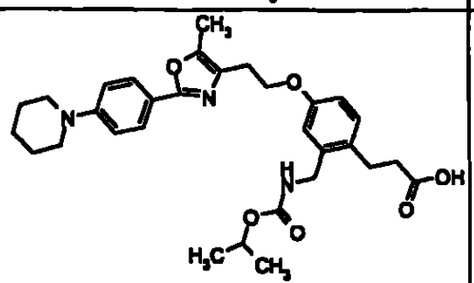
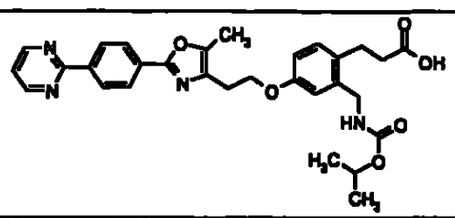
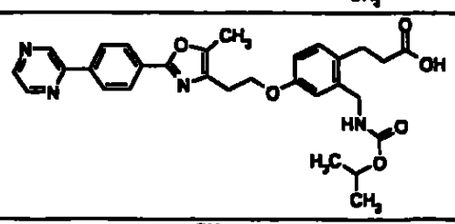
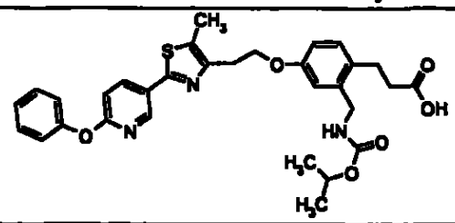
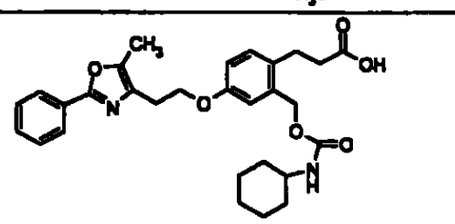
No.	Compound	name
1		3-{2-(Diphenylacetyl-aminomethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid
2		3-{2-[(2-Cyclopropylacetylamino) methyl]-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid

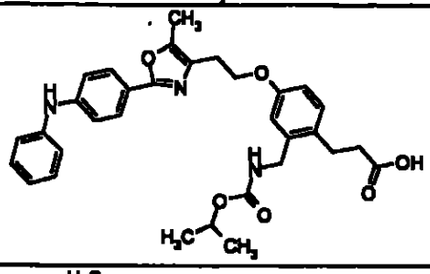
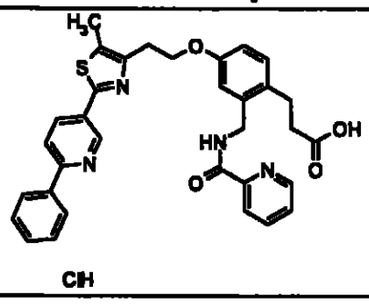
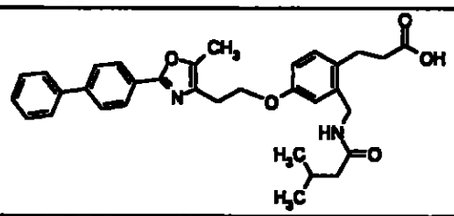
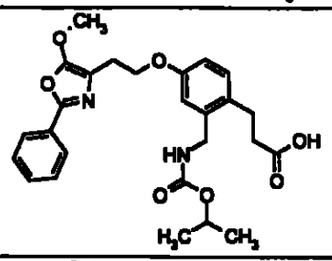
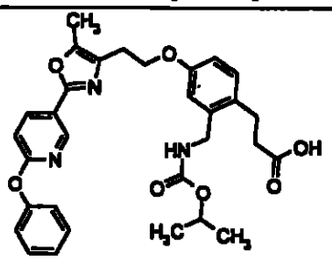
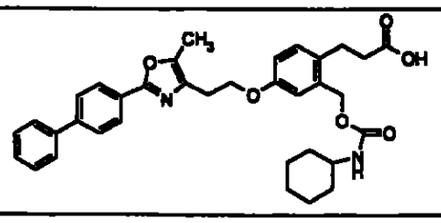
No.	Compound	name
3		3-{2-[(3-Methoxybenzoylamino) methyl]-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
4		3-{2-{[(Biphenyl-2-carbonyl) amino]methyl}-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid
5		3-(4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-{[(2,5-dichlorothiophene-3-carbonyl)amino]methyl}phenyl) propionic acid
6		3-{2-(Isopropoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl) ethoxy] phenyl} propionic acid
7		3-{2-(1,3-Dioxo-1,3-dihydroisoindol-2-ylmethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid
8		3-{4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-[(3-phenylureido)methyl] phenyl} propionic acid

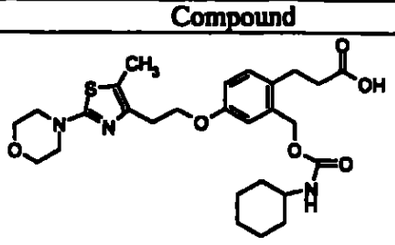
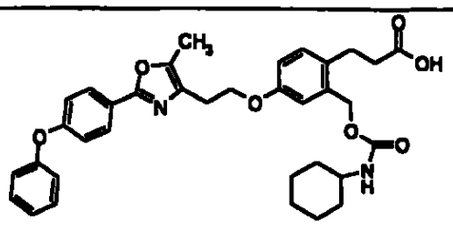
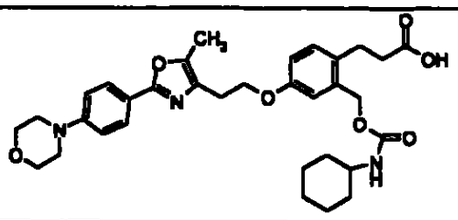
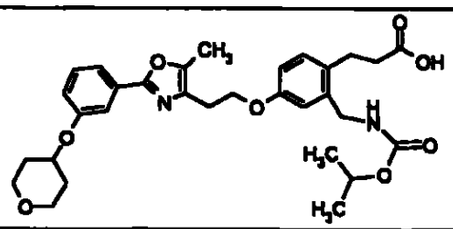
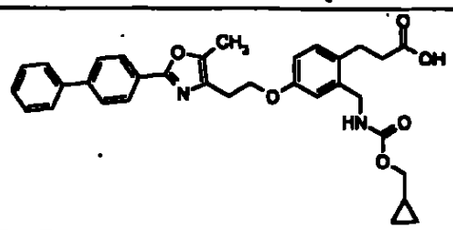
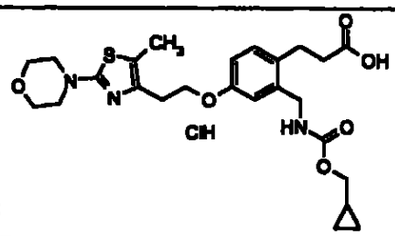
No.	Compound	name
9		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(isopropoxycarbonylaminomethyl) phenyl] propionic acid
10		3-{2-(Isopropoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl) ethoxy]phenyl} propionic acid
11		3-{2-(Benzoylaminomethyl)-4-[3-(biphenyl-4-yloxy)propoxy] phenyl} propionic acid
12		3-(4-[3-(Biphenyl-4-yloxy) propoxy]-2-{[(pyridine-2-carbonyl)amino]methyl}phenyl) propionic acid
13		3-{2-Benzylcarbamoyl-4-[2-(5-methyl-2-phenyloxazol-4-yl) ethoxy]phenyl} propionic acid
14		3-{2-Benzylcarbamoyl-4-[2-(2-biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]phenyl} propionic acid
15		3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-cyanophenyl} propionic acid

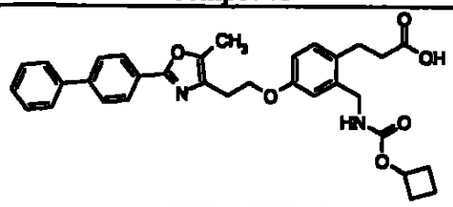
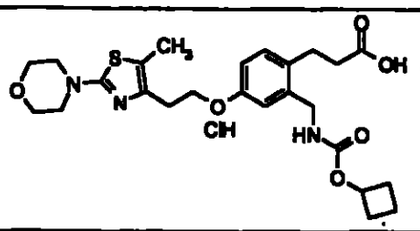
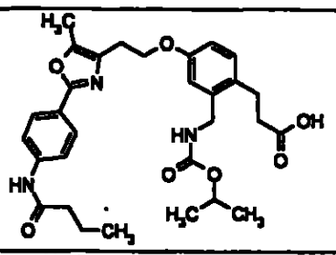
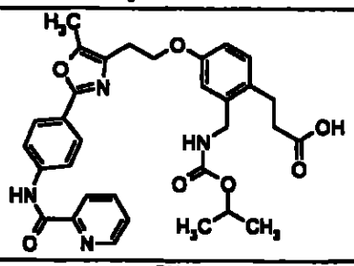
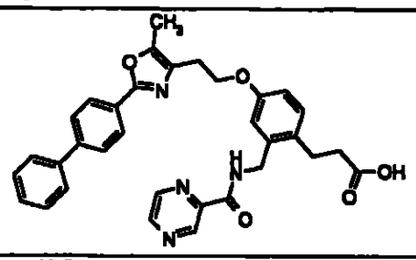
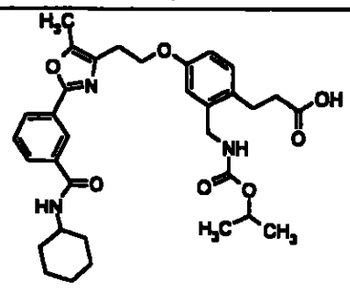
No.	Compound	name
16		3-[4-[2-(2-Biphenyl-3-yl-5-methyloxazol-4-yl)ethoxy]-2-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)phenyl] propionic acid
17		3-{2-(2-Isopropoxycarbonyl-aminoethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid
18		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
19		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(3-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
20		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(6-phenylpyridin-3-yl)thiazol-4-yl]ethoxy}phenyl) propionic acid

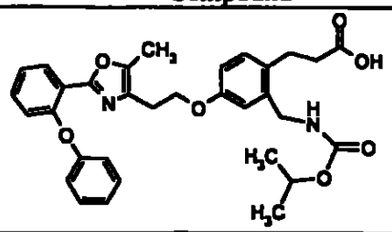
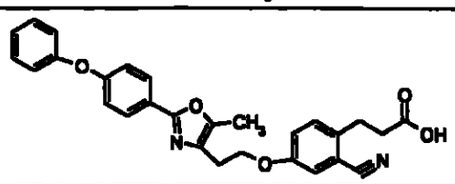
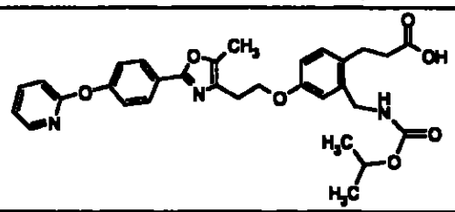
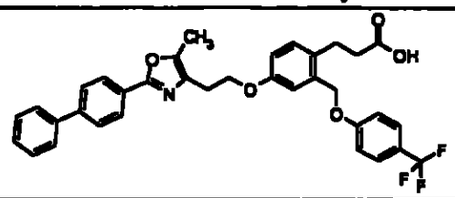
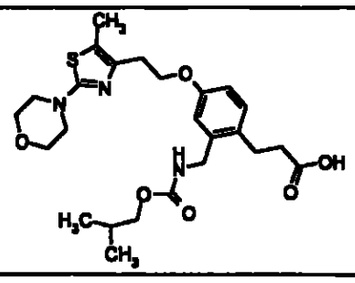
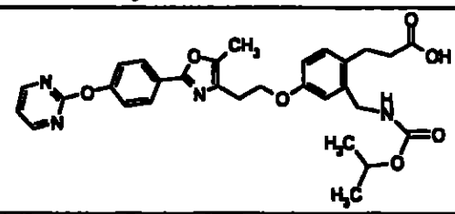
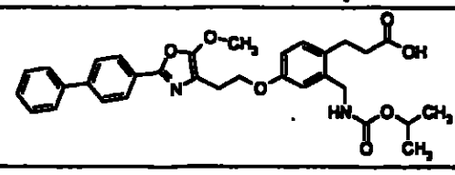
No.	Compound	name
21		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(2-isopropoxycarbonylaminoethyl) phenyl] propionic acid
22		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(isobutoxycarbonylaminomethyl) phenyl] propionic acid
23		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(cyclopentyloxycarbonyl-aminomethyl)phenyl] propionic acid
24		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[2-(4-isopropoxyphenyl)-5-methyloxazol-4-yl]ethoxy} phenyl) propionic acid
25		3-(2-Benzylcarbamoyl-4-{2-[5-methyl-2-(4-phenoxyphenyl) oxazol-4-yl]ethoxy}phenyl) propionic acid

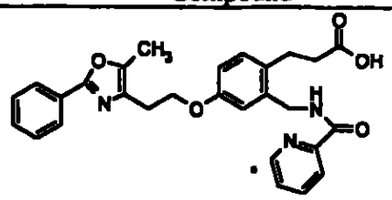
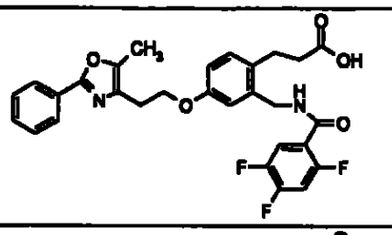
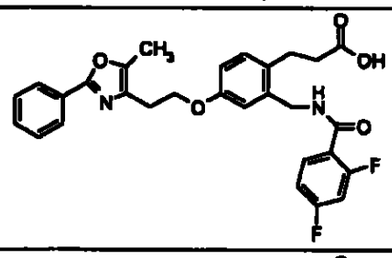
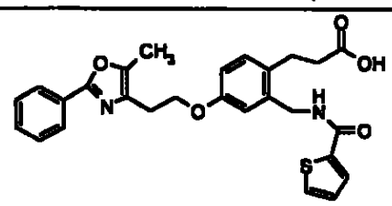
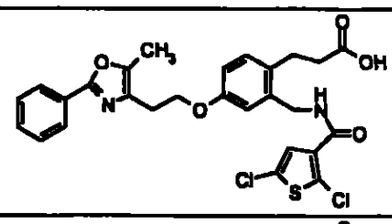
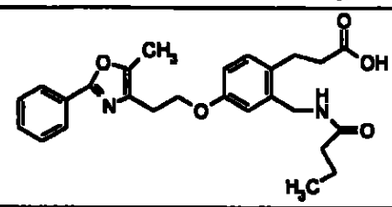
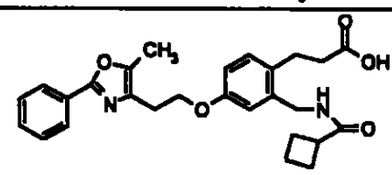
No.	Compound	name
26		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-morpholin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
27		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-piperidin-1-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
28		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-pyrimidin-2-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
29		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-pyrazin-2-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
30		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(6-phenoxypyridin-3-yl)thiazol-4-yl]ethoxy}phenyl) propionic acid
31		3-{2-Cyclohexylcarbamoyl-oxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid

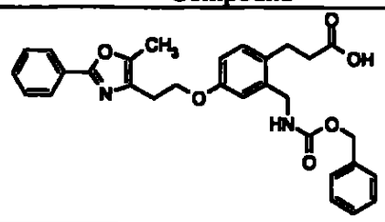
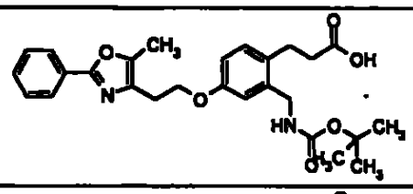
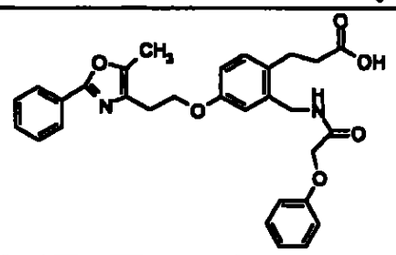
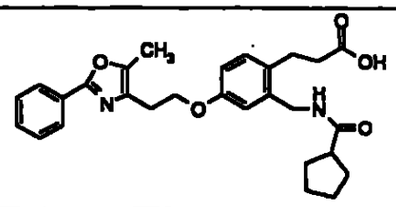
No.	Compound	name
32		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-phenylaminophenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
33		3-(4-{2-[5-Methyl-2-(6-phenylpyridin-3-yl)thiazol-4-yl]ethoxy}-2-{[(pyridine-2-carbonyl)amino]methyl}phenyl) propionic acid HCl salt
34		3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-[(3-methylbutyrylamino) methyl]phenyl} propionic acid
35		3-{2-(Isopropoxycarbonyl-aminomethyl)-4-[2-(5-methoxy-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
36		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(6-phenoxypyridin-3-yl)oxazol-4-yl]ethoxy}phenyl) propionic acid
37		3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-cyclohexylcarbamoyloxy-methylphenyl} propionic acid

No.	Compound	name
38		3-{2-Cyclohexylcarbamoyl-oxymethyl-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl)ethoxy]phenyl} propionic acid
39		3-(2-Cyclohexylcarbamoyl-oxymethyl-4-{2-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
40		3-(2-Cyclohexylcarbamoyl-oxymethyl-4-{2-[5-methyl-2-(4-morpholin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
41		3-[2-(Isopropoxycarbonyl-aminomethyl)-4-(2-{5-methyl-2-[3-(tetrahydropyran-4-yloxy)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid
42		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(cyclopropylmethoxycarbonylaminomethyl)phenyl] propionic acid
43		3-{2-(Cyclopropylmethoxy-carbonylaminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl)ethoxy]phenyl} propionic acid HCl salt

No.	Compound	name
44		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(cyclobutoxycarbonyl-aminomethyl)phenyl]propionic acid HCl salt
45		3-{2-(Cyclobutoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl) ethoxy]phenyl} propionic acid HCl salt
46		3-[4-{2-[2-(4-Butyrylaminophenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl) phenyl] propionic acid
47		3-{2-(Isopropoxycarbonyl- amino-methyl)-4-[2-(5-methyl-2-{4-[(pyridine-2-carbonyl)-amino]-phenyl}-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
48		3-(4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-{[(pyrazine-2-carbonyl) amino]methyl}phenyl) propionic acid
49		3-[4-{2-[2-(3-Cyclohexylcarbamoylphenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl) phenyl] propionic acid

No.	Compound	name
50		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(2-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
51		3-(2-Cyano-4-{2-[5-methyl-2-(4-phenoxy-phenyl)-oxazol-4-yl]-ethoxy}-phenyl) propionic acid
52		3-[2-(Isopropoxycarbonyl-aminomethyl)-4-(2-{5-methyl-2-[4-(pyridin-2-yloxy)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid
53		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(4-trifluoromethylphenoxymethyl) phenyl] propionic acid
54		3-{2-(Isobutoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl)ethoxy]phenyl} propionic acid
55		3-[2-(Isopropoxycarbonyl-aminomethyl)-4-(2-{5-methyl-2-[4-(pyrimidin-2-yloxy) phenyl] oxazol-4-yl}ethoxy)phenyl] propionic acid
56		3-[4-[2-(2-Biphenyl-4-yl-5-methoxyoxazol-4-yl)ethoxy]-2-(isopropoxycarbonylaminomethyl) phenyl] propionic acid

No.	Compound	name
57		3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid
58		3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(2,4,5-trifluoro-benzoylamino)-methyl]-phenyl}-propionic acid
59		3-{2-[(2,4-Difluoro-benzoylamino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
60		3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{[(thiophene-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid
61		3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{[(thiophene-2-carbonyl)-amino]-methyl}-phenyl)-proprionic acid
62		3-{2-(Butyrylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
63		3-{2-[(Cyclobutanecarbonyl-amino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

No.	Compound	name
64		3-{2-(Benzyloxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
65		3-{2-(tert-Butoxycarbonylamino - methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
66		3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(2-phenoxy-acetylamino)-methyl]-phenyl}-propionic acid
67		3-{2-[(Cyclopentanecarbonyl-amino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

Also encompassed by the present invention is a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and at least one compound of the present invention or a pharmaceutically acceptable salt, solvate or hydrate thereof.

Also encompassed by the present invention is a pharmaceutical composition comprising: (1) a compound of formula I according to Claim 1 or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof; (2) a second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acryl CoA:cholestrol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin; and (3) a pharmaceutically acceptable carrier.

Also encompassed by the present invention is a method of modulating a peroxisome proliferator activated receptor (PPAR), comprising the step of contacting the receptor with at least one compound of the present invention or a pharmaceutically acceptable salt, solvate or hydrate thereof. The peroxisome proliferator activated receptor is an alpha-receptor or a gamma-receptor.

Also encompassed by the present invention is a method for treating or preventing a peroxisome proliferator activated receptor-gamma mediated disease or condition comprising the step of administering a compound of Formula I or Formula Ia.

Also encompassed by the present invention is a method for lowering blood-glucose comprising the step of administering an effective amount of a compound of formula I or formula Ia.

Also encompassed by the present invention is a method of treating or preventing disease or condition selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of a compound of formula I or formula Ia.

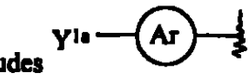
Also encompassed by the present invention is a method of treating or preventing diabetes mellitus in a mammal comprising the step of administering to a mammal a therapeutically effective amount of at least one compound of formula I or formula Ia.

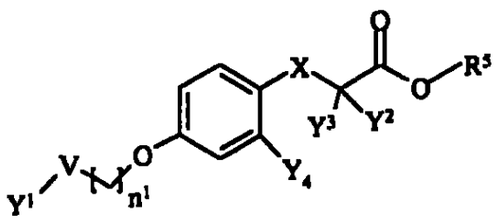
Also encompassed by the present invention is a method of treating or preventing cardiovascular disease in a mammal comprising the step of administering to a mammal a therapeutically effective amount of at least one compound of formula I or formula Ia, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

Also encompassed by the present invention is a method of treating or preventing syndrome X in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of formula I or formula Ia, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

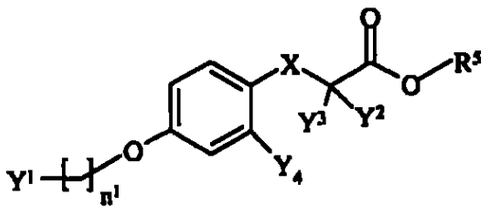
Also encompassed by the present invention is a method of treating or preventing disease or condition selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of a compound of formula I or Ia, and an effective amount of second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acryl CoA:cholestrol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin.

Also encompassed by the present invention is use of a compound of formula I or formula Ia and pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, for the manufacture of a medicament for the treatment of a condition modulated by a PPAR.

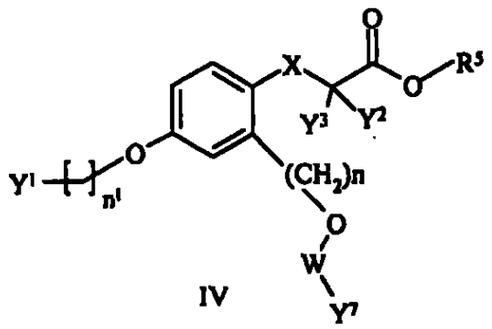
An embodiment of the present invention also includes the compounds having a structural formula II to IX as shown below. These compounds are within the scope of the compound represented by a structural Formula Ia. The substituent Y^1 of these compound includes  , where Y^{1a} and are defined above in formula I, and substituted groups includes substituents recited above and as defined in the embodiment herein.



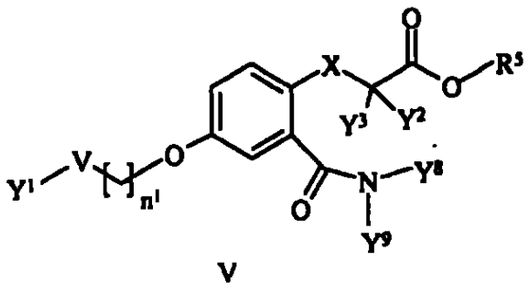
II ;



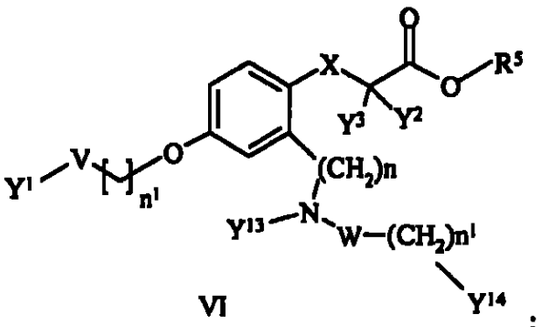
III ;



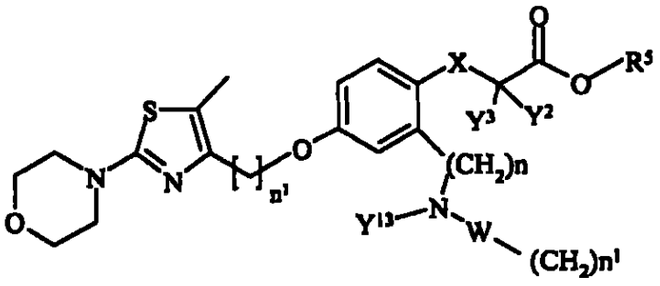
IV ;



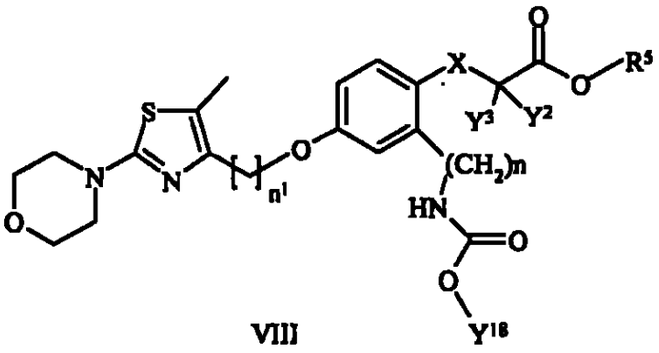
V ;



VI ;

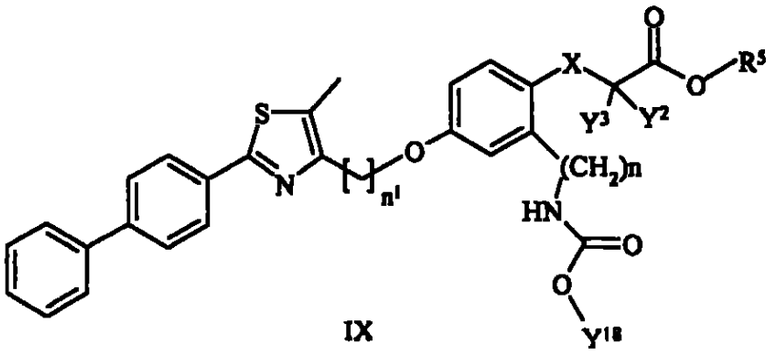


VII ;



VIII

wherein Y^{18} is (C_1-C_6) straight or branched alkyl; and



IX

wherein Y^{18} is (C_1-C_6) straight or branched alkyl.

designated number of substituents as set forth in the embodiment recited above.

The term "cycloalkyl" refers to a saturated or partially saturated carbocycle containing one or more rings of from 3 to 12 carbon atoms. Examples of cycloalkyl includes, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and the like. Cycloalkyl as defined above also includes a tricycle, such as adamantyl. Cycloalkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "halo" refers to fluoro, chloro, bromo and iodo.

The term "haloalkyl" is a C_1-C_6 alkyl group, which is substituted with one or more halo atoms selected from F, Br, Cl and I. An example of a haloalkyl group is trifluoromethyl.

The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like. Alkoxy as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "haloalkyloxy" represents a C_1-C_6 haloalkyl group attached through an oxygen bridge, such as OCF_3. The "haloalkyloxy" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "aryl" includes carbocyclic aromatic ring systems (e.g. phenyl), fused polycyclic aromatic ring systems (e.g. naphthyl and anthracenyl) and aromatic ring systems fused to carbocyclic non-aromatic ring systems (e.g., 1,2,3,4-tetrahydronaphthyl). "Aryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "heteroaryl" group, as used herein, is an aromatic ring system having at least one heteroatom such as nitrogen, sulfur or oxygen and includes monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from O, N, or S. The "heteroaryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heteroaryl are, but are not limited to, furanyl, thienyl (also referred to herein as "thiophenyl") thiazolyl, imidazolyl, isoxazoyl, oxazoyl,

pyrazoyl, pyrrolyl, pyrazinyl, pyridyl, pyrimidyl, pyrimidinyl and purinyl, cinnolinyl, benzofuranyl, benzothienyl, benzotriazolyl, benzoxazolyl, quinoline, isoxazolyl, isoquinoline and the like.

The term "heterocycloalkyl" refers to a non-aromatic ring which contains one or more oxygen, nitrogen or sulfur and includes a monocyclic, bicyclic or tricyclic non-aromatic ring of 5 to 14 carbon atoms containing one or more heteroatoms selected from O, N or S. The "heterocycloalkyl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heterocycloalkyl include, but are not limited to, morpholine, piperidine, piperazine, pyrrolidine, and thiomorpholine. The preferred heterocycloalkyl group is morpholine.

An aryl-C_1-C_4-alkyl group, as used herein, is an aryl substituent that is linked to a compound by an alkyl group having from one to four carbon atoms.

A heteroaryl- C_1-C_4-alkyl group, as used herein, is a heteroaryl substituent that is linked to a compound by an alkyl group having from one to four carbon atoms.

A cycloalkyl- C_1-C_4-alkyl group, as used herein, is a cycloalkyl substituent that is linked to a compound by an alkyl group having from one to four carbon atoms.

An aminoalkyl group is an alkyl group having from one to six carbon atoms, which is substituted with at least one amine represented by $NR^{12}R^{12}$ where each R^{12} is independently a C_1-C_6 alkyl or both R^{12} taken together with the nitrogen to which they are attached form a five or six membered heterocycloalkyl.

Unless otherwise indicated, substituents for alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocycloalkyl also include halo, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, nitro, cyano, CHO, hydroxyl, C_1-C_6 alkanoic acid and $-C(O)NR^{13}R^{13}$ where each R^{13} is independently hydrogen or a C_1-C_6 alkyl.

Substituents for thiophen-2,5-diyl and phenylene include H, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl and C_1-C_4 haloalkoxy.

The term "active ingredient" means the compounds generically described by formula I as well as the salts, solvates and prodrugs of such compounds.

The term "pharmaceutically acceptable" means that the carrier, diluents, excipients and salt must be compatible with the other ingredients of the composition, and not deleterious to the recipient thereof. Pharmaceutical compositions of the present

invention are prepared by procedures known in the art using well-known and readily available ingredients.

"Preventing" refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein.

"Treating" refers to mediating a disease or condition, and preventing or mitigating its further progression or ameliorate the symptoms associated with the disease or condition.

"Pharmaceutically-effective amount" means that amount of a compound of the present invention, or of its salt, solvate, hydrate or prodrug thereof that will elicit the biological or medical response of a tissue, system or mammal. Such an amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount when administered prophylactically to a patient can also be effective to prevent or lessen the severity of the mediated condition. Such an amount is intended to include an amount, which is sufficient to modulate a PPAR receptor such as a PPARα or PPARγ receptor to mediate a disease or condition. Conditions mediated by PPARα or PPARγ receptors include, for example, diabetes mellitus, cardiovascular disease, Syndrome X, obesity and gastrointestinal disease. Additional conditions associated with the modulation of a PPAR receptor include inflammation related conditions which include, for example, IBD (inflammatory bowel disease), rheumatoid arthritis, psoriasis, Alzheimer's disease, Chrohn's disease and ischemia reprofusion injury (stroke and miocardial infarction).

A "mammal" is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice, rats and the like.

Administration to a human is most preferred. A human to whom the compounds and compositions of the present invention are administered has a disease or condition in which control blood glucose levels are not adequately controlled without medical intervention, but wherein there is endogenous insulin present in the human's blood. Non-insulin dependent diabetes mellitus (NIDDM) is a chronic disease or condition characterized by the presence of insulin in the blood, even at levels above normal, but resistance or lack of sensitivity to insulin action at the tissues.

Those skilled in the art will recognize that sterocenters exist in compound of Formula I and Formula Ia. Accordingly, the present invention includes all possible stereoisomers and geometric isomers of formula I including racemic compounds and the optically active isomers.

The compounds of Formula I and Formula Ia contain one or more chiral centers and exist in different optically active forms. When compounds of formula I contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as racemic mixtures. Resolution of the final product, an intermediate or a starting material may be effected by any suitable method known in the art, for example by formation of diastereoisomeric salts which may be separated by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated by crystallization and gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent such as enzymatic esterification; and gas-liquid or liquid chromatography in a chiral environment such as on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. See also *Sterochemistry of Carbon Compounds* by E.L. Eliel (Mcgraw Hill, 1962) and *Tables of Resolving Agents* by S. H. Wilen. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation. In a more preferred embodiment, the compounds of the present invention are S-enantiomers.

When a compound of Formula I or Formula Ia has more than one chiral substituents, it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I or Ia may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of formula I and Ia and mixtures thereof.

Certain compound of formula I or Ia may exist in zwitterionic form, and the present invention includes each zwitterionic form of compounds of formula I or Ia and mixtures thereof.

Certain compounds of formula I or Ia and their salts may exist in more than one crystal form. Polymorphs of compounds of formula I form part of the present invention and may be prepared by crystallization of a compound of formula I or Ia under different conditions, such as using different solvents or different solvent mixtures for recrystallization; crystallization at different temperatures; and various modes of cooling ranging from very fast to very slow cooling during crystallization. Polymorphs may also be obtained by heating or melting a compound of Formula I or Formula Ia followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or other available techniques.

Certain compounds of formula I or Ia and their salts may exist in more than one crystal form, and the present invention includes each crystal form and mixtures thereof.

Certain compounds of formula I or Ia and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

"Pharmaceutically-acceptable salt" refers to salts of the compounds of formula I or Ia which are substantially non-toxic to mammals. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral, organic acid: an organic base or inorganic base. Such salts are known as base addition salts, respectively. It should be recognized that the particular counterion forming a part of any salt of the present invention is not of a critical nature so

long as the salt as a whole is pharmaceutically acceptable and the counterion does not contribute undesired qualities to the salt as a whole.

By virtue of its acidic moiety, a compound of formula I or Ia forms salts with pharmaceutically acceptable bases. Some examples of base addition salts include metal salts such as aluminum; alkali metal salts such as lithium, sodium or potassium; and alkaline earth metal salts such as calcium, magnesium, ammonium, or substituted ammonium salts. Examples of substituted ammonium salts include, for instance, those with lower alkylamines such as trimethylamine and triethylamine; hydroxyalkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine; cycloalkylamines such as bicyclohexylamine or dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydro-abietylamine, glucamine, N-piperazine methylglucamine; bases of the pyridine type such as pyridine, collidine, quinine or quinoline; and salts of basic amino acids such as lysine and arginine.

Examples of inorganic bases include, without limitation, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

Compounds of formula I or Ia, which are substituted with a basic group, may exist as salts with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

Certain compounds of formula I or Ia and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

The compounds of present invention, which bind to and activate the PPARs, lower one or more of glucose, insulin, triglycerides, fatty acids and/or cholesterol, and are therefore useful for the treatment and/or prevention of hyperglycemia, dyslipidemia and in particular Type II diabetes as well as other diseases including syndrome X, Type I diabetes, hypertriglyceridemia, insulin resistance, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, heart failure, coagulopathy,

hypertension, and cardiovascular diseases, especially arteriosclerosis. In addition, these compounds are indicated to be useful for the regulation of appetite and food intake in subjects suffering from disorders such as obesity, anorexia bulimia and anorexia nervosa.

The compounds and compositions of the present invention are also useful to treat acute or transient disorders in insulin sensitivity, which sometimes occurs following a surgery, trauma, myocardial infarction and the like. The compounds and compositions of the present invention are also useful for lowering serum triglyceride levels. Elevated triglyceride level, whether caused by genetic predisposition or by a high fat diet, is a risk factor for the development of heart disease, stroke, and circulatory system disorders and diseases. The physician of ordinary skill will know how to identify humans who can benefit from administration of the compounds and compositions of the present invention.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or non-human mammal which comprises administering an effective, non-toxic amount of a compound of formula I, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycemic human or non-human mammal in need thereof.

The compounds of the present invention are useful as therapeutic substances in preventing or treating Syndrome X, diabetes mellitus and related endocrine and cardiovascular disorders and diseases in human or non-human animals.

The present invention also relates to the use of a compound of formula I as described above for the manufacture of a medicament for treating a PPARα or PPARγ mediated condition, separately or in combination.

A therapeutically effective amount of a compound of formula I can be used for the preparation of a medicament useful for treating Syndrome X, diabetes, treating obesity, lowering tryglyceride levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing arteriosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. In general, a therapeutically effective amount of a compound of formula I of the present invention typically reduces serum glucose levels, more specifically HbA1c, of a patient by about

0.7% or more; typically reduces serum triglyceride levels of a patient by about 20% or more; and increases serum HDL levels in a patient. Preferably, HDL levels can be increased by about 30% or more.

Additionally, an effective amount of a compound of formula I and a therapeutically effective amount of one or more active agents selected from antihyperlipidemic agent, plasma HDL-raising agents, antihypercholesterolemic agents, fibrates, vitamins, aspirin, insulin secretogogues, insulin and the like can be used together for the preparation of a medicament useful for the above described treatments.

Advantageously, compositions containing the compound of formula I or the salts thereof may be provided in dosage unit form, preferably each dosage unit containing from about 1 to about 500 mg. It is understood that the amount of the compounds or compounds of formula I that will be administered is determined by a physician considering of all the relevant circumstances.

Syndrome X includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidemia, hyperglycemia obesity, coagulopathy, hypertension and other complications associated with diabetes. The methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any combination of the following: pre-diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, Type II or non-insulin dependent diabetes, dyslipidemia, hyperglycemia, obesity and the complications associated with diabetes including cardiovascular disease, especially arteriosclerosis.

The compositions are formulated and administered in the same general manner as detailed herein. The compounds of the present invention may be used effectively alone or in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage composition, which contains a compound of formula I and one or more additional active agents, as well as administration of a compound of formula I and each active agent in its own separate pharmaceutical dosage formulation. For example, a compound of formula I or thereof and an insulin secretogogue such as biguanides, thiazolidinediones, sulfonylureas, insulin or α-glucosidose inhibitors can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or

each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, a compound of formula I and one or more additional active agents can be administered at essentially the same time, i.e., concurrently or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

An example of combination treatment or prevention of arteriosclerosis may involve administration of a compound of formula I or salts thereof in combination with one or more of second active therapeutic agents: antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin and the like. As noted above, the compounds of formula I can be administered in combination with more than one additional active agent.

Another example of combination therapy can be seen in treating diabetes and related disorders wherein the compounds of formula I or salts thereof can be effectively used in combination with second active therapeutic, such as sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, other insulin secretogogues, insulin as well as the active agents discussed above for treating arteriosclerosis.

The examples of second therapeutic agents are insulin sensitizers, PPARγ agonists, glitazones, troglitazone, pioglitazone, englitazone, MCC-555, BRL 49653, biguanides, metformin, phenformin, insulin, insulin minetics, sufonylureas, tolbutamide, glipizide, alpha-glucosidase inhibitors, acarbose, cholesterol lowering agent, HMG-CoA reductase inhibitors, lovastatin, simvastatin, pravastatin, fluvastatin, atrovastatin, rivastatin, other statins, sequestrates, cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran, nicotinyl alcohol, nicotinic acid: a nicotinic acid salt, PPARα agonists, fenofibric acid derivatives, gemfibrozil, clofibrate, fenofibrate, benzafibrate, inhibitors of cholesterol absorption, beta-sitosterol, acryl CoA:cholesterol acyltransferase inhibitors, melinamide, probucol, PPARδ agonists, antiobesity compounds, fenfluramine, dexfenfluramine, phentiramine, sulbitramine, orlistat, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, and ileal bile acid transporter inhibitors.

The compounds of the present invention and the pharmaceutically acceptable salts, solvates and hydrates thereof have valuable pharmacological properties and can be used in pharmaceutical compositions containing a therapeutically effective amount of a compound of the present invention, or pharmaceutically acceptable salts, esters or prodrugs thereof, in combination with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material and other conventional adjuvants. Proper formulation is dependent upon the route of administration chosen. Pharmaceutical compositions typically contain from about 1 to about 99 weight percent of the active ingredient, which is a compound of the present invention.

Preferably, the pharmaceutical formulation is in unit dosage form. A "unit dosage form" is a physically discrete unit containing a unit dose suitable for administration in human subjects or other mammals. For example, a unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts considering various factors, such as without limitation, the species, age, weight, sex, medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed, and the like.

Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses of two, three or more times per day. Where delivery is via transdermal forms, administration is continuous.

Suitable routes of administration of pharmaceutical compositions of the present invention include, for example, oral, eye drop, rectal, transmucosal, topical or intestinal administration; parenteral delivery (bolus or infusion), including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraven-tricular, intravenous, intraperitoneal, intranasal, or intraocular injections. The compounds of the present invention can also be administered in a targeted drug delivery system, such as in a liposome coated with endothelial cell-specific antibody.

For oral administration, the compounds of the present invention can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the present invention to be formulated as tablets, pills, powders, sachets, granules, dragees, capsules, liquids, elixirs, tinctures, gels, emulsions, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compound with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.

For oral administration in the form of a tablet or capsule, the active ingredient may be combined with an oral, non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, methyl cellulose, calcium carbonate, calcium phosphate, calcium sulfate, sodium carbonate, mannitol, sorbitol, and the like; together with, optionally, disintegrating agents, such as, without limitation, cross-linked polyvinyl pyrrolidone, maize, starch, methyl cellulose, agar, bentonite, xanthan gum, alginic acid: or a salt thereof such as sodium alginate, and the like; and, optionally, binding agents, for example, without limitation, gelatin, acacia, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethyl-cellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid: sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances, which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile liquid formulations include suspensions, emulsions, syrups, and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active

compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

All formulations for oral administration should be in dosages suitable for such administration. Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules.

For parental administration the compounds of the present invention or salts thereof can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. Formulations for injection may be presented in unit dosage form, such as in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that each syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against any contamination. The carrier can be solvent or dispersion medium containing, for example, water, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in a conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of a dry powder inhaler, or an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, lyophilized solid or paste, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing for example up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

The following pharmaceutical formulations 1 through 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active Ingredient" refers to a compound of the present invention according to formula I and/or Ia or salts thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight
Active Ingredient	0.25
Ethanol	25.75
Propellant 22 (chlorodifluoromethane)	74.00
Total	100.00

The Active Ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active Ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The Active Ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules, each containing 80 mg of Active Ingredient, are made as follows:

Active Ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The Active Ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of Active Ingredient, are made as follows:

Active Ingredient	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The Active Ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2g capacities and allowed to cool.

Formulation 7

Suspensions each containing 50 mg of Active Ingredient per 5 ml dose are made as follows:

Active Ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active Ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

An intravenous formulation may be prepared as follows:

Active Ingredient	100 mg
Isotonic saline	1,000 ml

The solution of the above materials generally is administered intravenously to a subject at a rate of 1 ml per minute.

In yet another embodiment of the present invention, the compound is radiolabelled, such as with carbon-14 or tritiated. Said radiolabelled or tritiated compounds are useful as reference standards for in vitro assays to identify new PPARα and PPARγ agonists.

Binding and Cotransfection Studies

The in vitro potency of compounds in modulating PPARγ, PPARα and PPARδ receptors are determined by the procedures detailed below. DNA-dependent binding (ABCD binding) is carried out using Scintillation Proximity Assay (SPA) technology with PPAR receptors. Tritium-labeled PPARα and PPARγ agonists are used as radioligands for generating displacement curves and IC_{50} values with compounds of the present invention. Cotransfection assays are carried out in CV-1 cells. The reporter plasmid contains an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the luciferase reporter cDNA. Appropriate PPARs and RXRα are constitutively expressed using plasmids containing the CMV promoter. Since for PPARα and PPARβ, interference by endogenous PPARγ in CV-1 cells is an issue, in order to eliminate such interference, a GAL4 chimeric system is used in which the DNA binding domain of the transfected PPAR is replaced by that of GAL4, and the GAL4 response element is utilized in place of the AOX PPRE. Cotransfection efficacy is determined relative to PPARα agonist and PPARγ agonist reference molecules. Efficacies are determined by computer fit to a concentration-response curve, or in some cases at a single high concentration of agonist (10 μM). A typical range for concentration determination (IC_{50}) is from 1nM to 10μM. For binding or cotransfection studies with receptors other than

PPARs, similar assays are carried out using appropriate ligands, receptors, reporter constructs and etc. for that particular receptor.

These studies are carried out to evaluate the ability of compounds of the present invention to bind to and/or activate various nuclear transcription factors, particularly huPPARα ("hu" indicates "human"), huPPARγ and huPPARδ. These studies provide in-vitro data concerning efficacy and selectivity of compounds of the present invention. Furthermore, binding and cotransfection data for compounds of the present invention are compared with corresponding data for reference compounds that act on either huPPARα or huPPARγ. The typical range of concentration for binding is from 1nM to 10μM. The concentration of test compound required to effect 50% maximal activation of PPARα ($IC_{50}\alpha$) and PPARγ ($IC_{50}\gamma$) is determined.

Evaluation of Triglyceride and Cholesterol Level in HuapoAI Transgenic Mice

Five to six week old male mice, transgenic for human apoAI [C57Bl/6-tgn(apoa1)1rub, Jackson Laboratory, Bar Harbor, ME] are housed five per cage (10"x20"x8" with aspen chip bedding) with food (Purina 5001) and water available at all times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed and assigned to groups based on body weight. Beginning the following morning, mice are dosed daily by oral gavage for 7 days using a 20 gauge, 1½" curved disposable feeding needle. Treatments are test compounds (30 mg/kg), a positive control (fenofibrate, 100 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/ 0.25% Tween80 (w/v); 0.2 ml/mouse]. Prior to termination on day 7, mice are weighed and dosed. Three hours after dosing, animals are anesthetized by inhalation of isoflurane (2-4%) and blood obtained via cardiac puncture (0.7-1.0 ml). Whole blood is transferred to serum separator tubes (Vacutainer SST), chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for triglycerides, total cholesterol, compound levels and serum lipoprotein profile by fast protein liquid chromatography (FPLC) coupled to an inline detection system. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

The animals dosed with vehicle have average triglycerides values of about 60 to 80 mg/dl, which are reduced by the positive control fenofibrate (33-58 mg/dl with a mean reduction of 37%). The animals dosed with vehicle have average total serum

cholesterol values of about 140 to180 mg/dl, which are increased by fenofibrate (about 190 to 280 mg/dl with a mean elevation of 41%). When subject to FPLC analysis, pooled sera from vehicle-treated hu apoAI transgenic mice have a high-denaity lipoprotein cholesterol (HDLc) peak area which ranges from 47v-sec to 62v-sec. Fenofibrate increases the amount of HDLc (68-96v-sec with a mean percent increase of 48%). Test compounds evaluated in terms of percent increase in the area under the curve. Representative compounds of the present invention are tested using the above methods or substantially similar methods.

Evaluation of Glucose Levels in db/db Mice

Five week old male diabetic (db/db) mice [C57BlKs/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor, ME] or lean littermates (db+) are housed 6 per cage (10"x20"x8" with aspen chip bedding) with food (Purina 5015) and water available at all times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed and bled via the tail vein for determination of initial glucose levels. Blood is collected (100 µl) from unfasted animals by wrapping each mouse in a towel, cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized capillary tube balanced on the edge of the bench. Sample is discharged into a heparinized microtainer with gel separator (VWR) and retained on ice. Plasma is obtained after centrifugation at 4°C and glucose is measured immediately. Remaining plasma is frozen until the completion of the experiment, and glucose and triglycerides are assayed in all samples. Animals are grouped based on initial glucose levels and body weights. Beginning the following morning, mice are dosed daily by oral gavage for 7 days using a 20 gauge, 1½" curved disposable feeding needle. Treatments are test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice are weighed and bled (tail vein) for about 3 hours after dosing. Twenty-four hours after the 7th dose (i.e., day 8), animals are bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 are assayed for glucose. After 24 hour bleed, animals are weighed and dosed for the final time. Three hours after dosing on day 8, animals are anesthetized by inhalation of isoflurane, and blood obtained is via cardiac puncture (0.5-0.7 ml). Whole blood is transferred to serum separator tubes, chilled on ice and permitted to clot. Serum is

obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

The animals dosed with vehicle have average triglycerides values of about 170 to 230 mg/dl, which are reduced by the positive PPARγ control (about 70 to 120 mg/dl with a mean reduction of 50%). Male db/db mice are hyperglycemic (average glucose of about 680 to 730 mg/dl on the 7th day of treatment), while lean animals have average glucose levels between about 190 and 230 mg/dl. Treatment with the positive control agent reduces glucose significantly (about 350 to 550 mg/dl with a mean decrease towards normalization of 56%).

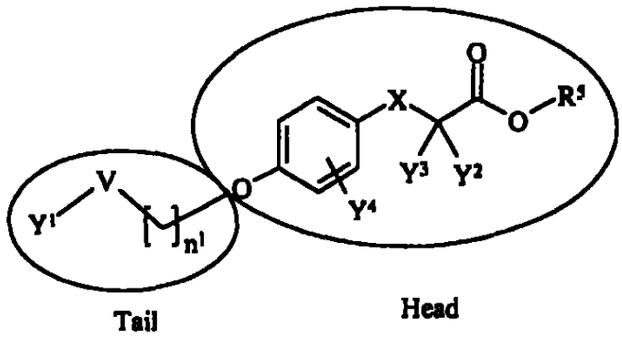
Glucose is measured colorimetrically by using commercially purchased reagents (Sigma #315-500). According to the manufacturers, the procedures are modified from published work (McGowan et al. *Clin Chem*, 20:470-5 (1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129th Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide for each mole of analyte coupled with a color reaction first described by Trinder (Trinder, P. *Ann Clin Biochem*, 6:24 (1969)). The absorbance of the dye produced is linearly related to the analyte in the sample. The assays are further modified for use in a 96 well format. Standards (Sigma #339-11, Sigma #16-11, and Sigma #CC0534 for glucose, triglycerides and total cholesterol, respectively), quality control plasma (Sigma # A2034), and samples (2 or 5 µl/well) are measured in duplicate using 200 µl of reagent. An additional aliquot of sample, pipetted to a third well and diluted in 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature (18, 15, and 10 minutes for glucose, triglycerides and total cholesterol, respectively) on a plate shaker and absorbance read at 500 nm (glucose and total cholesterol) or 540 nm (triglycerides) on a plate reader. Sample absorbance is compared to a standard curve (100-800, 10-500, and 100-400 mg/dl for glucose, triglycerides and total cholesterol, respectively). Values for the quality control sample are consistently within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment are assayed at the same time to minimize inter-assay variability.

Serum lipoproteins are separated and cholesterol is quantitated with an in-line detection system. Sample is applied to a Superose® 6 HR 10/30-size exclusion column (Amersham Pharmacia Biotech) and eluted with phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16 ml/min is mixed with the column effluent through a T-connection, and the mixture is passed through a 15 m x 0.5 mm id knitted tubing reactor immersed in a 37°C water bath. The colored product produced in the presence of cholesterol is monitored in the flow stream at 505 nm, and the analog voltage from the monitor is converted to a digital signal for collection and analysis. The change in voltage corresponding to change in cholesterol concentration is plotted against time, and the area under the curve corresponding to the elution of VLDL, LDL and HDL is calculated (Perkin Elmer Turbochrome software).

The compounds of the present invention can be prepared according to the procedures of the following schemes and examples, which may further illustrate details for the preparation of the compounds of the present invention. The compounds illustrated in the schemes and examples are, however, not to be construed as forming the only genus that is considered as the present invention.

General Reaction Scheme:

The compounds of the present invention, in general, may be prepared according to the Reaction Schemes described below. When describing various aspects of the present compounds, the terms "Tail" and "Head" are used as their concept is illustrated below.



Tail Head

Reaction Scheme 1:

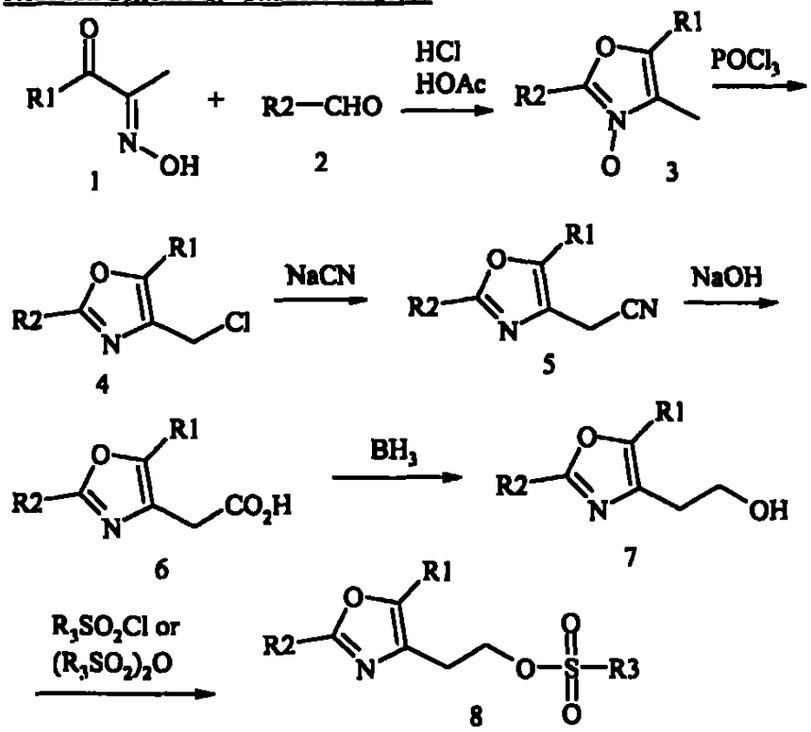
Tail—Z_1 + HO—Head' ⟶ Tail—Head

Z_1 = leaving group

Head'=modified headpiece to show OH substitution

As shown in Reaction Scheme I, the compounds of the present invention, in general, can be divided into Tail and Head regions where a nucleophilic headpiece is coupled with an electrophilic tailpiece. These regions can be further modified as shown in the following reaction schemes.

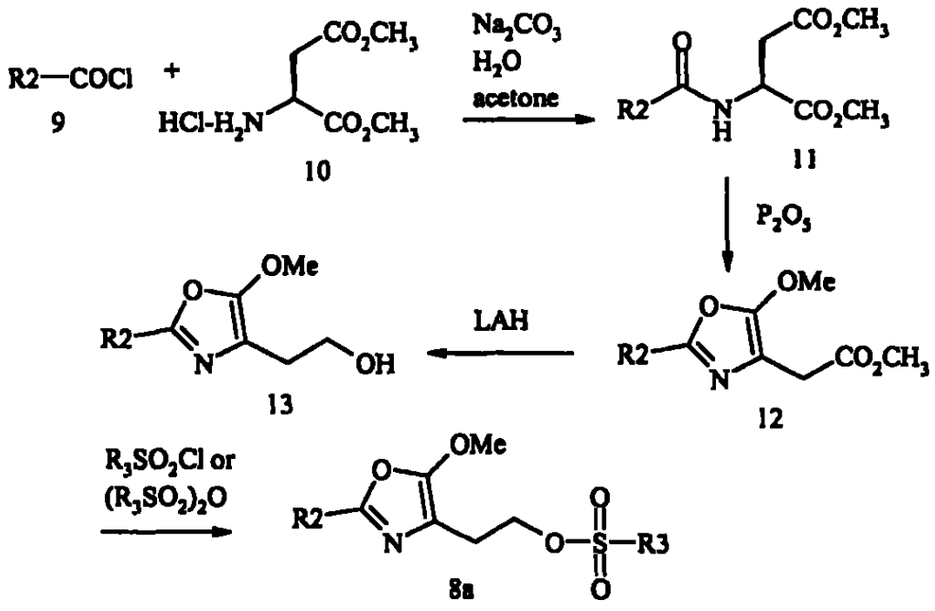
Reaction Scheme 2: Oxazole tailpiece



R1 is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, haloalkyl or haloalkoxy;
R2 is Y^{1a};
R3 is alkyl (methyl) or tolyl.

As shown in Reaction Scheme 2, an intermediate oxazole tailpiece can be prepared by a condensation of dionemonoxime (1) with aldehyde (2) such as bromobenzaldehyde in the presence of acid such as hydrochloric acid or acetic acid to give an oxazole n-oxide compound (3). The oxazole n-oxide is then treated with phosphorous oxychloride in an organic solvent to form chloromethyl substituted-oxazole (4). Compound (4) is further treated with a cyanide to form cyanomethyl oxazole compound (5). The cyano group of compound (5) is converted to a carboxylic acid group by treatment with an alkali metal hydroxide such as NaOH to form carboxymethyl substituted oxazole (6), which is further treated with a carboxylic acid reducing agent, such as borane or lithium aluminum hydride (LAH) to form compound (7). Compound (7) can be converted to oxazolyl sulfonyl ester (8) in the presence of a base by treatment with a sulfonyl halide or sulfonyl anhydride (R_3SO_2Cl or $(R_3SO_2)_2O$), such as tosyl anhydride, mesyl anhydride, tosyl chloride or mesyl chloride.

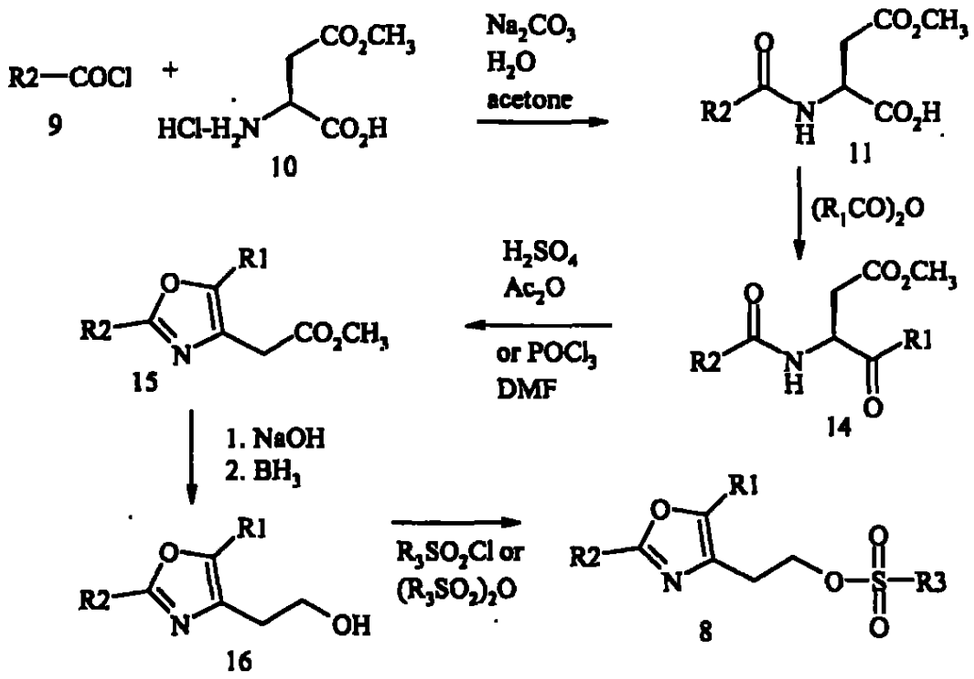
Reaction Scheme 3: Oxazole tailpiece



Alternatively, an intermediate of oxazole tailpiece can be prepared as shown in Reaction Scheme 3. Acid chloride (9) is reacted with L-aspartic acid dimethyl ester (10) to give amide compound (11), which undergoes cyclization to form an oxazole

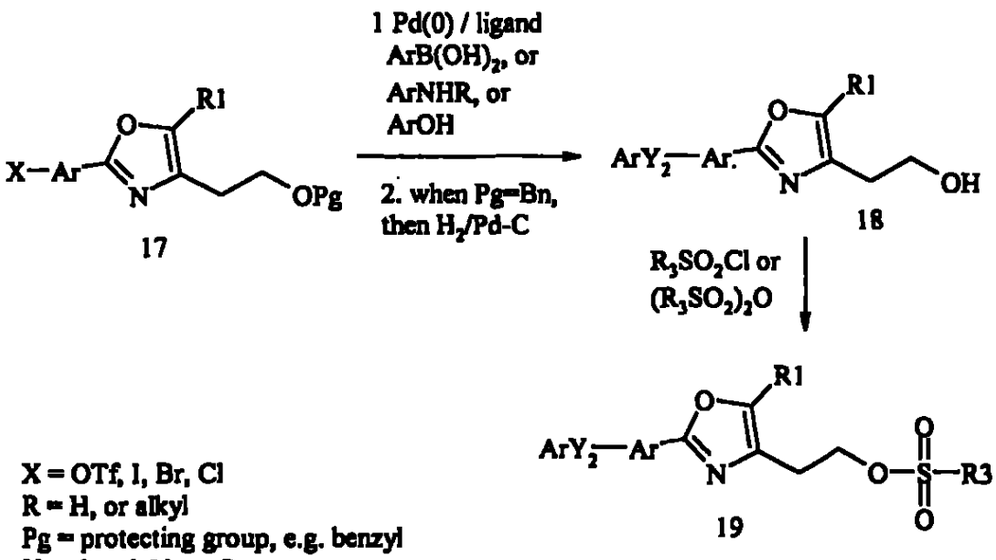
ring (12) by treatment with a dehydrating agent such as P_2O_5. The ester compound (12) is reduced by treating with LAH to give alcohol (13), which is then converted to oxazolyl sulfonyl ester (8a) as described above in Reaction Scheme 2.

Reaction Scheme 4: Oxazole tailpiece



Another route to an intermediate of oxazole tailpiece is shown in Reaction Scheme 4. Acid chloride (9) and L-aspartic acid monomethyl ester (10) are reacted to give amide compound (11), which is further reacted to give ketone (14). The ketone compound undergoes a cyclization in the presence of dehydrating agent such as $POCl_3$ or H_2SO_4/acetic anhydride to form oxazole ring (15). Compound (15) undergoes reduction to give alcohol (16), which is then converted to oxazolyl sulfonyl ester (8) as described above in Reaction Scheme 2.

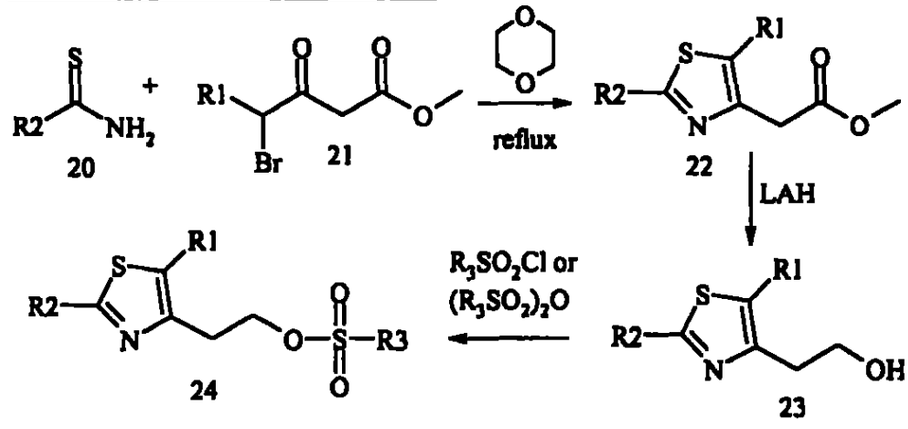
Reaction Scheme 5: Oxazole tailpiece



X = OTf, I, Br, Cl
R = H, or alkyl
Pg = protecting group, e.g. benzyl
Y_2 = bond, N, or O
ArY_2 - Ar = Y^{1a}

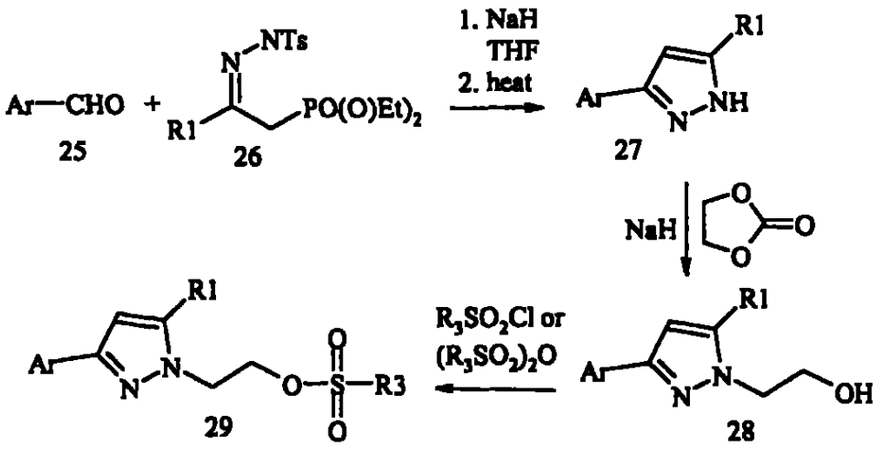
Another route to an intermediate of the oxazole tailpiece is shown in Reaction Scheme 5. The oxazole compound (17) can undergo a coupling reaction in the presence of palladium catalyst with an aryl boronic acid, aryl alcohol or aryl amine followed by deprotection to yield the corresponding compound (18). Compound (18) is then converted to oxazolyl sulfonyl ester (19) as described above in Reaction Scheme 2.

Reaction Scheme 6: Thiazole tailpiece



As shown in Reaction Scheme 6, an intermediate thiazole tailpiece can be prepared by the condensation of compound (20) with bromo alkyl ester (21) in the presence of 1,4-dioxane followed by cyclization to give thiazole compound (22). The thiazole (22) then undergoes an ester reduction to give alcohol (13), which is further converted to thiazole sulfonyl ester (8) as described above in Reaction Scheme 2.

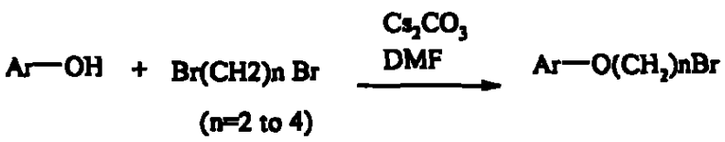
Reaction Scheme 7: Pyrazole tailpiece



Ar = Y^{1a}

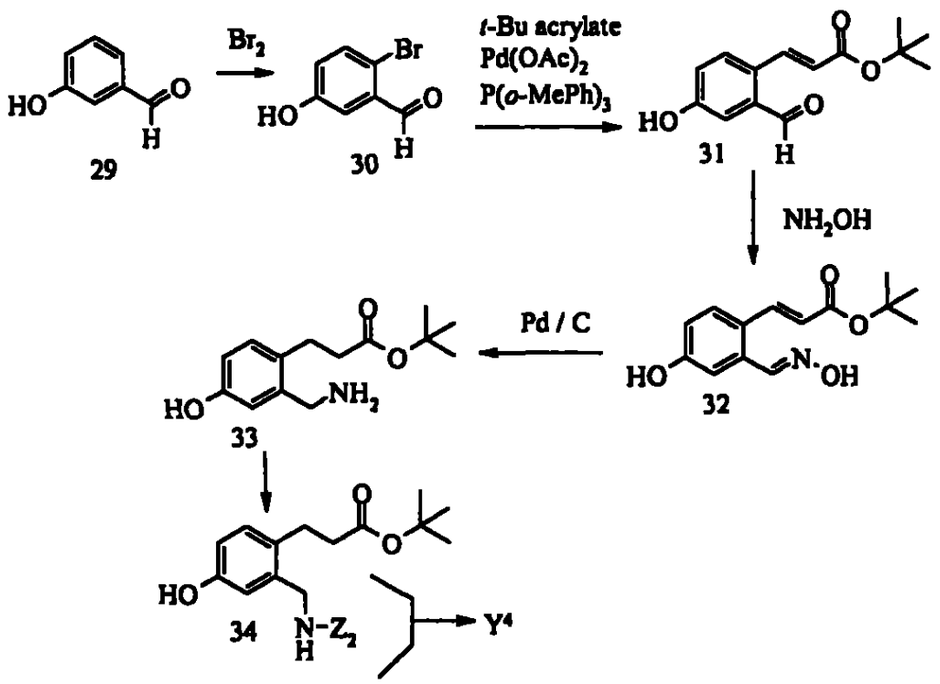
As shown in Reaction Scheme 7, an intermediate pyrazole tailpiece can be prepared by the condensation of arylaldehyde (25) with compound (26) in the presence of base followed by cyclization to give pyrazole compound (27). Compound (27) is treated with ethylene carbonate in the presence of base such as NaH to give alkylated compound (28), which is then converted to pyrazole sulfonyl ester (29) as described above in Reaction Scheme 2.

Reaction Scheme 8: Preparation of arylether bromide



Reaction Scheme 8 shows the preparation of arylether bromide by a nucleophilic substitution reaction of an aryl alcohol with a dibromide in the presence of a base.

Reaction Scheme 9: Preparation of Aminomethyldihydrocinnamate

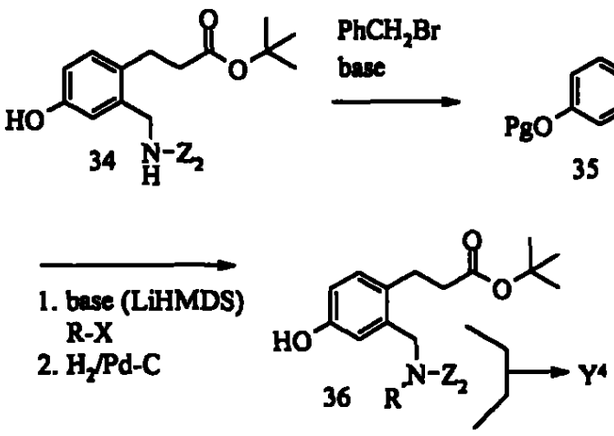


Z_2 = COR, CONHR, CSNHR, COOR, SO_2R;
where R is selected from Y^7

Reaction Scheme 9 shows the synthetic route to prepare aminomethyldihydrocinnamate headpiece. 3-Hydroxybenzaldehyde (29) is reacted with bromine to give 2-bromo-5-hydroxybenzaldehyde (30), which is then coupled to t-butylacrylate to give the compound (31). Compound (31) is treated with NH_2OH to give oxime (32), which undergoes hydrogenation to give aminomethyldihydrocinnamate (33).

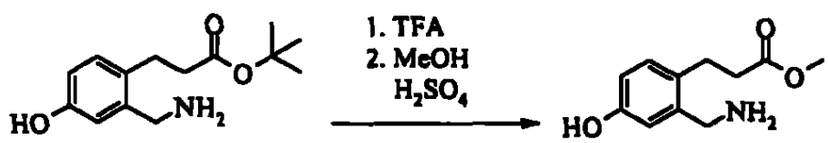
Various functional groups (Z_2) can be introduced at the aminomethyl portion of compound (33) to afford compound (34).

Reaction Scheme 10: N-alkyl headpiece



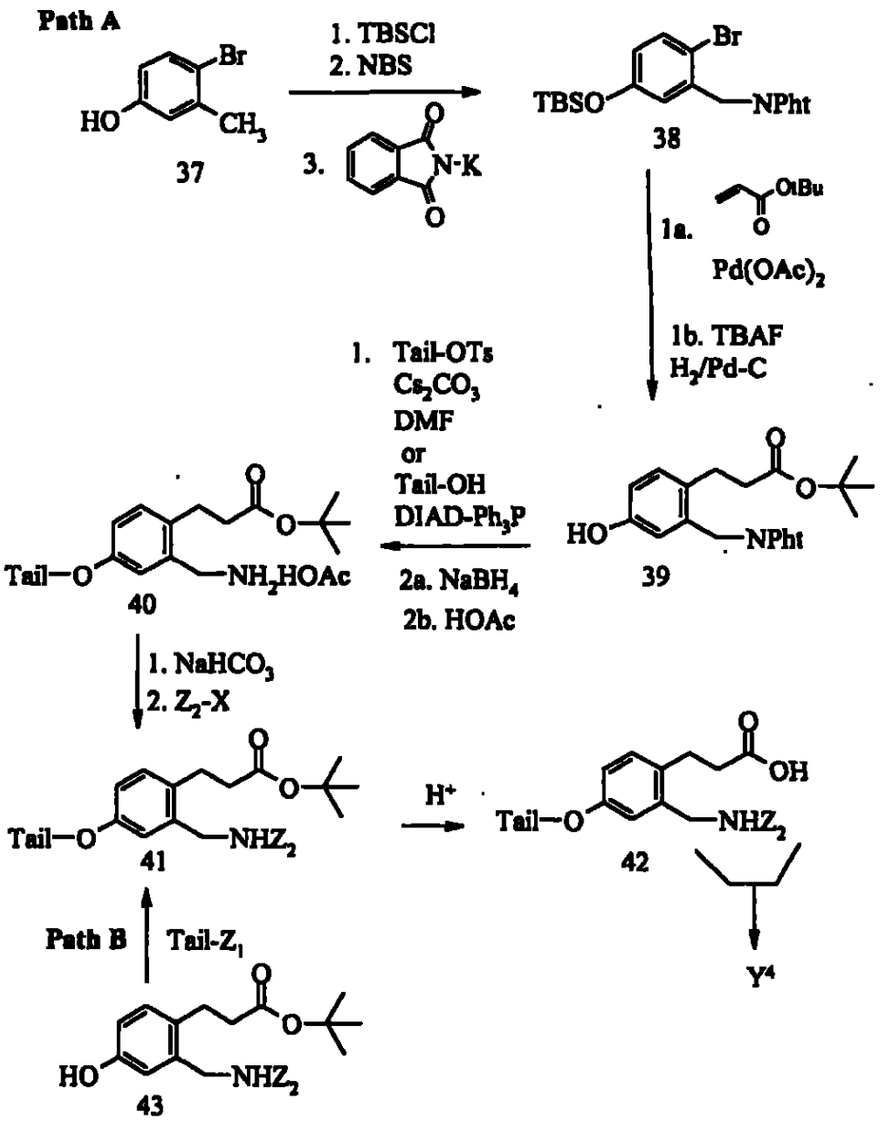
As shown in Reaction Scheme 10, aminomethyl portion of the headpiece compound (34) can be further modified. Phenol (34) is protected with a protecting group such as a benzyl group to give compound (35). Compound (35) undergoes a nucleophilic substitution reaction with an alkyl halide (RX) under basic conditions followed by a deprotection to give phenol compound (36).

Reaction Scheme 11: Transesterification



Reaction Scheme 11 illustrates a transesterification reaction of the compound as shown above. The tert-butyl ester can be cleaved under acidic conditions such as TFA. The corresponding carboxylic acid group can be re-esterified with an appropriate alcohol, such as methanol in the presence of an acid such as H_2SO_4.

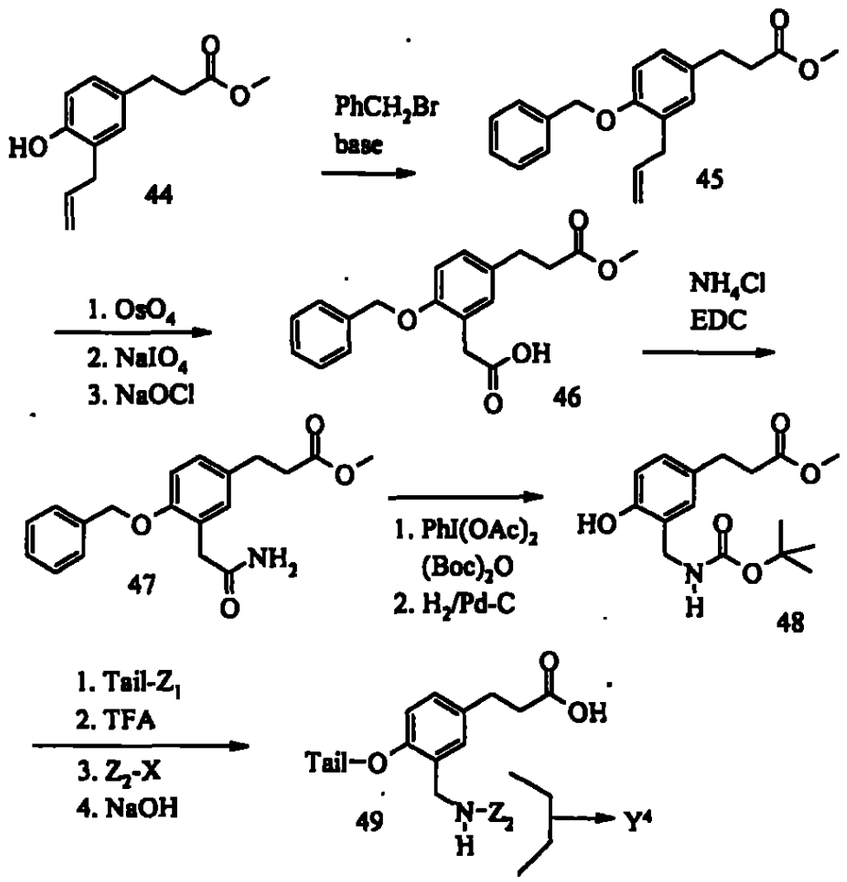
Reaction Scheme 12: Tail-Head coupling with aminomethyldihydrocinnamates



As shown in Reaction Scheme 12, headpiece and tailpiece can be modified to introduce various functional groups. In Path A, the protecting group (TBS) is first attached to the phenol of compound (37) and then radical bromination followed by alkylation with potassium phthalimide yields compound (38). Compound (38) undergoes a Heck coupling reaction with tert-butyl acrylate in the presence of palladium catalyst and then deprotection of silyl group followed by hydrogenation to give compound (39). Compound (39) is coupled with a tailpiece and removal of phthaloyl group yields

compound (40). After neutralization, the amino function of (40) can be modified to give (41). Easter hydrolysis under acidic conditions gives (42). Alternatively, as shown in Path B, compound (42) can be obtained by coupling headpiece (43) with a tailpiece to give compound (41) followed by ester hydrolysis.

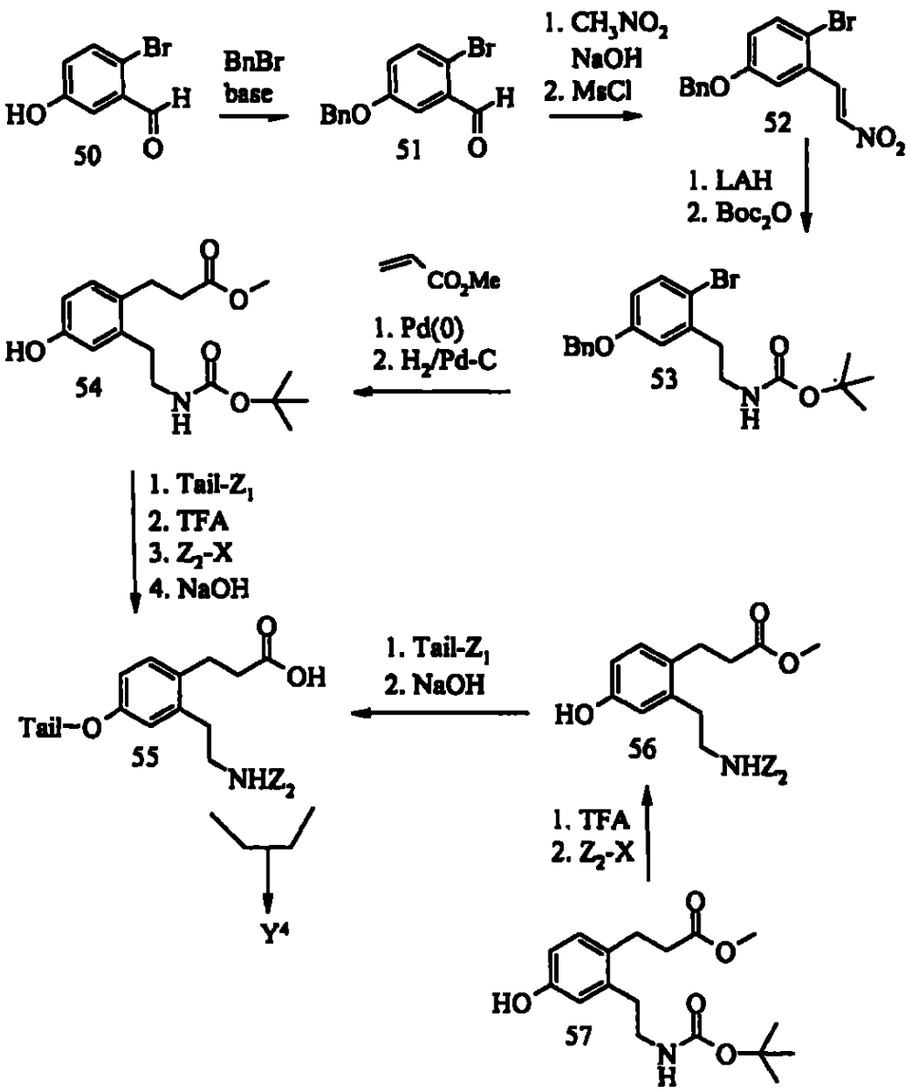
Reaction Scheme 13: Synthesis of meta-aminomethyldihydrocinnamates



Reaction Scheme 13 shows a synthesis for meta-substituted aminomethyldihydrocinnamates. A protecting group such as benzyl is attached to the phenol of compound (44) to give protected compound (45). Compound (45) undergoes glycol formation followed by cleavage and oxidation reactions to give carboxylic acid compound (46), which is then converted to amide compound (47). Compound (47) undergoes a rearrangement and subsequent amine protection with Boc anhydride followed by deprotection of benzyl ether to afford phenol (48). Compound (48) is

coupled with a tailpiece followed by deprotection to give the intermediate, which then undergoes further modification at the aminomethyl portion of the compound followed by hydrolysis to give compound (49).

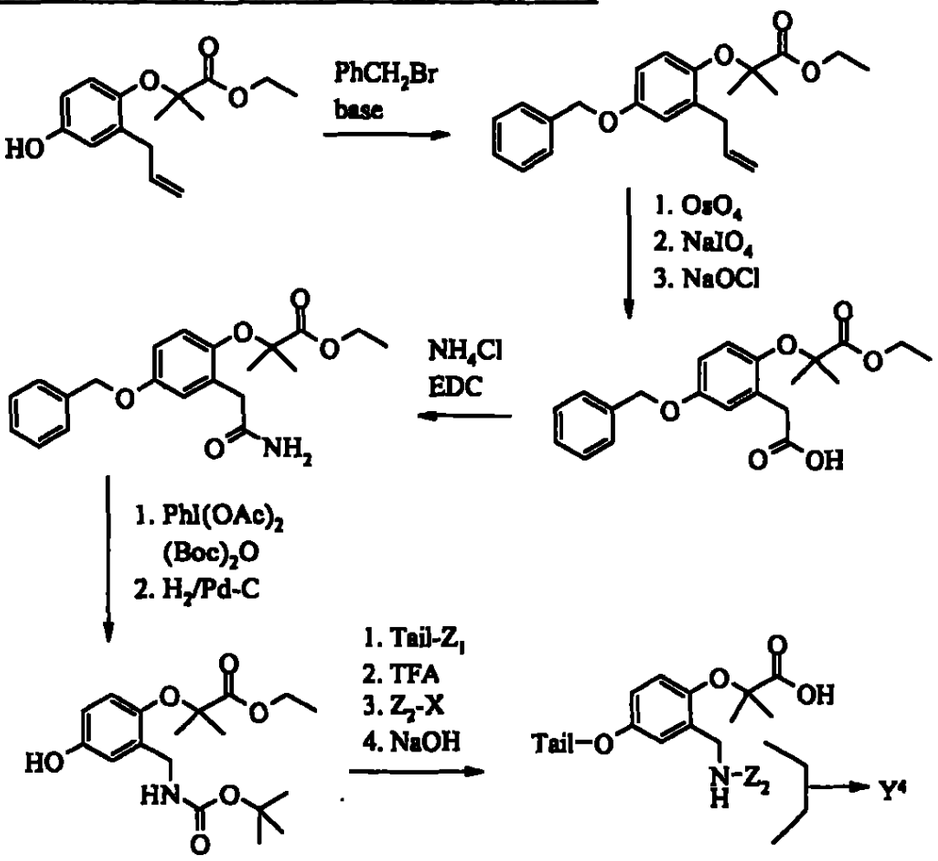
Reaction Scheme 14: Synthesis of Aminoethyldihydrocinnamates



Reaction Scheme 14 shows the synthetic route to prepare aminoethyldihydrocinnamate headpiece. A protecting group such as benzyl is attached to aryl alcohol of compound (50) to give protected compound (51), which is then converted to nitro-olefin compound (52). Compound (52) undergoes reduction of the nitro-olefin by

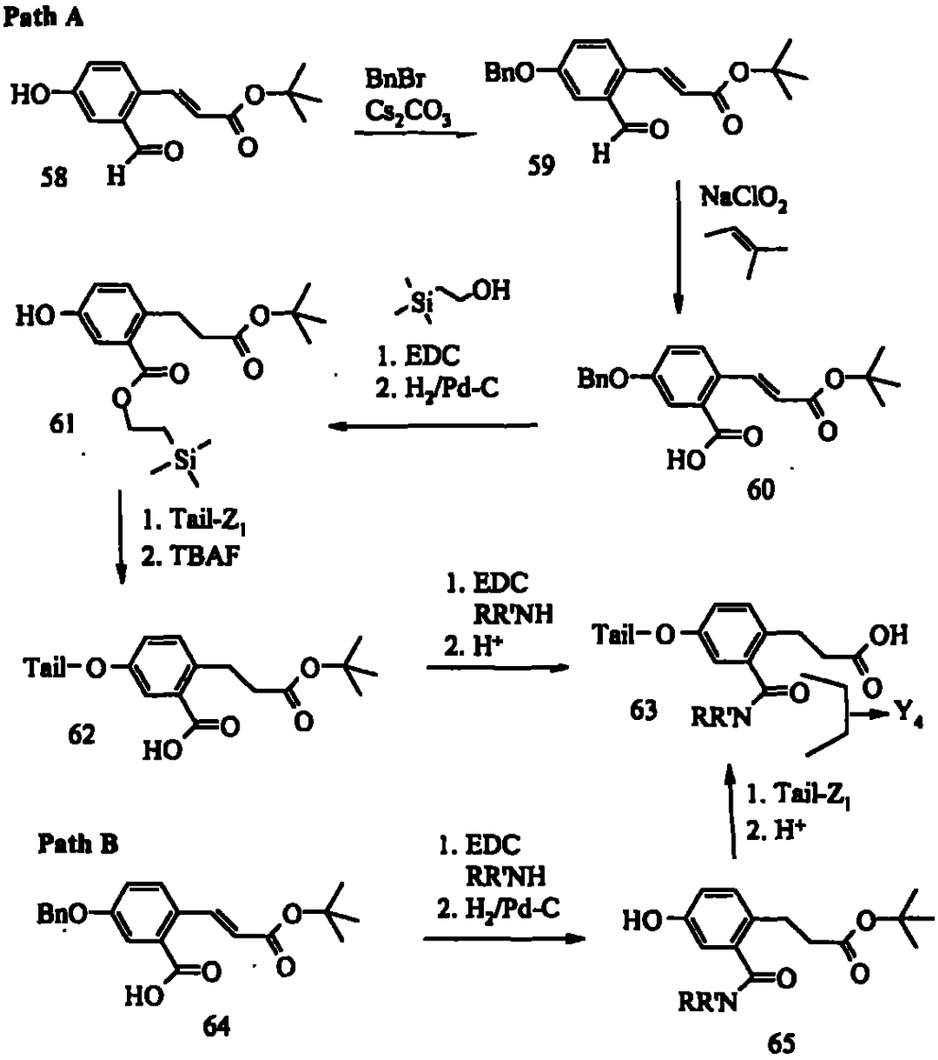
treatment with LAH followed by introduction of an amine protecting group such as Boc to give compound (53). Compound (53) undergoes a coupling reaction with methyl acrylate in the presence of a palladium catalyst followed by deprotection of phenol group to give the phenol compound (54). Compound (54) is then coupled with a tailpiece followed by deprotection of Boc group to give the intermediate compound, which then can undergo further modification at the aminoethyl portion of the compound followed by hydrolysis to give compound (55). Alternatively, compound (57) is deprotected followed by modification at the aminoethyl portion of the compound to give compound (56). Compound (56) can be coupled with a tailpiece followed by ester hydrolysis to afford compound (55).

Reaction Scheme 15: Synthesis of Aminomethylfibrates



Reaction Scheme 15 shows a synthetic route to prepare aminomethylfibrate compounds. The reaction is carried out by following a substantially similar synthetic route as described in Reaction Scheme 13.

Reaction Scheme 16: Synthesis of Carboxamidodihydrocinnamates

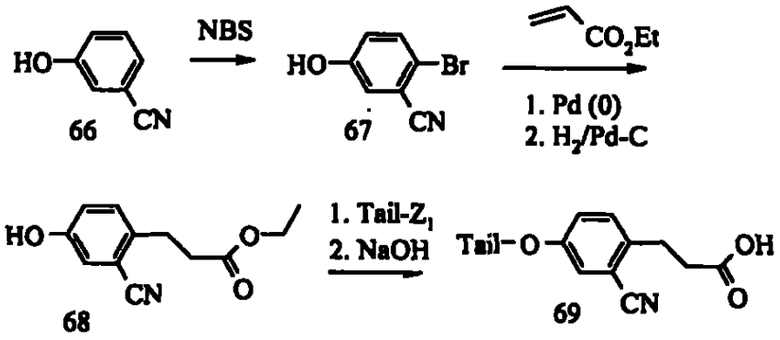


$Y^4 = (C_0\text{-}C_3)C(O)NR^5(C_0\text{-}C_5)\text{-}Y^7$

Reaction Scheme 16 shows the synthetic routes to carboxamidodihydrocinnamates by Path A or Path B. Path A allows for rapic amide variation and Path B for tailpiece variation. In path A, the protecting group such as benzyl is attached to the phenol of compound (58) to give protected compound (59). Compound (59) is oxidized to give carboxylic acid compound (60), which then undergoes esterification followed by deprotection of the phenol to give compound (61). Compound (61) is coupled with a tailpiece followed by deprotection of carboxylic acid group to give

compound (62), which then undergoes amide formation followed by ester hydrolysis to afford compound (63). Alternatively as shown in path B, compound (64) can undergo an amide formation followed by reduction and deprotection of phenol group to give compound (65). Compound (65) then can be coupled with a tailpiece followed by ester hydrolysis to yield compound (63).

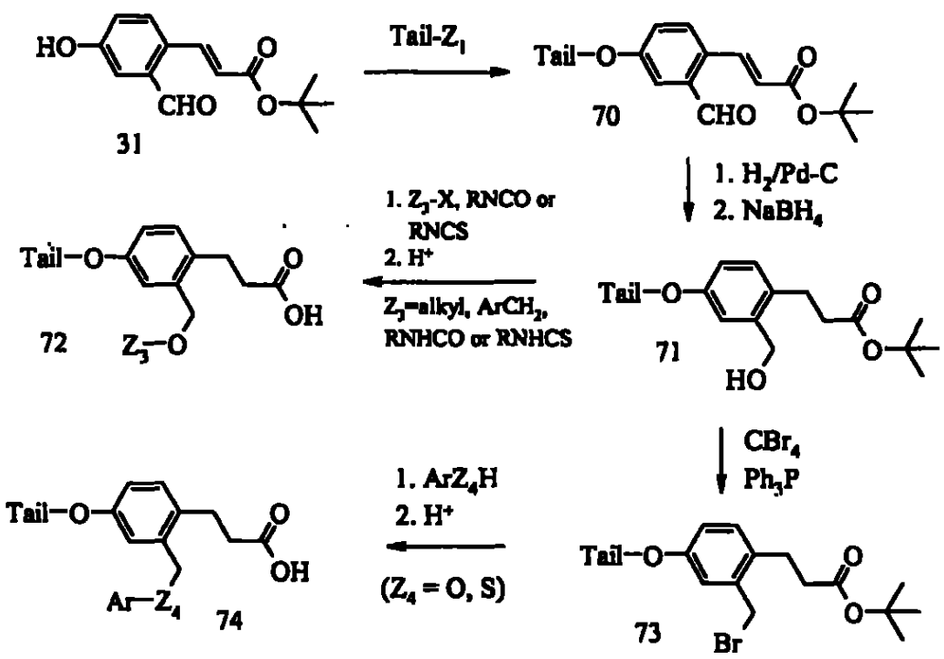
Reaction Scheme 17: Synthesis of Cyanodihydrocinnamates



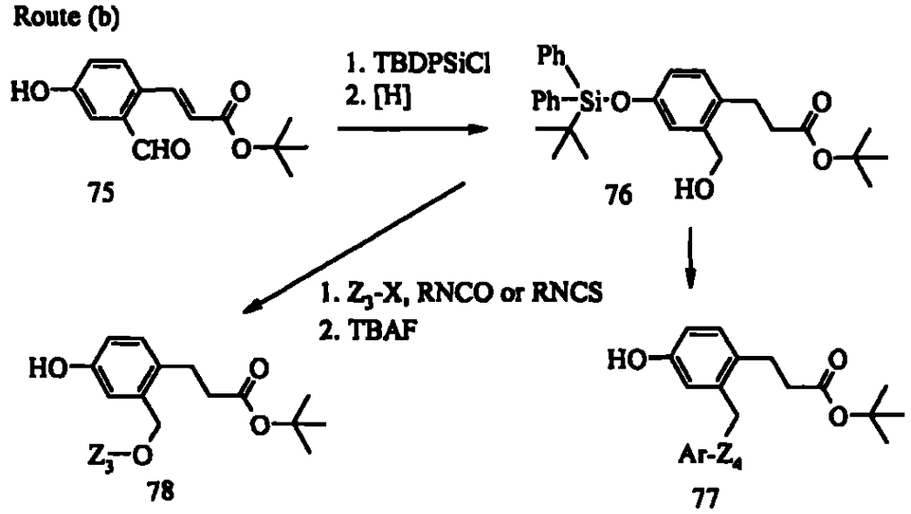
Cyanodihydrocinnamates can be prepared as shown in Reaction Scheme 17. Compound (66) is brominated with a brominating agent such as NBS to give compound (67), which is then undergoes a Heck coupling reaction with ethyl acrylate in the presence of palladium catalyst followed by hydrogenation to give compound (68). Compound (68) is coupled with a tailpiece followed by ester hydrolysis to yield carboxylic acid compound (69).

5 Reaction Scheme 18: Synthesis of alkoxydihydrocinnamates

Route (a)



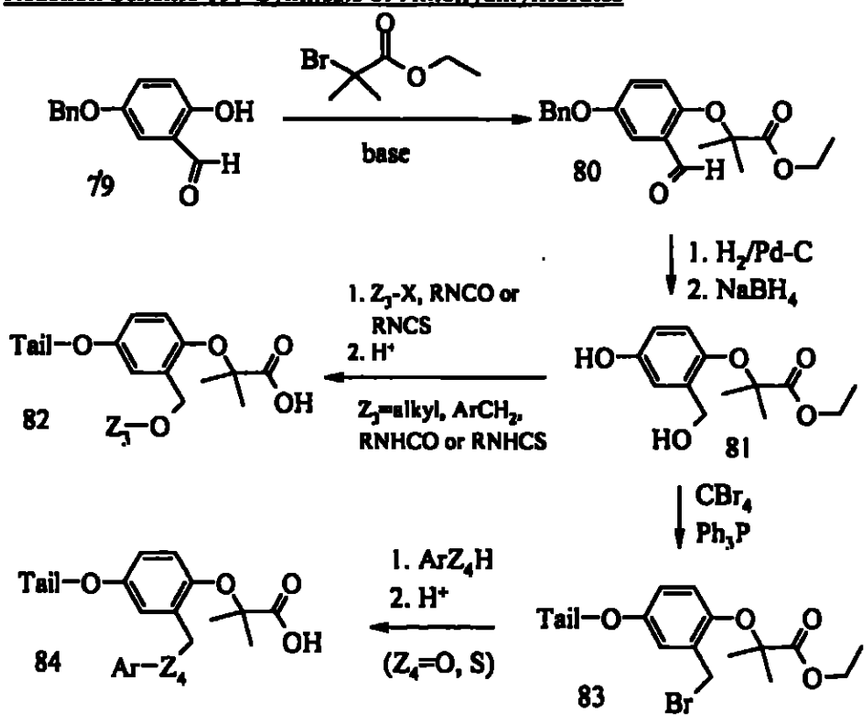
Route (b)



Alkoxydihydrocinnamates can be prepared as shown in Reaction Scheme 18. In route (a), compound (31) is coupled with a tailpiece to give compound (70), which then undergoes sequential reduction of double bond and aldehyde to give alcohol compound (71). Compound (71) undergoes the condensation reaction with an isocyanate or thioisocyanate, alkyl halide or arylic halide followed by ester hydrolysis to give compound (72). Alternatively, compound (71) can be converted to the corresponding halide (73) using a carbon tetrahalide and triphenylphosphine. A nucleophilic substitution reaction followed by ester hydrolysis affords compound (74).

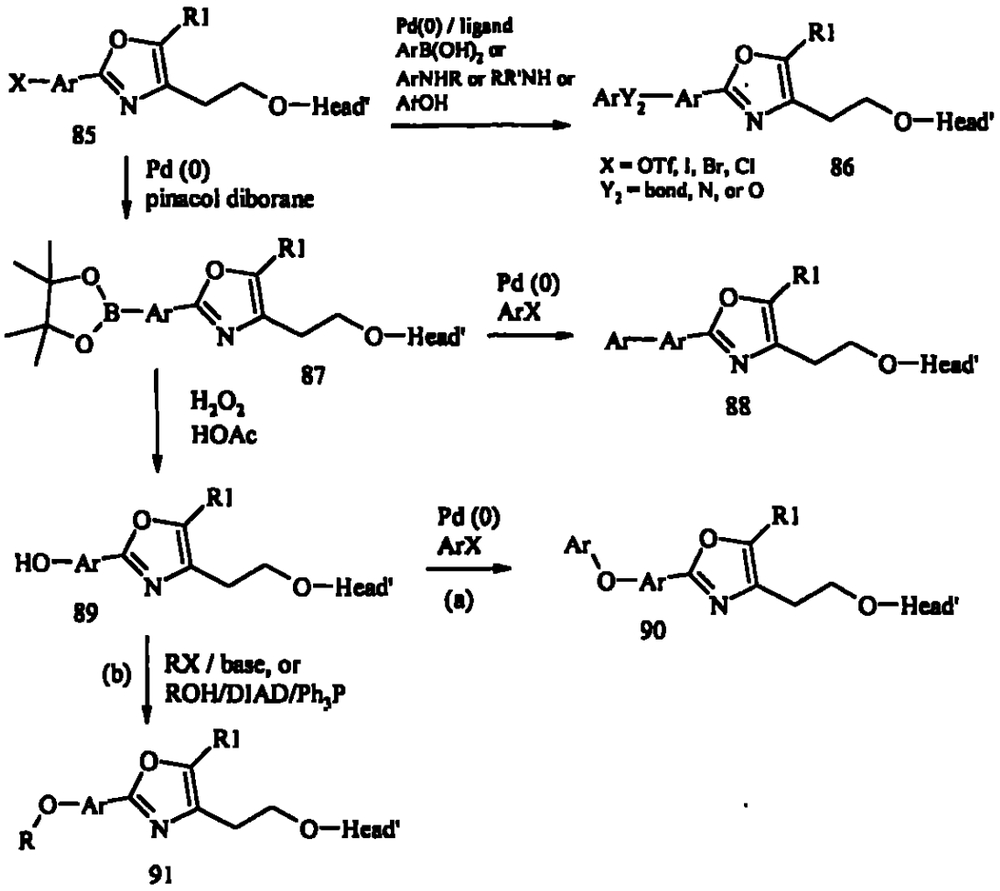
In route (b), the protecting group such as TBDPSi is attached to the aryl alcohol of compound (75) to give compound (76), which then undergoes a similar reaction sequence as described in route (a) to give phenol (77). Alternatively, compound (76) can undergo the condensation reaction with Z_3-X followed by deprotection to afford phenol (78). Phenol compounds (77) and (78) can be taken separately to final compounds by reaction with a tailpiece followed by acid hydrolysis.

Reaction Scheme 19: Synthesis of Alkoxyalkylfibrates



Reaction Scheme 19 illustrates a synthetic route to prepare alkoxyalkylfibrate compounds. Compound (79) is reacted with ethyl 2-bromoisobutyrate in the presence of base to give compound (80). The phenol of compound (80) is deprotected followed by aldehyde reduction in the presence of a reducing agent such as $NaBH_4$ to give compound (81). Phenol (81) then can undergo reaction with Z_3-X followed by hydrolysis to give alkoxyalkylfibrate compound (82). Alternatively, phenol compound (81) can be converted to the corresponding halide (83) using a carbon tetrahalide and triphenylphosphine. Treatment of compound (83) with ArZ_4H followed by ester hydrolysis affords compound (84).

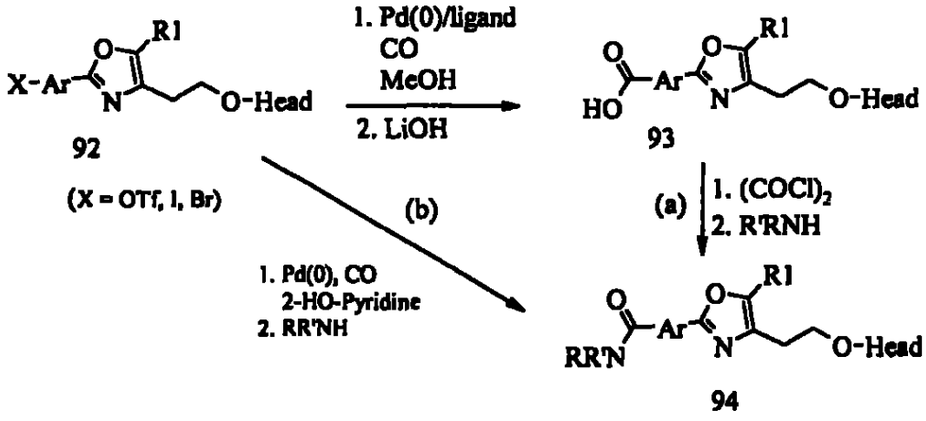
Reaction Scheme 20: Modification to the tailpiece



Ar-Y^7-Ar; Ar-Ar; Ar-O-Ar = Y^{18}
R = H, or alkyl

Reaction Scheme 20 illustrates the synthetic routes to compounds with modified tailpieces. Oxazole compound (85) can undergo a coupling reaction with an arylboronic, aryl alcohol, aryl amine or secondary amine in the presence of palladium catalyst to give modified tailpiece compound (86). Alternatively, compound (85) undergoes a coupling reaction with pinacol diborane in the presence of palladium catalyst to give compound (87), which then is further coupled with arylhalide to give biaryl compound (88). Alternatively, the compound (87) can be oxidized to give phenol (89), which is then coupled with arylhalide in the presence of palladium catalyst to give aryl-aryloxy compound (90) as shown in route (a). Alternatively, compound (89) can undergo a nucleophilic reaction with an alkyl halide or alcohol as shown in route (b) to form ether compound (91).

Reaction Scheme 21: Modification to the tailpiece

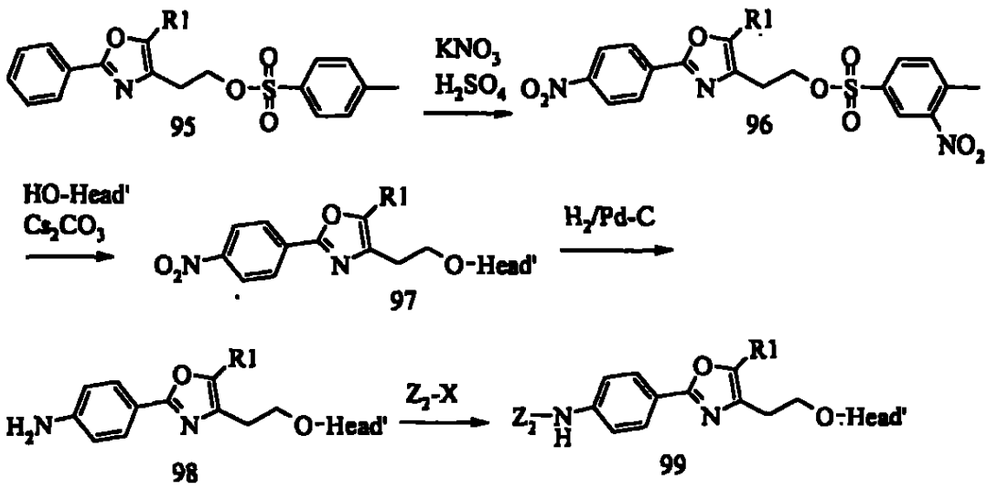


Ar-C(O)NRR' = Y^{1a}

NR'R = substituents defined in Y^{1a}

Reaction Scheme 21 shows a synthetic route to modify the tailpiece of the present compounds. In route (a), the oxazole tailpiece compound (92) undergoes carbonylation to give carboxylic acid compound (93), which is converted to the acid chloride followed by reaction with an amine to form amide compound (94). Similarly in route (b), modified compound (94) is achieved by palladium catalyzed carbonylation to form an intermediate hydroxypyridine ester followed by a reaction with amine to form amide compound.

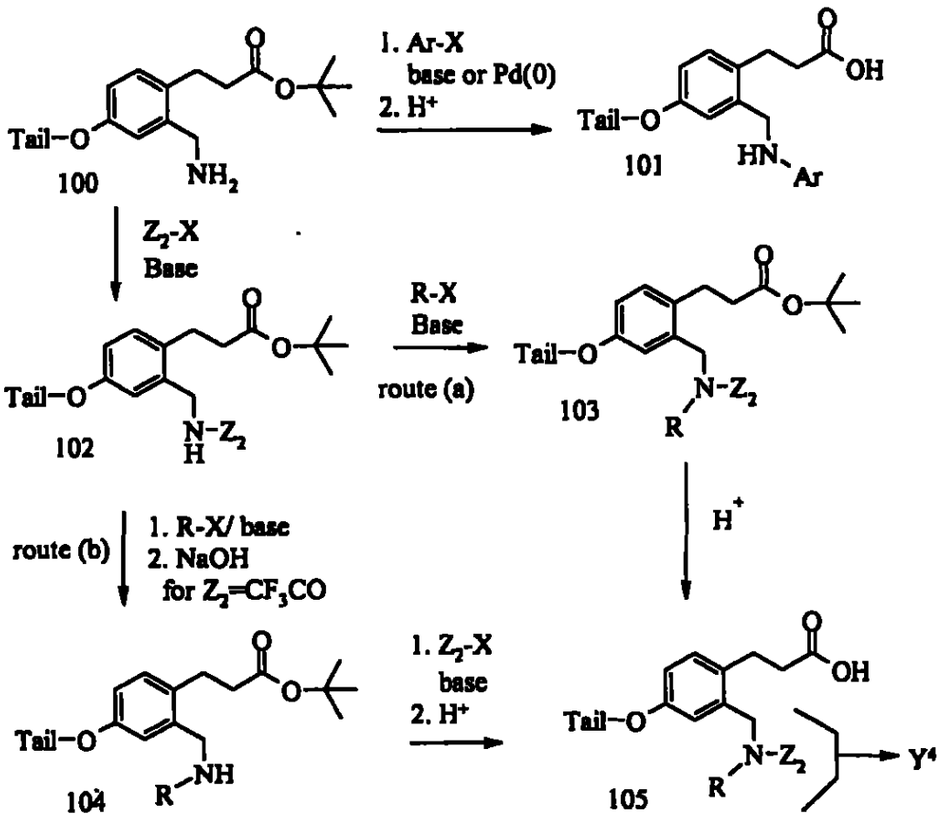
Reaction Scheme 22: Modification to the tailpiece



$NH\text{-}Z^2$ = substituents defined in Y^{1a}

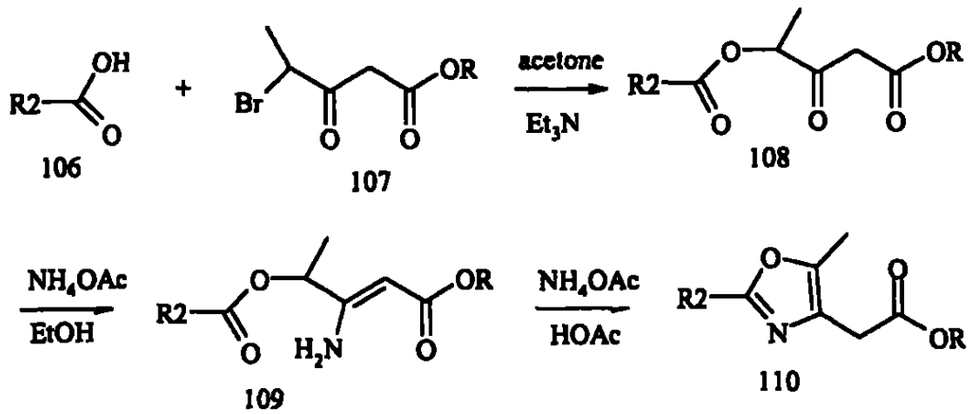
Reaction Scheme 22 shows a synthetic route to modify the tailpiece of the present compounds. Compound oxazolyl sulfonyl ester (95) is nitrated to give compound (96), which then undergoes a coupling reaction with a headpiece to give compound (97). The nitro group of the phenyl ring is reduced to give aniline compound, which is modified to give compound (99).

Reaction Scheme 23: Modification to the headpiece N



Reaction Scheme 23 shows a synthetic route to modify the headpiece of the present compounds. The headpiece compound (100) can be modified by coupling with arylhalide (Ar-X) in the presence of palladium catalyst followed by ester hydrolysis to give the compound (101). Alternatively, compound (100) can be reacted with Z_2-X in the presence of base to give the modified aminomethyl compound (102). In route (a), compound (102) can undergo nucleophilic substitution at the amine followed by ester hydrolysis to give acid compound (105). Alternatively, by route (b) with Z_2 as a trifluoro acetyl group, alkylation under basic conditions followed by aqueous base hydrolysis gives secondary amine compound (104). Subsequent finctionalization of the amine with Z_2-X followed by acid hydrolysis affords compound (105).

Reaction Scheme 24: Oxazole tailpiece



R2 = Y^{1a} such as aryl, aryl-Z-aryl or heteroaryl-Z-aryl, or alkyl
R = alkyl

An alternative synthetic route to oxazole tailpiece is shown in Reaction Scheme 24. Carboxylic acid (106) is condensed with 2-bromo-3-oxopentanoate (preferably methyl ester) (107) to give ketoester (108). The latter is converted to an intermediate enamine (109) by treatment with anhydrous ammonium acetate. Subsequent cyclization of compound (109) in acetic acid in the presence of anhydrous ammonium acetate gives compound (110). The use of anhydrous ammonium acetate obtained by azeotropic evaporation with ethanol eliminates water in the reaction, which causes decarboxylation of compound (110). Additionally, some of the water liberated in the reaction is removed at the enamine stage. These modifications along with a simplified isolation procedure lead to higher yields of oxazole (110).

In the Schemes, Preparations and Examples below, various reagent symbols and abbreviations have the following meanings:

BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	t-butoxycarbonyl
CBZ	benzyloxycarbonyl
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DI	deionized

	DIAD	diisopropyl azodicarboxylate
	DIPEA	diisopropylethylamine
	DMAP	4-dimethylamino pyridine
	DMF	N,N-dimethylformamide
	DMSO	dimethylsulfoxide
	eq. (equiv)	equivalent(s)
	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl
	ESI-MS	electron spray ion-mass spectroscopy
	Et	ethyl
	EtOAc	ethyl acetate
	FMOC	9-Flurorenylmethyl carbamate
	HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
	HOAc	acetic acid
	HOAT:	1-hydroxy-7-azabenzotriazole
	HOBT	1-hydroxybenzotriazole hydrate
	HPLC	high performance liquid chromatography
	HRMS	high resolution mass
	h	hour(s)
	LRMS	low resolution mass
	LAH	lithium aluminum hydride
	Me	methyl
	Ms	methanesulfonyl
	NBS	N-bromosuccinimide
	$Pd_2(dba)_3$	tris(dibenzylideneacetone) dipalladium(0)
	Ph	phenyl
	Phe	phenylalanine
	Pr	propyl
	r.t.	room temperature
	TBAF	tetrabutylammonium fluoride
	TBS	tertbutyldimethylsilyl
	TFA	trifluoroacetic acid

TEA	triethylamine
THF	tetrahydrofuran
TLC	thin-layer chromatography

Standard Procedure

The following standard procedures (A) to (E) are used for preparing the compounds of the present invention as illustrated in Examples below.

Standard Procedure (A): Mitsunobu Coupling of Aryl alcohol Headpieces with Alcohol Tailpieces

A mixture of 2-(5-methyl-2-naphthalen-2-yl-oxazol-4-yl)-ethanol (112 mg, 0.442 mmol, 1 equiv), 3-[4-hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid *tert*-butyl ester (150 mg, 0.445 mmol, 1.00 equiv), and triphenylphosphine (116 mg, 0.442 mmol, 1.00 equiv) in toluene (10 mL) at room temperature was treated with diisopropyl azodicarboxylate (90 µL, 92 mg, 0.46 mmol, 1.0 equiv) over a period of about 3 minutes. The mixture was stirred for about 23 hours and concentrated. The crude material was purified by silica gel chromatography.

Standard Procedure (B): Ester Hydrolysis under Acidic Conditions

A solution of tert-butyl ester-containing compound (0.5 mmol) in CH_2Cl_2 (6 mL) was treated with 90 % trifluoroacetic acid/water (3 mL) and stirred at ambient temperature for about 3 hours and then concentrated to give the corresponding carboxylic acid compound. The crude material was purified by silica gel chromatography if necessary.

Standard Procedure (C): Ester Hydrolysis under Acidic Conditions

A mixture of tert-butyl ester-containing compound (0.2 mmol) in 4 M HCl in 1,4-dioxane (5 mL) was stirred at ambient temperature for about 16 hours and concentrated to give the corresponding carboxylic acid compound. The crude material was purified by silica gel chromatography if necessary.

Standard Procedure (D): Ester Hydrolysis under Basic Conditions:

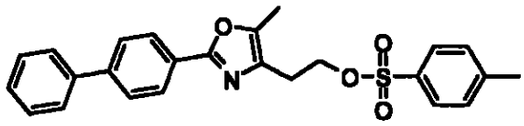
A solution of ester (0.25 mmol) in MeOH (3 mL) and THF (1.5 mL) was treated with 2N NaOH (1 mL) and heated at 55°C for about 2 hours. The mixture was cooled and concentrated. The residue was partitioned between CH_2Cl_2 (10 mL), brine (5 mL) and 5N HCl (1 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude material was purified by silica gel chromatography if necessary.

PREPARATION OF INTERMEDIATES

Tailpiece Preparation - Oxazoles

Preparation 1

Toluene-4-sulfonic acid 2-(2-biphenyl-4-yl-5-methyl-oxazol-4-yl)ethyl ester



Step A: 4,5-Dimethyl-2-(4-bromophenyl)-oxazole oxide

A solution of 2,3-butanedione monooxime (50 g, 0.49 mol) and 4-bromobenzaldehyde (101 g, 0.54 mol) in acetic acid (500 mL) was cooled to 0°C and then gaseous HCl was bubbled through the solution for 35 min while the reaction was stirred in an ice bath. Diethyl ether (500 mL) was added to the reaction to precipitate the product, and the resultant slurry was stirred 45 min at 0°C before being filtered. The solids were rinsed with Et_2O (50 mL), taken up in water (1 L), and conc. NH_4OH (60 mL) was added to the slurry. This mixture was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and concentrated to give 97.4 g (74%) of 4,5-dimethyl-2-(4-bromophenyl)-oxazole oxide as a white solid. This compound should be used directly within 24–48 h. ^1H NMR (500 MHz, $CDCl_3$) 8.34 (d, J = 9.0 Hz, 2H), 7.61 (d, J = 9.0 Hz, 2H), 2.35 (s, 3H), 2.20 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) 142.1, 131.9, 129.5, 126.3, 124.1, 122.2, 11.1, 6.2; IR (KBr) 1685, 1529, 1418, 1377, 1233, 1165 cm^{-1}; UV (EtOH) λ_{max} 307 nm (24371); HRMS (TOF) m/z calculated for $C_{11}H_{11}{}^{79}BrNO_2$: 267.997, found 267.9951.

Step B: 2-(4-Bromophenyl–4-(chloromethyl)–5-methyloxazole

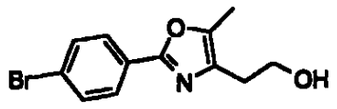
A solution of 4,5-dimethyl-2-(4-bromophenyl)-oxazole oxide (96.6 g, 0.36 mol) in $CHCl_3$ (0.90 L) was treated dropwise with phosphorous oxychloride (61.1 g, 0.40 mol) allowing the reaction to exotherm and then was stirred at reflux for 30 min. The reaction was cooled to room temperature and washed with water (2 x 1 L). The combined aqueous washes were back extracted with CH_2Cl_2 (2 x 400 mL). The organic layers were dried ($MgSO_4$) and concentrated to give crude product that was recrystallized from hot hexanes (300 mL), decanting the hot supernatant away from a dark oily material. The remaining dark oil was agitated in additional hot hexanes (200 mL), and the combined supernatants were cooled to 0°C. The product was isolated by filtration as a lime-green powder (74.2 g, 72%): Rf = 0.39 in 20% ethyl acetate/hexanes. ^1H NMR (500 MHz, $CDCl_3$) 7.88–7.86 (m, 2H), 7.59–7.56 (m, 2H), 4.54 (s, 2H), 2.42 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) 159.2, 146.9, 133.2, 132.0, 127.6, 126.1, 124.7, 37.1, 11.5; IR (KBr) 2970, 1633, 1599, 1481, 1401, 1258, 1117, 1008 cm^{-1}; UV (EtOH) $_{max}$ 281 nm (21349); HRMS (FAB) m/z calculated for $C_{11}H_{10}{}^{79}BrClNO$: 285.9634, found 285.9641; Anal. Calculated for $C_{11}H_9ClBrNO$: C, 46.11; H, 3.17; N, 4.89; Cl, 12.37; Br, 27.88. Found C, 46.28; H 3.07; N, 4.81; Cl, 12.36; Br, 27.88.

Step C: 2-(4-Bromophenyl)-5-methyl-4-oxazoleacetic acid

To a solution of 2-(4-bromophenyl–4-(chloromethyl)–5-methyloxazole (64.8 g, 0.23 mol) in DMF (400 mL) was added powdered potassium cyanide (22.1 g, 0.34 mol) and potassium iodide (28.6 g, 0.17 mol), and the resultant mixture was heated to 85°C for 3.5 h. The reaction mixture was cooled to room temperature. Potassium carbonate (5 g) was dissolved in water (800 mL) and added dropwise to the reaction to precipitate 2-(4-bromophenyl–4-(cyanomethyl)–5-methyloxazole (stir vigorously 15 min following addition) which was isolated by filtration and washed with water (2 x 400 mL). The crude 2-(4-bromophenyl–4-(cyanomethyl)–5-methyloxazole was used in the next step without purification. ^1H NMR (300 MHz, $CDCl_3$) 7.85 (m, 2H), 7.58 (m, 2H), 3.64 (s, 3H), 2.43 (s, 3H).

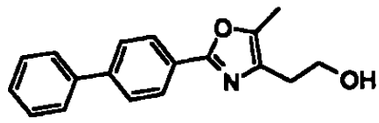
The crude 2-(4-bromophenyl–4-(cyanomethyl)–5-methyloxazole (assume 0.22 mol) was combined with 2-methoxyethanol (630 mL) and 85% solid KOH (74.6 g, 1.33 mol) in water (360 mL) was added to the reaction. The mixture was heated to reflux for 3 h, cooled, quenched with 2 M HCl (500 mL), and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated, using toluene to remove residual 2-methoxyethanol azeotropically. The crude product (57.3 g) was recrystallized from toluene (450 mL) to give 39.8 g (60%) of 2-(4-bromophenyl)-5-methyl-4-oxazoleacetic acid as an off-white powder. Rf = 0.23 in 10% MeOH/CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$) 9.00 (br s, 1H), 7.85–7.83 (m, 2H), 7.58–7.56 (m, 2H), 3.62 (s, 3H), 2.36 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) 173.8, 159.0, 146.2, 132.0, 129.1, 127.6, 125.9, 124.7, 31.5, 10.2; IR ($CHCl_3$) 2923, 1699, 1641, 1481, 1428, 1306, 1234, 1010, 829, 727 cm^{-1}; UV $(EtOH)_{max}$ 288 nm (19626).

Step D: 2-(4-Bromophenyl)-5-methyl-4-oxazoleethanol



A solution of 2-(4-bromophenyl)-5-methyl-4-oxazoleacetic acid (39.1 g, 0.13 mol) in dry THF (175 mL) was treated dropwise with borane/THF complex (227 mL of a 1.0 M solution in THF, 1.3 mol) over 2 h at about 35°C. After stirring 2 h at room temperature under N_2, the reaction was quenched with slow addition of methanol (60 mL) and stirred overnight at room temperature. The reaction was diluted with 1 N NaOH (50 mL) and extracted with CH_2Cl_2 (2 x 200 mL). The organic layer was washed with H_2O (3 x 100 mL), dried ($MgSO_4$), and concentrated. The crude product (38.7 g) was recrystallized from toluene (200 mL, wash solid with cold hexanes) to give 26.9 g (72%) of 2-(4-bromophenyl)-5-methyl-4-oxazoleethanol as a white powder. Rf = 0.37 in 10% MeOH/CH_2Cl_2. ^{1}H NMR (500 MHz, $CDCl_3$) 7.84–7.82 (m, 2H), 7.57–7.55 (m, 2H), 3.91 (q, J = 5.5 Hz, 2H), 3.14 (t, J = 6 Hz, OH), 2.72 (t, J = 5.5 Hz, 2H), 2.33 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) 158.7, 144.5, 134.2, 131.9, 127.4, 126.4, 124.3, 61.8, 28.1, 10.1; IR (KBr) 3293, 2948, 1642, 15985, 1480, 1472, 1401, 1053, 1003, 836, 734 cm^{-1}; UV (EtOH) $_{max}$ 290 nm (20860); Anal. Calculated for $C_{12}H_{12}BrNO_2$: C, 51.09; H, 4.29; N, 4.96; Br, 28.32. Found C, 51.31; H 4.06; N, 4.90; Br, 28.19.

Step E: 2-(Biphenyl-4-yl-5-methyl-oxazol-4-yl)ethanol



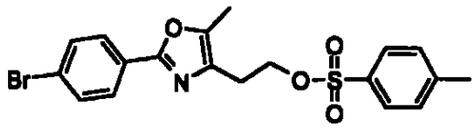
2-(4-Bromophenyl)-5-methyl-4-oxazoleethanol (10.0 g, 35.0 mmol) and phenylboronic acid (4.5 g, 38.0 mmol) were dissolved in n-propanol (120 mL) before adding triphenylphosphine (165.2 mg, 0.63 mmol), palladium acetate (46 mg, 2.1 mmol), and Na_2CO_3 (4.5 g, 42 mmol dissolved in 30 mL distilled H_2O). The solution was heated at reflux and stirred for 1.5 h. After cooling to ambient temperature, the mixture was concentrated and then partitioned between CH_2Cl_2 (100 mL) and 1N NaOH (100 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to provide 2-(4-biphenyl)-5-methyl-4-oxazoleethanol (9.5 g, 97% yield) as a white solid which was used directly without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) 8.01 (d, 2H), 7.77-7.50 (m, 4H), 7.46 (m, 2H), 7.38 (m, 1H), 3.91 (q, J = 5.5 Hz, 2H), 3.18 (t, J = 6 Hz, OH), 2.72 (t, J = 5.5 Hz, 2H), 2.33 (s, 3H).

Step F: Toluene-4-sulfonic acid 2-(2-biphenyl-4-yl-5-methyl-oxazol-4-yl)ethyl ester

To a solution of 2-(biphenyl-4-yl-5-methyl-oxazol-4-yl)ethanol (15.8 g, 56.6 mmol) in CH_2Cl_2 (250 mL) at room temperature under N_2 was added pyridine (14.7 g, 185 mmol, 15.0 mL), DMAP (2.03 g, 16.6 mmol), and then tosyl anhydride (24.57 g, 75.2 mmol) portion wise. The reaction exothermed to 32°C and was stirred 30 min before additional tosyl anhydride (2.3 g) was added. The mixture was diluted with CH_2Cl_2 (100 mL) and stirred vigorously with 1N HCl (150 mL) for 15 min. The organic phase was dried ($MgSO_4$) and filtered through a pad of silica gel (100 mL, packed with CH_2Cl_2). The silica gel was eluted with ethyl acetate (100 mL), and the solution was concentrated to give toluene-4-sulfonic acid 2-(2-biphenyl-4-yl-5-methyl-oxazol-4-yl)ethyl ester as a white solid (23.3 g, 95%). Rf = 0.51 in 60% ethyl acetate/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) 7.97 (d, 2H), 7.70 (d, 2H), 7.66 (t, 2H), 7.65 (d, 2H), 7.51 (t, 1H), 7.42 (d, 2H), 7.24 (d, 2H), 4.37 (t, 2H), 2.88 (t, 2H), 2.37 (s, 3H), 2.26 (s, 3H).

Preparation 2

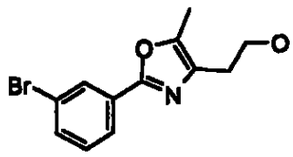
Toluene-4-sulfonic acid 2-(4-Bromophenyl-5-methyl-oxazol-4-yl)ethyl ester



The title compound was prepared from 2-(4-bromophenyl)-5-methyl-4-oxazoleethanol according to Procedure 1, Step F: MS (ESI) m/z 436.0 $(M+H)^+$.

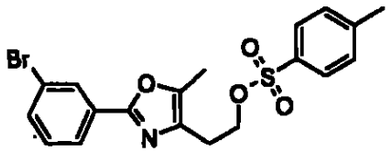
The following intermediate compounds are prepared by a substantially similar manner as described in Preparations 1 and 2.

2-(3-Bromophenyl)-5-methyl-4-oxazoleethanol:



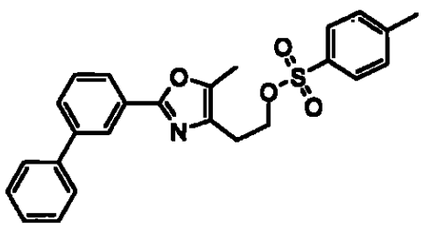
^{1}H NMR (300 MHz, d_6-DMSO) δ 7.99 (s, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.7 Hz, 1H), 4.61 (t, J = 5.5 Hz, OH), 3.63 (q, J = 5.5 Hz, 2H), 2.60 (t, J = 6.6 Hz, 2H), 2.32 (s, 3H);

Toluene-4-sulfonic acid 2-(3-bromophenyl-5-methyl-oxazol-4-yl)ethyl ester



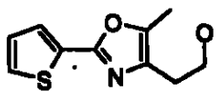
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, J = 1.6 Hz, 1H) 7.80 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.53 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 4.30 (t, J = 6.4 Hz, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.31 (s, 3H), 2.24 (s, 3H); MS (ESI) m/z 436.0 $(M+H)^+$.

Toluene-4-sulfonic acid 2-(2-biphenyl-3-yl-5-methyl-oxazol-4-yl)ethyl ester



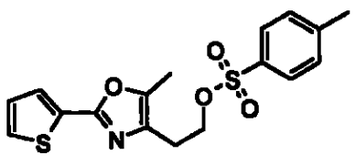
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.64 (d, 8.0 Hz, 1H), 7.51 (d, J = 9.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 9.0 Hz, 1H), 4.30 (t, J = 7.0 Hz, 2H), 2.80 (t, J = 7.0 Hz, 2H), 2.30 (s, 3H), 2.23 (s, 3H).

2-(5-Methyl-2-thiophen-2-yl-4-oxazoleethanol



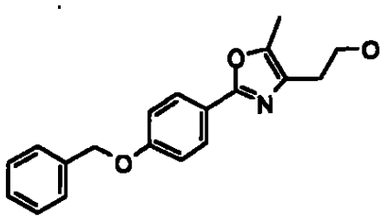
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (m, 1H), 7.33 (m, 1H), 7.03 (m, 1H), 3.87 (t, J = 5.8 Hz, 2H), 3.5 (s, 1H), 2.67 (t, J = 5.8 Hz, 2H), 2.25 (s, 3 H)

Toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yloxazol-4-yl)ethyl ester



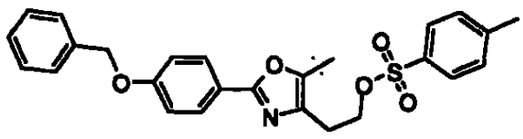
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.3 Hz, 2H), 7.51 (dd, J = 3.8, 1.4 Hz, 1H), 7.37 (dd, J = 4.9, 1.2 Hz, 1H), 7.21 (d, J = 7.9 Hz, 2H), 7.08 (dd, J = 4.8, 3.5 Hz, 1H), 4.28 (t, J = 6.3 Hz, 2H) , 2.80 (t, J = 6.3 Hz, 2H), 2.28 (s, 3H), 2.26 (s, 3 H); mp 107-109°C.

2-[2-(4-Benzyloxy-phenyl)-5-methyl-oxazol-4-yl]-ethanol



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, 2H, J = 8.60 Hz), 7.45-34 (m, 5H), 7.02 (d, 2H, J = 8.60 Hz), 5.11 (s, 2H), 3.91 (t, 2H , J = 5.7 Hz), 2.71 (t, 2H, J = 5.7 Hz), 2.31 (s, 3H); MS (ES^+) Calculated for $C_{19}H_{20}NO_3$: Found m/e 310 (M + 1, 100%)

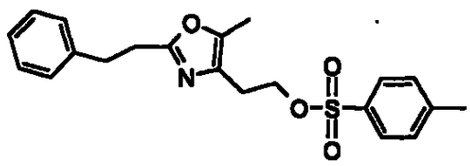
Toluene-4-sulfonic acid 2-[2-(4-benzyloxy-phenyl)-5-methyl-oxazol-4-yl]-ethyl ester



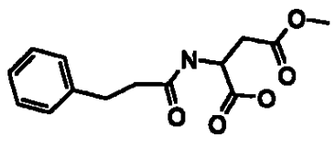
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.78 (m, 2H), 7.67-7.65 (m, 2H), 7.45-7.34 (m, 5H), 7.25-7.17 (m, 2H), 7.02-6.99 (m, 2H), 5.12 (s, 2H), 4.29 (t, 2H, J = 6.45 Hz), 2.80 (t, 2H, J = 6.45 Hz), 2.27 (s, 3H), 2.22 (s, 3H); HRMS (ES^+) m/z exact mass calculated for $C_{26}H_{26}NO_5S$ 464.1532, found 464.1531; Anal. Calculated for $C_{26}H_{25}NO_5S$: C, 67.37; H, 5.44; N, 3.02. Found C, 66.59; H 5.33; N, 3.06.

Preparation 3

Toluene-4-sulfonic acid 2-(5-methyl-2-phenethyl-oxazol-4-yl)-ethyl ester

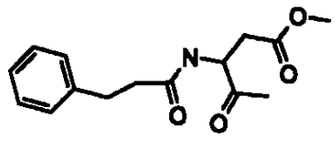


Step A: 2-(3-Phenyl-propionylamino)-succinic acid 4-methyl ester



Methyl L-aspartate (15.0 g, 0.082 mol), DI water (245 mL), acetone (20 mL), and Na_2CO_3 (30.8 g, 0.286 mol) were combined and cooled the solution to 5°C. The compound 3-phenyl-propionyl chloride (13.3 mL, 0.089 mol) was added dropwise via addition funnel over 10 min. The reaction was allowed to warm to ambient temperature and stir for 2 h. Conc. HCl (50 mL) was added to the thick slurry until the pH was ≤ 4.0. The reaction mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with water, dried ($MgSO_4$), filtered, and concentrated. The clear, colorless oil was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.28-7.17 (m, 5H), 6.57 (d, J = 7.6 Hz, 1H), 4.87 (m, 1H), 3.67 (s, 3H), 2.96 (t, J = 7.6 Hz, 2H), 2.89 (A of ABX, J_{AB} = 17.6 Hz, J_{AX} = 4.8 Hz, 1H), 2.88 (B of ABX, J_{BA} = 17.6 Hz, J_{BX} = 4.0 Hz, 1H), 2.69 (t, J = 7.6 Hz, 2H); MS (EI+) 280 (M+H), 302 (M+H+Na).

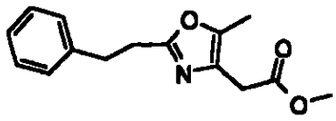
Step B: 4-Oxo-3-(3-phenyl-propionylamino)-pentanoic acid methyl ester



2-(3-Phenyl-propionylamino)-succinic acid 4-methyl ester (10 g, 36 mmol), pyridine (50 mL) and acetic anhydride (45 mL) were combined in a 500 mL flask. The reaction mixture was heated at 90°C for 2 h and then cooled to ambient temperature. After concentrating the reaction mixture under reduced pressure, DI water was added

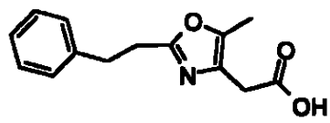
(100 mL). The reaction mixture was partitioned between water and CH_2Cl_2 (200 mL). The organic phase was washed with 1N HCl (50 mL), dried ($MgSO_4$), filtered, and concentrated. The material was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.20 (m, 5H), 6.79 (br d, J = 7.6 Hz, 1H), 4.72 (X of ABX, 1H), 3.65 (s, 3H), 3.01-2.93 (m, 3H), 2.71-2.62 (m, 3H), 2.11 (s, 3H); MS (EI) 278.1 (M+H).

Step C: (5-Methyl-2-phenethyl-oxazol-4-yl)-acetic acid methyl ester



In a 100 mL flask, 4-oxo-3-(3-phenyl-propionylamino)-pentanoic acid methyl ester (10 g, 36 mmol) and acetic anhydride (28 mL) were combined. Following addition of concentrated H_2SO_4 (1 mL), the solution was heated to 90°C for 30 min and cooled to ambient temperature. The reaction was slowly diluted with DI water (30 mL, potential exotherm). The reaction mixture was partitioned between CH_2Cl_2 (150 mL) and water (150 mL). The organic phase was washed with DI water, 10% $NaHCO_3$ (aq), brine (150 mL), and then was dried ($MgSO_4$) and concentrated to a brown oil. The residue was purified by column chromatography (600 mL SiO_2, 35% EtOAc/hexanes) to provide the desired product (3.25 g) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.20 (m, 5H), 3.72 (s, 3H), 3.47 (s, 2H), 3.08-2.96 (m, 4H), 2.24 (s, 3H); MS (EI+) 260 (M+H).

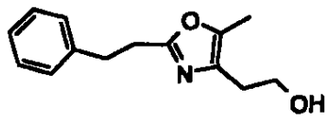
Step D: (5-Methyl-2-phenethyl-oxazol-4-yl)-acetic acid



(5-Methyl-2-phenethyl-oxazol-4-yl)-acetic acid methyl ester (8.75 g, 33.8 mmol), in MeOH (120 mL) was treated with 5N NaOH (40 mL), and then the solution was warmed to 40 °C. After 40 min, the reaction mixture was concentrated. The residue was suspended in water (75 ml) and acidified to pH=1 with 5N HCl. The mixture was extracted with EtOAc (2x), dried ($MgSO_4$), and concentrated to provide 5.25 g (63%) of

the product as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.20 (m, 5H), 3.52 (s, 2H), 3.06-3.03 (m, 4H), 2.24 (s, 3H).

Step E: 2-(5-Methyl-2-phenethyl-oxazol-4-yl)-ethanol



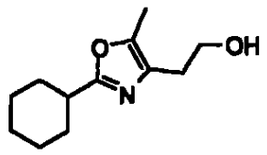
BH_3-THF complex (49 mL of a 1.0 M solution in THF) was added dropwise via addition funnel over 50 min to a solution of (5-methyl-2-phenethyl-oxazol-4-yl)-acetic acid (5.05 g, 20.6 mmol) in THF (35 mL). The reaction mixture was stirred at ambient temperature for 3 h, and then quenched with MeOH (12 mL). After heating at 50 °C for 2 h, the reaction mixture was cooled to ambient temperature, and then partitioned between CH_2Cl_2 and 1N NaOH. The organic phase was washed with brine (1x 50 mL), dried over $MgSO_4$ and concentrated to obtain a residue, which was purified by column chromatography (500 mL SiO_2, 35% EtOAc/hexanes) to provide 3.99 g (84%) of the desired product as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.20 (m, 5H), 3.84 (q, J = 5.6 Hz, 2H), 3.06-2.67 (m, 4H), 2.62 (t, J = 5.6 Hz, 2H), 2.22 (s, 3H); MS (EI+) 232.19 (M+H); 254.15 (M+H+Na).

Step F: Toluene-4-sulfonic acid 2-(5-methyl-2-phenethyl-oxazol-4-yl)-ethyl ester

A solution of 2-(5-methyl-2-phenethyl-oxazol-4-yl)-ethanol (1.2 g, 5.19 mmol) in CH_2Cl_2 at 0°C was treated with pyridine (1.64 g, 20.7 mmol, 1.68 mL), DMAP (190 mg, 1.56 mmol), and tosyl anhydride (2.2 g, 6.75 mmol). The reaction was warmed to ambient temperature and, after 90 min, the solution was filtered through a pad of silica gel (rinsed with CH_2Cl_2). The product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.31-7.17 (m, 7H), 4.21 (t, J = 6.8 Hz, 2H), 3.01-2.88 (m, 4H), 2.75 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H), 2.19 (s, 3H).

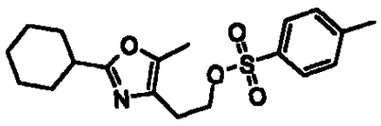
The following intermediate compounds are prepared by a substantially similar manner as described in Preparations 3.

2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethanol:



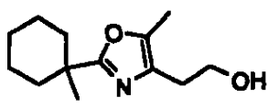
^{1}H NMR (400 MHz, $CDCl_3$) δ3.73 (t, J = 6.8 Hz, 2H), 2.58 (tt, J = 11.6, 3.6 Hz, 1H), 2.54 (t, J = 6.8 Hz, 2H), 2.13 (s, 3H), 1.93-1.89 (m, 2H), 1.74 (dt, J = 12.8, 3.6 Hz, 2H), 1.67-1.62 (m, 1H), 1.41 (qd, J = 12.0, 3.2 Hz, 1H), 1.33-1.17 (m, 4H); MS (EI+) 210.1 (M+H).

Toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester



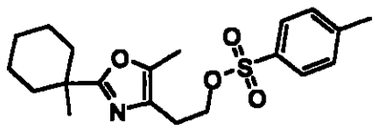
^{1}H NMR (400 MHz, $CDCl_3$) δ7.67 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.16 (t, J = 6.8 Hz, 2H), 2.70 (t, J = 6.8 Hz, 2H), 2.56 (tt, J = 11.6, 3.6 Hz, 1H), 2.39 (s, 3H), 2.13 (s, 3H), 1.93-1.89 (m, 2H), 1.74 (dt, J = 12.8, 3.6 Hz, 2H), 1.67-1.62 (m, 1H), 1.41 (qd, J = 12.0, 3.2 Hz, 1H), 1.33-1.17 (m, 4H); MS (EI+) 364.1 $(M+H)^+$.

2-[5-Methyl-2-(1-methylcyclohexyl)oxazol-4-yl]ethanol



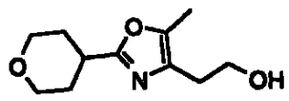
MS (EI+) 224.1 $(M+H)^+$.

Toluene-4-sulfonic acid 2-[5-methyl-2-(1-methylcyclohexyl)oxazol-4-yl]ethyl ester



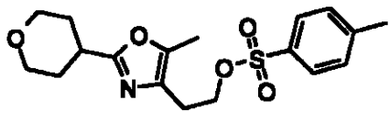
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.30 (t, J = 8.4 Hz, 2H), 4.12 (t, J = 6.6 Hz, 2H), 2.76 (t, J = 6.6 Hz, 2H), 2.42 (s, 3H), 2.17 (s, 3H), 2.61-2.02 (m, 2H), 1.56-1.30 (m, 8H), 1.19 (s, 3H); MS (EI) 378.2 $(M + H)^+$.

2-[5-Methyl-2-(tetrahydro-pyran-4-yl)-oxazol-4-yl]-ethanol



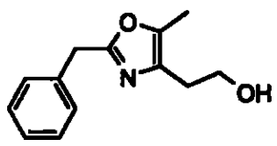
MS (EI) 212.2 $(M + H)^+$.

Toluene-4-sulfonic acid 2-[5-methyl-2-(tetrahydro-pyran-4-yl)-oxazol-4-yl]-ethyl ester



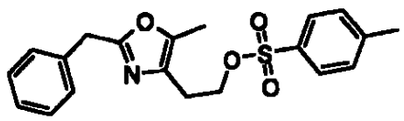
MS (EI) 366.2 $(M + H)^+$.

2-(2-Benzyl-5-methyl-oxazol-4-yl)-ethanol



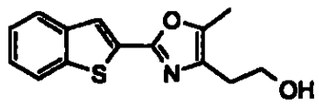
MS (EI) 218.0 $(M + H)^+$.

Toluene-4-sulfonic acid 2-(2-benzyl-5-methyl-oxazol-4-yl)-ethyl ester



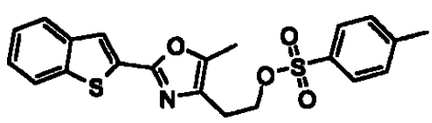
MS (EI) 372.1 $(M + H)^+$.

2-(2-Benzo[b]thiophen-2-yl-5-methyl-oxazol-4-yl)-ethanol



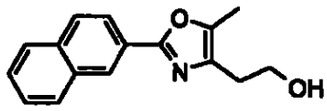
^1H NMR ($CDCl_3$) δ 7.81 (m, 3 H), 7.38 (m, 2 H), 3.94 (m, 2 H), 3.07 (br s, 1 H), 2.73 (t, 2 H, J = 6 Hz), 2.34 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.9, 145.0, 140.5, 139.8, 134.5, 129.9, 125.9, 125.1, 124.7, 123.7, 122.7, 61.9, 28.5, 10.4; MS (EI) 260.1 $(M + H)^+$.

Toluene-4-sulfonic acid 2-(2-benzo[b]thiophen-2-yl-5-methyl-oxazol-4-yl)-ethyl ester



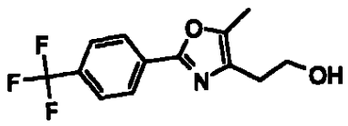
^1H NMR ($CDCl_3$) δ 7.85 (m, 1 H), 7.84 (m, 1 H), 7.75 (s, 1 H), 7.67 (d, 2 H, J = 8 Hz), 7.39 (m, 2 H), 7.21 (m, 2 H), 4.31 (t, 2 H, J = 2 Hz), 2.83 (t, 2 H, J = 6 Hz), 2.32 (s, 3 H), 2.19 (s, 3 H).

2-(5-Methyl-2-naphthalen-2-yl-oxazol-4-yl)-ethanol



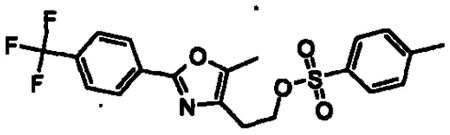
HRMS Calcd for $C_{16}H_{16}NO_2$: m/z 254.1181. Found: 254.1167.

2-[5-Methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-yl]-ethanol



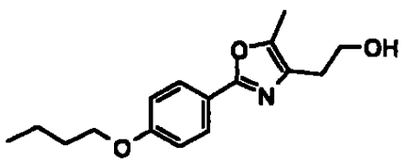
MS (EI) 272 $(M + H)^+$.

Toluene-4-sulfonic acid 2-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-yl]-ethyl ester



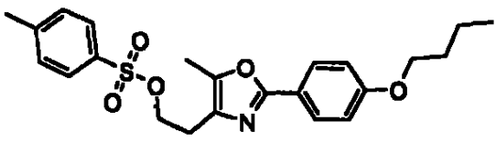
MS (EI) 426 $(M + H)^+$; mp 110.2°C.

2-[2-(4-Butoxy-phenyl)-5-methyl-oxazol-4-yl]-ethanol



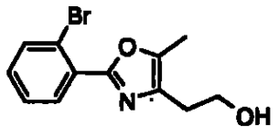
MS (EI) 276 $(M + H)^+$.

Toluene-4-sulfonic acid 2-[2-(4-butoxy-phenyl)-5-methyl-oxazol-4-yl]-ethyl ester



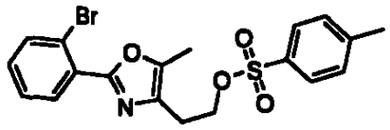
MS (EI) 430 $(M + H)^+$; mp 84.9°C.

2-(2-Bromophenyl-5-methyl-oxazol-4-yl)-ethanol



MS (EI) 282.1 $(M + H)^+$.

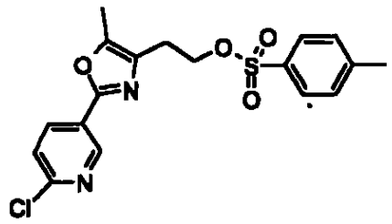
Toluene-4-sulfonic acid 2-(2-bromophenyl-5-methyl-oxazol-4-yl)ethyl ester



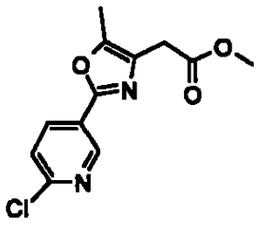
MS (EI) 438.1 $(M + H)^+$.

Preparation 4

Toluene-4-sulfonic acid 2-[2-(6-chloro-pyridn-3-yl)-5-methyl-oxaxol-4-yl]-ethyl ester

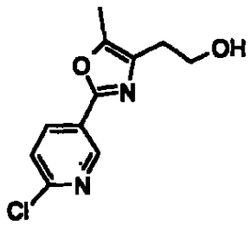


Step A: 3-[2-(6-Chloro-pyridin-3-yl)-5-methyl-oxazole-4-yl]-acetic acid methyl ester



According to Preparation 3, Steps A to C, 6-chloronicotinic acid was converted into the title compound. MS (ESI) m/z 267 $(M+H)^+$.

Step B: 3-[2-(6-Chloro-pyridin-3-yl)-5-methyl-oxazole-4-yl]-ethanol



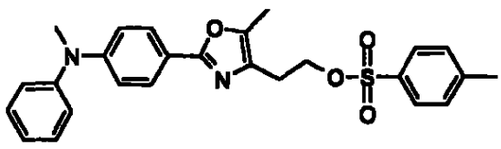
A solution of 3-[2-(6-chloro-pyridin-3-yl)-5-methyl-oxazole-4-yl]-acetic acid methyl ester (500 mg, 1.88 mmol) in THF (20 mL) at 0°C was treated LAH (90 mg, 2.3 mmol). The reaction mixture was stirred for 1 h and was quenched with water (0.1mL), 15% NaOH (0.1 mL), and water (0.3 mL). The mixture was filtered through Celite and concentrated to give the title alcohol which as used in the next step without further purification. MS (ESI) m/z 239 $(M+H)^+$.

Step C: Toluene-4-sulfonic acid 2-[2-(6-chloro-pyridn-3-yl)-5-methyl-oxaxol-4-yl]-ethyl ester

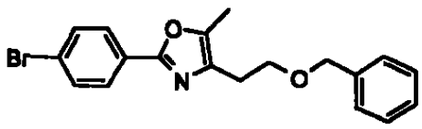
A solution of crude 3-[2-(6-chloro-pyridin-3-yl)-5-methyl-oxazole-4-yl]-ethanol (1.88 mmol max) in CH_2Cl_2 (10 mL) was treated with *para*-toluenesulfonyl chloride (0.4 g, 2.3 mmol), DMAP (40 mg), and triethylamine (0.4 mL, 2.82 mmol). The reaction mixture was stirred at ambient temperature overnight and was diluted with CH_2Cl_2 (20 mL). The mixture was washed with water, and the organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by silica gel chromatography (hexanes/EtOAc 10/1 to 2/1) to afford the title compound (295 mg, 40% over two steps). MS (ESI) m/z 393 $(M+H)^+$.

Preparation 5

Toluene-4-sulfonic acid 2-{5-methyl-2-[4-(methyl-phenyl-amino)-phenyl]-oxazol-4-yl}-ethyl ester

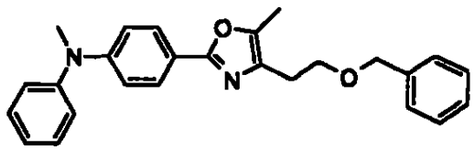


Step A: 4-(2-Benzyloxy-ethyl)-2-(4-bromo-phenyl)-5-methyl-oxazole



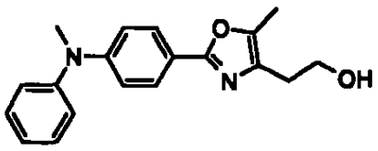
A solution of 2-[2-(4-bromo-phenyl)-5-methyl-oxazol-4-yl]-ethanol (3.17 g, 11.2 mmol) in DMF (25 mL) was treated with NaH (0.67 g, 60% oil dispersion) at 0°C and stirred for 5 min. Benzyl bromide (2.90 g, 16.9 mmol) was added, and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with water, and the mixture was extracted with EtOAc (2 x 150 mL). The combined organics were dried (Na_2SO_4), concentrated, and purified by silica gel chromatography column (10% EtOAc/hexanes) to yield the title compound as an oil (2.50 g, 60%).

Step B: {4-[4-(2-Benzyloxy-ethyl)-5-methyl-oxazol-2-yl]-phenyl}-methyl-phenyl-amine



A solution of 4-(2-benzyloxy-ethyl)-2-(4-bromo-phenyl)-5-methyl-oxazole (200 mg, 0.538 mmol) in toluene (5.0 mL) in a seal tube under nitrogen gas flow was treated with $Pd(OAc)_2$ (50 mg), 2-(di-t-butylphosphino)biphenyl (20 mg), N-methyl aniline (115 mg, 1.08 mmol), and sodium t-butoxide (104 mg, 1.08 mmol). The tube was sealed and heated at 105 °C for 14 h. The mixture was cooled and purified directly by silica gel column chromatography (30-50% EtOAc/hexanes) to yield the title compound (195 mg, 91%). MS (ESI) m/z 399.3 $(M+H)^+$.

Step C: 2-{5-Methyl-2-[4-(methyl-phenyl-amino)-phenyl]-oxazol-4-yl}-ethanol



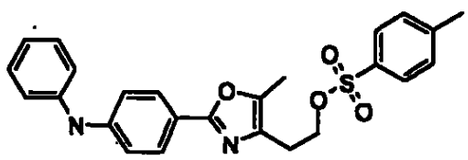
A solution of {4-[4-(2-benzyloxy-ethyl)-5-methyl-oxazol-2-yl]-phenyl}-methyl-phenyl-amine (195 mg, 0.490 mmol) in THF (2 mL) and EtOH (10 mL) was treated a slurry of Pd/C (200 mg) in EtOH (2 mL). The resulting mixture was treated with hydrogen under balloon pressure for 14 h and filtered through a pad of Celite. The filtrate was concentrated, and crude product was purified by silica gel chromatography column (50% EtOAc/hexanes) to yield the title compound (91 mg, 60%).

Step D: Toluene-4-sulfonic acid 2-{5-methyl-2-[4-(methyl-phenyl-amino)-phenyl]-oxazol-4-yl}-ethyl ester

A solution of 2-{5-methyl-2-[4-(methyl-phenyl-amino)-phenyl]-oxazol-4-yl}-ethanol (91 mg, 0.30 mmol) in CH_2Cl_2 (4.0 mL) was treated with *para*-toluenesulfonyl chloride (68 mg, 0.36 mmol), triethyl amine (0.20 mL) and a few crystals of DMAP. The resulting mixture was stirred at room temperature for 14 h and was quenched with water (0.2 mL). The mixture was purified directly by silica gel column chromatography (40% EtOAc/hexanes) to yield the title compound (120 mg, 83%). MS (ESI) m/z 463.1 $(M+H)^+$.

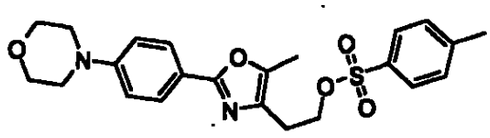
The following intermediate compounds are prepared by a substantially similar manner as described in Preparation 5.

Toluene-4-sulfonic acid 2-[5-methyl-2-(4-phenylamino-phenyl)-oxazol-4-yl]-ethyl ester



MS (ESI) m/z 449.1 $(M+H)^+$.

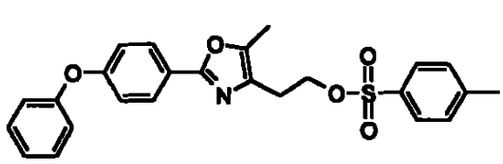
Toluene-4-sulfonic acid 2-[5-methyl-2-(4-morpholin-4-yl-phenyl)-oxazol-4-yl]-ethyl ester



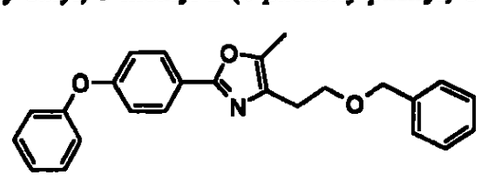
MS (ESI) m/z 443.1 $(M+H)^+$.

Preparation 6

Toluene-4-sulfonic acid 2-[5-methyl-2-(4-phenoxy-phenyl)-oxazol-4-yl]-ethyl ester



Step A: 4-(2-Benzyloxy-ethyl)-5-methyl-2-(4-phenoxy-phenyl)-oxazole



A mixture of 4-(2-benzyloxy-ethyl)-2-(4-bromo-phenyl)-5-methyl-oxazole (0.025 mol, 9.2 g), phenol (0.03 mol, 2.8 g), K_3PO_4 (0.05 mol, 10.6 g), 2-(di-*tert*-butylphosphino)biphenyl (1.8 mmol, 0.54 g) and $Pd(OAc)_2$ (1.2 mmol, 0.28 g) in toluene (350 mL) was degassed with nitrogen and heated at 100°C for 18 h. Additional $Pd(OAc)_2$ (0.5 g) and phosphine ligand (1.0 g) were added, and the mixture was heated 5 h at

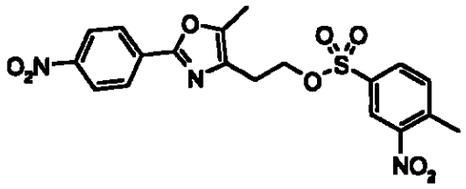
100°C. The reaction was concentrated and purified directly by silica gel chromatography (4/1 hexanes/ethyl acetate) to give the title compound (7.6 g).

Step B: Toluene-4-sulfonic acid 2-[5-methyl-2-(4-phenoxy-phenyl)-oxazol-4-yl]-ethyl ester

According to Preparation 5, Steps C to D, 4-(2-benzyloxy-ethyl)-5-methyl-2-(4-phenoxy-phenyl)-oxazole was converted into the title compound. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.81 (d, 2H, J=9.1 Hz), 7.67 (d, 2H, J=8.2 Hz), 7.37 (t, 2H, J=8.2 Hz), 7.15 (m, 3H), 7.12 (m, 4H), 4.39 (t, 2H, J=6.4 Hz), 2.81 (t, 2H, 6.4 Hz), 2.30 (s, 3H), 2.25 (s, 3H).

Preparation 7

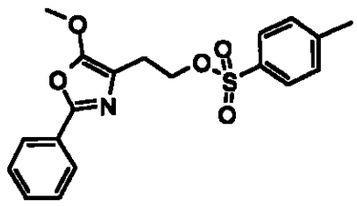
4-Methyl-3-nitro-benzenesulfonic acid 2-[5-methyl-2-(4-nitro-phenyl)-oxazol-4-yl]-ethyl ester



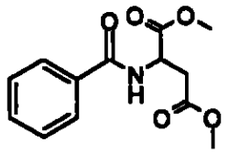
A mixture of potassium nitrate (3.0 g, 30 mmol, 2.7 equiv) and sulfuric acid (10 mL, 18 g, 94 mmol, 17 equiv) was cooled to 0°C. Toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl ester (4.00 g, 11.2 mmol, 1 equiv) was added and the ice bath was removed. The reaction mixture was heated with a heat gun until the tosylate dissolved. After 30 min, the solution was poured into H_2O (100 mL) and extracted with EtOAc (100 mL). The organic layer was dried (Na_2SO_4) and concentrated (75°C) to an orange oil (4.41 g). The crude product was purified by silica gel flash chromatography (30-50% EtOAc/hexanes) to give the title compound as a yellow solid (3.64 g, 73%). MS (ESI) m/z 447 $(M+H)^+$.

Preparation 8

Toluene-4-sulfonic acid 2-(5-methoxy-2-phenyl-oxazol-4-yl)-ethyl ester

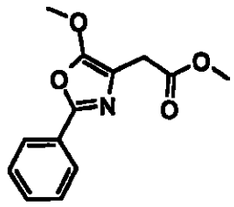


Step A: 2-Benzoylamino-succinic acid dimethyl ester



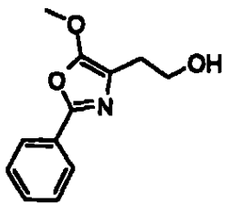
A mixture of benzoyl chloride (3.20 mL, 27.7 mmol), L-aspartic acid dimethyl ester (5.0 g, 25.2 mmol) and triethyl amine (5.3 mL, 38 mmol) in CH_2Cl_2 (50 mL) was stirred at ambient temperature for 2 h and diluted with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel chromatography (hexanes/EtOAc 1/1) to afford a white solid (5.3 g, 79%). MS (ESI) m/z 266 $(M+H)^+$.

Step B: 3-(5-Methoxy-2-phenyl-oxazol-4-yl)-acetic acid methyl ester



A mixture of 2-benzoylamino-succinic acid dimethyl ester (5.3 g, 20 mmol) in 1,2-dichloroethane (15 mL) was treated with P_2O_5 (5.3g, 30 mmol) and Celite (3.2 g) and was heated at 85°C for 2 h. The solvent was decanted and concentrated. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel chromatography (hexanes/EtOAc 10/1 to 3/1) to afford the title compound (2.9 g, 59%). MS (ESI) m/z 247 $(M+H)^+$.

Step C: 3-(5-Methoxy-2-phenyl-oxazol-4-yl)-ethanol



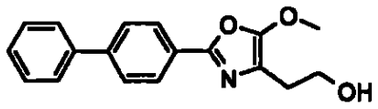
A suspension of LAH (0.56 g, 14.1 mmol) in THF (100 mL) at -78°C was treated dropwise with a solution of 3-(5-methoxy-2-phenyl-oxazol-4-yl)-acetic acid methyl ester (2.9 g, 11.7 mmol) in THF (100 mL). After the addition was completed, the reaction mixture was warmed up to ambient temperature, cooled to -20°C, and quenched with H_2O (0.8 mL), 15% NaOH (0.8 mL), and H_2O (2.4 mL). The mixture was filtered through Celite and concentrated to the title compound as an oil. MS (ESI) m/z 220.3 $(M+H)^+$.

Step D: Toluene-4-sulfonic acid 2-(5-methoxy-2-phenyl-oxazol-4-yl)-ethyl ester

A solution of crude 3-(5-methoxy-2-phenyl-oxazol-4-yl)-ethanol (11.7 mmol max) in CH_2Cl_2 (100 mL) was treated with *para*-toluenesulfonyl chloride (2.7 g, 14.0 mmol), DMAP (100 mg), and triethylamine (2.5 mL, 17.6 mmol). The reaction mixture was stirred at ambient temperature for 16h and was washed with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel chromatography (hexanes/EtOAc, 10/1 to 1/1) to afford the title compound (2.0 g, 46% over two steps). MS (ESI) m/z 374 $(M+H)^+$.

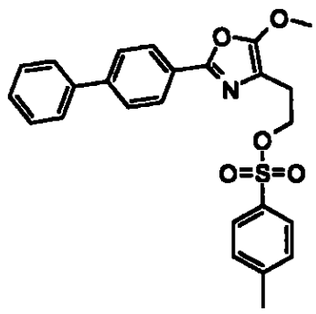
The following intermediate compounds are prepared by a substantially similar manner as described in Preparation 8.

2-(2-Biphenyl-4-yl-5-methoxy-oxazol-4-yl)-ethanol



MS (ESI) m/z 296.0 $(M+H)^+$.

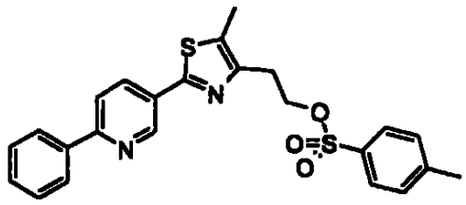
Toluene-4-sulfonic acid 2-(2-biphenyl-4-yl-5-methoxy-oxazol-4-yl)-ethyl ester



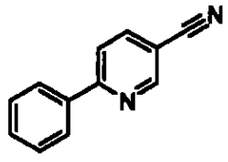
MS (ESI) m/z 450.1 $(M+H)^+$.

Preparation 9

Toluene-4-sulponic acid 2-[5-methyl-2-(6-phenyl-pyridin-3-yl)thiazol-4-yl]ethyl ester



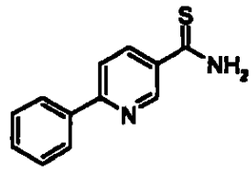
Step A: 2-Phenyl-5-cyanopyridine



5-Cyano-2-chloropyridine (5.0 g, 36.1 mmol), phenylboronic acid (6.6 g, 54 mmol), tetrakis(triphenylphosphine) palladium (0) (0.5 g), and aqueous Na_2CO_3 (7.6 g), in toluene (100 mL) were heated at 90°C for 16 h. The mixture was diluted with

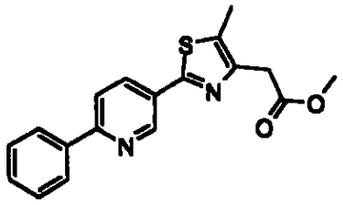
EtOAc and washed with H_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel chromatography (hexanes/EtOAc 2/1) to afford the title compound (6.1 g, 94%). MS (ESI) m/z 181$(M+H)^+$.

Step B:



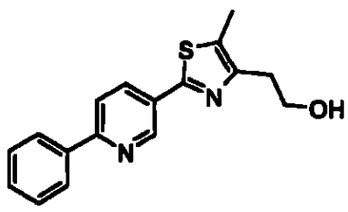
A mixture of 2-phenyl-5-cyanopyridine (6.0 g, 33 mmol) and thioacetamide (4.0 g, 53 mmol) in 4N HCl in 1,4-dioxane (50 mL) was heated at 98°C for 20 h. The reaction mixture was cooled and poured into aqueous saturated $NaHCO_3$. The precipitate was collected, washed with water, and dried under vacuum (60°C) to afford the title compound as a yellow solid (7.0 g, 99%).

Step C: [5-Methyl-2-(6-phenyl-pyridin-3-yl)-thiazol-4-yl]-acetic acid methyl ester



A mixture of 6-phenyl-thionicotinamide (7.0 g) and 4-bromo-3-oxo-pentanoic acid methyl ester (9.15 g, 35 mmol) in 1,4-dioxane (30 mL) was heated at reflux for 4 h. The reaction mixture was cooled, poured into aqueous saturated $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel chromatography (hexanes/EtOAc, 2/1) to afford the title compound (6.0 g, 56%). MS (ESI) m/z 325 $(M+H)^+$.

Step D: [5-Methyl-2-(6-phenyl-pyridin-3-yl)-thiazol-4-yl]-ethanol



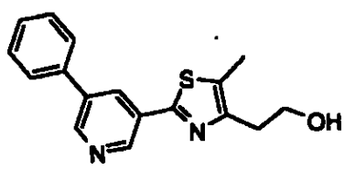
A solution of [5-methyl-2-(6-phenyl-pyridin-3-yl)-thiazol-4-yl]-acetic acid methyl ester (6.0 g, 18.5 mmol) in THF (500 mL) was added dropwise to a suspension of LAH (0.90 g, 22.2 mmol) in THF (300 mL) at -78°C. After the addition was completed, the reaction mixture was allowed to warm to ambient temperature, cooled to -20 °C, and quenched sequentially with H_2O (1.1 mL), 15% NaOH (1.1 mL), and H_2O (3.3 mL). The mixture was filtered through Celite, and the filtrated was concentrated to give the title compound as an oil that was used directly in the next step.

Step E: Toluene-4-sulponic acid 2-[5-methyl-2-(6-phenyl-pyridin-3-yl)thiazol-4-yl]ethyl ester

A mixture of [5-methyl-2-(6-phenyl-pyridin-3-yl)-thiazol-4-yl]-ethanol (18.5 mmol max), *para*-toluenesulfonyl chloride (3.89 g, 20.5 mmol), DMAP (500 mg), and triethylamine (4.0 mL, 28.0 mmol) in CH_2Cl_2 (300 mL) was stirred at ambient temperature for 2.5 h. The reaction mixture was diluted with water, and the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel chromatography (hexanes/EtOAc, 10/1 to 1/1) to afford the title compound as a solid (2.0 g, 46% over two steps). MS (ESI) m/z 451 $(M+H)^+$.

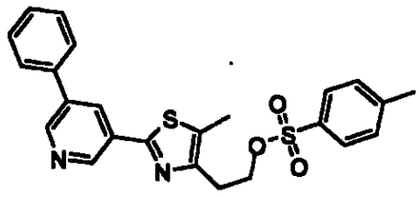
The following intermediate compounds are prepared by a substantially similar manner as described in Preparation 9.

2-[5-Methyl-2-(5-phenyl-pyridin-3-yl)-thiazol-4-yl]-ethanol



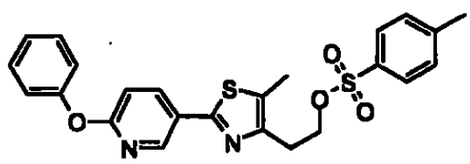
MS (ESI) m/z 297 $(M+H)^+$.

Toluene-4-sulfonic acid 2-[5-methyl-2-(5-phenyl-pyridin-3-yl)thiazol-4-yl]ethyl ester



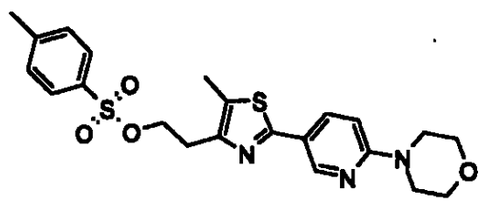
MS (ESI) m/z 451 $(M+H)^+$.

Toluene-4-sulfonic acid 2-[5-methyl-2-(6-phenoxy-pyridin-3-yl)-thiazol-4-yl]-ethyl ester



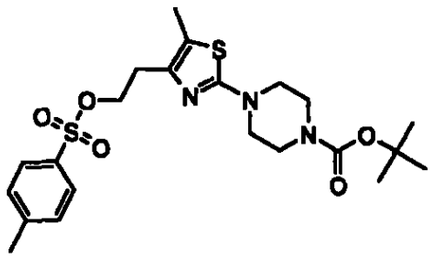
^{1}HNMR 400 MHz ($CDCl_3$) δ8.52 (2, 1H), 8.03 (d, 1H, J=6.9 Hz), 7.63 (d, 2H, J=8.6 Hz), 7.42 (t, 2H, J=7.7 Hz), 7.2 (m,5H), 6.91 (1H, d, J=7.7 Hz), 4.37 (t, 2H, J=6.3 Hz), 3.02 (t, 2H, J=6.3 Hz), 2.39 (s, 3H), 2.28 (s, 3H).

Toluene-4-sulfonic acid 2-[5-methyl-2-(6-morpholin-4-yl-pyridin-3-yl)-thiazol-4-yl]-ethyl ester



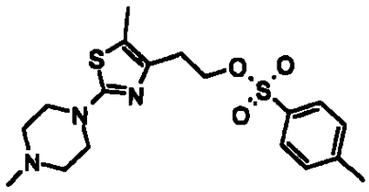
^{1}HNMR 400 MHz ($CDCl_3$) δ8.51 (s, 1H), 7.82 (d, 1H, J=8.5 Hz), 7.63 (d, 2H, J=7.8 Hz), 7.19 (d, 2h, J=7.8 Hz), 6.61 (d, 1H, J=8.5 Hz), 4.37 (t, 2H, J=6.5 Hz), 3.82 (t, 2H, J=5.2 Hz), 3.58 (t, 2H, J=5.2 Hz), 2.99 (t, 2H, J=6.5 Hz), 2.35 (s, 3H), 2.27 (s, 3H).

4-{5-Methyl-4-[2-(toluene-4-sulfonyloxy)-ethyl]-thiazol-2-yl}-piperazine-1-carboxylic acid tert-butyl ester



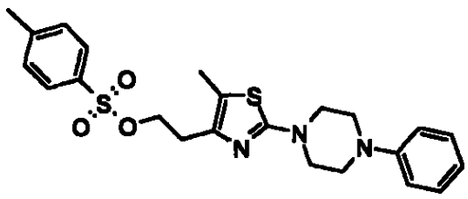
MS (ESI) m/z 482 $(M+H)^+$.

Toluene-4-sulfonic acid 2-[5-methyl-2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-ethyl ester



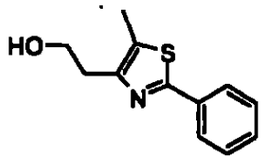
MS (ESI) m/z 396.1 $(M+H)^+$.

Toluene-4-sulfonic acid 2-[5-methyl-2-(4-phenyl-piperazin-1-yl)-thiazol-4-yl]-ethyl ester



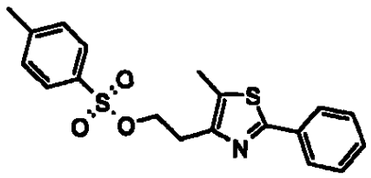
MS (ESI) m/z 458.1 $(M+H)^+$.

2-(5-Methyl-2-phenyl-thiazol-4-yl)-ethanol



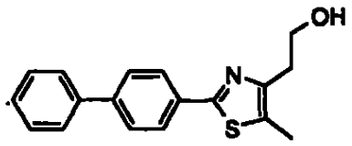
MS (ESI) m/z 220 $(M+H)^+$.

Toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-thiazol-4-yl)-ethyl ester:



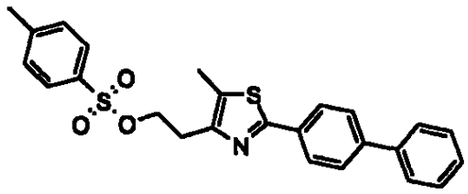
MS (ESI) m/z 374 $(M+H)^+$.

2-(2-Biphenyl-4-yl-5-methyl-thiazol-4-yl)-ethanol



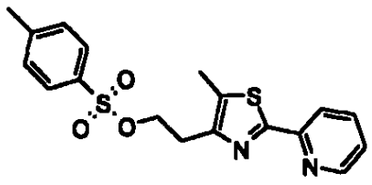
MS (ESI) m/z 296 $(M+H)^+$.

Toluene-4-sulfonic acid 2-(2-biphenyl-4-yl-5-methyl-thiazol-4-yl)-ethyl ester



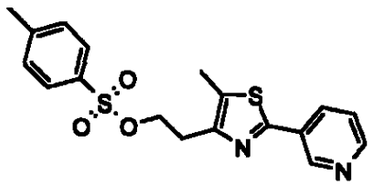
MS (ESI) m/z 450 $(M+H)^+$.

Toluene-4-sulfonic acid 2-(5-methyl-2-pyridin-2-ylthiazol-4-yl) ethyl ester



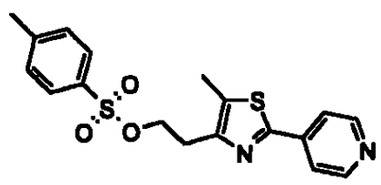
MS (ESI) m/z 375.1 $(M+H)^+$.

Toluene-4-sulfonic acid 2-(5-methyl-2-pyridin-3-ylthiazol-4-yl) ethyl ester



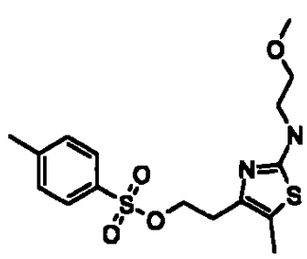
MS (ESI) m/z 375.1 $(M+H)^+$.

Toluene-4-sulfonic acid 2-(5-methyl-2-pyridin-4-ylthiazol-4-yl) ethyl ester



MS (ESI) m/z 375 $(M+H)^+$. MS (ESI) m/z 383.1 $(M+H)^+$.

Toluene-4-sulfonic acid 2-[2-(2-methoxyethylamino)-5-methylthiazol-4-yl] ethyl ester

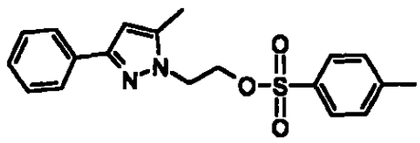


MS (ESI) m/z 371 $(M+H)^+$.

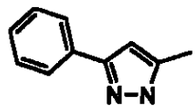
Pyrazoles

Preparation 10

Toluene-4-sulfonic acid 2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethyl ester

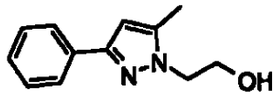


Step A: 5-Methyl-3-phenyl-1*H*-pyrazole



Hydrazine hydrate (9.0 mL, 99 mmol, 35 wt.% in H_2O; 0.64 equiv) was added to a solution of benzoylacetone (25.00 g, 154.1 mmol, 1 equiv) in ethanol (250 mL). After stirring 14 h, more hydrazine hydrate (8.0 mL, 88 mmol, 0.57 equiv) was added. After 2 h, the reaction solution was concentrated (95°C) to give the title compound as a white solid (24.31 g, 99.7%). HRMS Calculated for $C_{10}H_{11}N_2$: *m/z* 159.0922. Found: 159.0917

Step B: 2-(5-Methyl-3-phenyl-pyrazol-1-yl)-ethanol



Sodium hydride (2.5 g, 1.5 g NaH, 62 mmol, 1.1 equiv) was added over a period of 3 min to a solution of 5-methyl-3-phenyl-1*H*-pyrazole (9.00 g, 56.9 mmol, 1 equiv) in DMF (90 mL) cooled to 0 °C in an ice bath. After stirring 15 min, ethylene carbonate (7.6 mL, 10 g, 110 mmol, 2.0 equiv) was added. The bath was removed, and the reaction mixture was stirred for 15 h. The mixture was treated with 4 M aq K_2CO_3 (90 mL), heated at reflux for 5 h, and diluted with H_2O (200 mL). After allowing the hot mixture to cool for 15 min, more H_2O (100 mL) and then hexanes (100 mL) were added. The mixture was shaken vigorously and then allowed to separate. Crystals formed and stayed with the top organic layer. The aqueous layer was separated, and the crystals were collected by vacuum filtration and washed with hexanes (2 x 50 mL). The crystals were dissolved in Et_2O/EtOAc (1:1; 200 mL), and the solution was dried (Na_2SO_4), filtered,

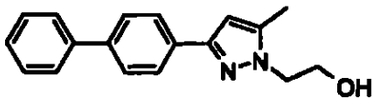
and concentrated (75 °C) to give the title compound as an off-white crystalline solid (6.86 g, 59.6%). HRMS Calculated for $C_{12}H_{15}N_2O$: m/z 203.1184. Found: 203.1168

Step C: Toluene-4-sulfonic acid 2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethyl ester

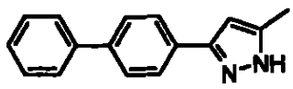
According to Preparation 9, Step E, 2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethanol was converted into the title compound. MS (ESI) m/z 357 $(M+H)^+$.

Preparation 11

2-(3-Biphenyl-4-yl-5-methyl-pyrazol-1-yl)-ethanol



Step A: 5-Biphenyl-4-yl-3-methyl-1*H*-pyrazole



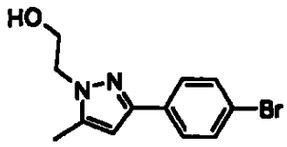
To a stirred mixture of NaH (1.98 g, .049 mol, 60% oil dispersion) in dry THF (30 mL) was added a suspension of diethoxyphosphorylacetone tosyl hydrazone (8.97 g, .024 mol; N Almirante *Syn. Lett.* 1999, 302.) in a mixture of THF (35 mL) and DMF (5.0 mL) dropwise over 15 min. The yellow suspension was stirred at 0-5°C for 30 min and was treated with a 4-biphenyl carboxaldehyde (3.10 g, .0169 mol) in dry THF (30 mL) at 0-5°C over 15 min. The orange solution was heated and stirred at reflux for 4 h and stirred at ambient temperature overnight. The mixture was poured into 5% aq. NaH_2PO_4 (350 mL) and extracted with EtOAc (2 x 200mL). The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated to a yellow semi-solid. This material was triturated with hot EtOAc (20 mL) and filtered. The solid was washed with EtOAc (2 x 10 mL) and dried under high vacuum to give the title compound (2.61 g, 47%): HRMS Calculated for $C_{16}H_{13}N_2$: m/z 235.1235. Found: 235.1230.

Step B: 2-(3-Biphenyl-4-yl-5-methyl-pyrazol-1-yl)-ethanol

The title compound was prepared from 5-biphenyl-4-yl-3-methyl-1*H*-pyrazole according to the Preparation 10, Step B. HRMS Calculated for $C_{18}H_{19}N_2O$: m/z 279.1497. Found: 279.1496.

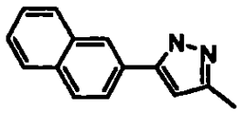
The following intermediate compounds are prepared by a substantially similar manner as described in Preparations 10 and 11.

2-[3-(4-Bromo-phenyl)-5-methyl-pyrazol-1-yl]-ethanol



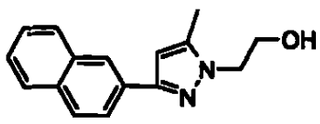
HRMS Calculated for $C_{12}H_{14}BrN_2O$: m/z 281.0289. Found: 281.0288.

3-Methyl-5-naphthalen-2-yl-1*H*-pyrazole



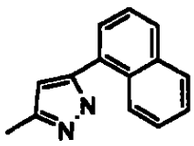
HRMS Calculated for $C_{14}H_{12}N_2$: m/z 208.1001. Found: 208.0981.

2-(5-Methyl-3-naphthalen-2-yl-pyrazol-1-yl)-ethanol



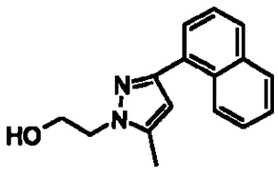
HRMS Calculated for $C_{16}H_{17}N_2O$: m/z 253.1341. Found: 253.1339.

3-Methyl-5-naphthalen-1-yl-1*H*-pyrazole



Anal Calculated for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.93; H, 5.70; N, 13.42; mp 115-117°C.

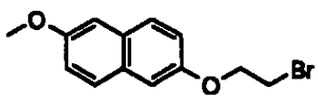
2-(5-Methyl-3-naphthalen-1-yl-pyrazol-1-yl)-ethanol.



Arylether bromide Preparations

Preparation 12

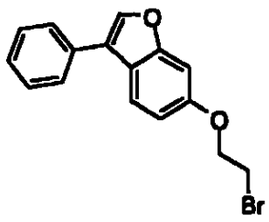
2-(2-Bromo-ethoxy)-6-methoxynaphthalene



To a solution of 6-methoxynaphthalen-2-ol (1.07 g, 6.14 mmol) in DMF (4 mL) were added cesium carbonate (3.11 g, 9.55 mmol) and dibromoethane (2.5 mL, 29 mmol). The mixture was stirred and heated at 55°C for 48 h. The reaction mixture was cooled, filtered, diluted with EtOAc, and washed with brine (2 x 30 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified using radial chromatography (2:98 to 25:75 EtOAc:Hex) to give the title compound as a white solid (0.52 g, 30 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (t, J= 6.1 Hz, 2H), 3.82 (s, 3H), 4.30 (t, J= 6.4 Hz, 2H), 7.01-7.08 (m, 4H), 7.56 (dd, J= 12.0, 9.0 Hz, 2H).

The following intermediate compounds are prepared by a substantially similar manner as described in Preparation 12.

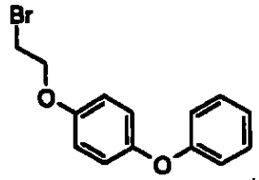
6-(2-Bromoethoxy)-3-phenylbenzofuran



The above compound is prepared from 3-phenylbenzofuran-6-ol (see *Bull. Soc. Chim. Fr.*, 942 (1962)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (t, J= 6.4 Hz, 2H), 4.28 (t, J= 6.4

Hz, 2H), 6.88 (dd, J= 8.8, 2.4 Hz, 1H), 7.00 (d, J= 2.4 Hz, 1H), 7.26-7.30 (m, 1H), 7.36-7.44 (m, 2H), 7.52-7.56 (m, 2H), 7.63 (d, J= 9.8 Hz, 2H).

4-(2-Bromoethoxy)-1-phenoxybenzene



^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (t, J= 6.4 Hz, 2H), 4.19 (t, J= 6.1 Hz, 2H), 6.80-6.90 (m, 6H), 6.96 (t, J= 7.3 Hz, 1H), 7.17-7.24 (m, 2H).

4-(3-Bromoethoxy)biphenyl: MS (ESI) m/z 295 $(M+NH_3)^+$.

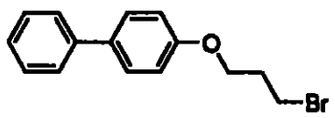
3-(2-Bromoethoxy)biphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (t, J= 6.4 Hz, 2H), 4.27 (t, J= 6.4 Hz, 2H), 6.81 (dd, J= 8.3, 2.4 Hz, 1H), 6.90 (d, J= 8.8 Hz, 1H), 7.13 (dd, J= 7.8, 1.0 Hz, 1H), 7.26-7.33 (m, 2H), 7.34-7.37 (m, 2H), 7.43-7.50 (m, 2H).

6-(4-Bromopropoxy)-3-phenylbenzofuran: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26-2.33 (m, 2H), 3.57 (t, J= 6.4 Hz, 2H), 4.11 (t, J= 5.9 Hz, 2H), 6.89 (dd, J= 8.6, 2.2 Hz, 1H), 7.01 (d, J= 2.0 Hz, 1H), 7.29 (t, J= 7.6 Hz, 1H), 7.40 (t, J= 7.6 Hz, 2H), 7.56 (d, J= 6.8 Hz, 2H), 7.57-7.65 (m, 2H).

2-(4-Bromopropoxy)-6-methoxynaphthalene: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (t, J= 6.1 Hz, 2H), 3.56 (t, J= 6.4 Hz, 2H), 3.81 (4.11 (t, J= 5.9 Hz, 2H), 7.01-7.14 (m, 4H), 7.52-7.57 (m, 2H).

3-(4-Bromopropoxy)biphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (t, J= 6.1 Hz, 2H), 3.55 (t, J= 6.6 Hz, 2H), 4.09 (t, J= 5.9 Hz, 2H), 6.81 (dd, J= 2.9, 1.0 Hz, 1H), 7.05 (t, J= 2.0 Hz, 1H), 7.07 (t, J= 2.0 Hz, 1H), 7.22-7.24 (m, 2H), 7.26-7.37 (m, 2H), 7.43-7.52 (m, 3H).

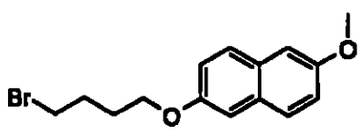
4-(3-Bromopropoxy)-biphenyl:



^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.57-7.29 (m, 7H), 6.98 (dd, 2H, J=6.72, 1.88), 4.15 (t, 2H, J=5.92), 3.62 (t, 2H, J=6.44), 2.34 (qn, 2H, J=5.92).

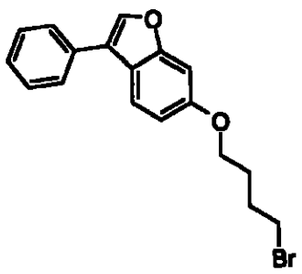
4-(3-Bromoproxy)-1-phenoxybenzene: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.3(2H, m), 7.1(2H, m), 7.0(2H, m), 6.9(2H, m), 4.1(2H, m); 3.6(2H, m); 2.3(2H, m).

2-(4-Bromobutoxy)-6-methoxynaphthalene



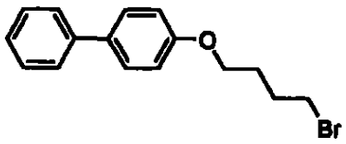
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88-1.97 (m, 2H), 1.99-2.10 (m, 2H), 3.41-3.48 (m, 2H), 3.81 (s, 3H), 4.00 (t, J= 5.9 Hz, 2H), 7.00-7.05 (m, 3H), 7.13-7.19 (m, 1H), 7.54 (t, J= 8.1 Hz, 2H).

6-(4-Bromobutoxy)-3-phenylbenzofuran



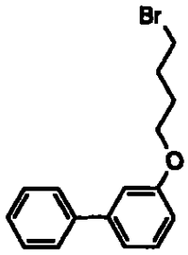
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90-1.98 (m, 2H), 2.01-2.04 (m, 2H), 3.41-3.44 (m, 2H), 3.94-3.99 (m, 2H), 6.83-6.91 (m, 1H), 6.96-6.97 (m, 1H), 7.27-7.29 (m, 1H), 7.36-7.43 (m, 2H), 7.53-7.62 (m, 4H).

4-(4-Bromobutoxy)biphenyl



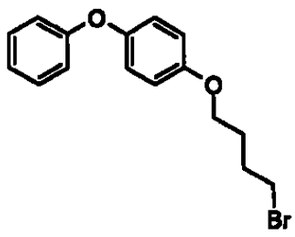
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (t, J= 6.8 Hz, 2H), 3.42 (t, J= 6.6 Hz, 2H), 3.96 (t, J= 6.5 Hz, 2H), 6.87 (d, J=7.8 Hz, 2H), 7.17-7.23 (m, 3H), 7.32 (t, J= 7.6 Hz, 1H), 7.42-7.47 (m, 4H).

3-(4-Bromobutoxy)biphenyl



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86-1.95 (m, 2H), 1.96-2.05 (m, 2H), 2.42 (t, J= 6.6 Hz, 2H), 3.98 (t, J= 6.1 Hz, 2H), 6.79 (dd, J= 7.3, 2.0 Hz, 1H), 7.03-7.11 (m, 1H), 7.26 (t, J= 7.8 Hz, 2H), 7.35 (t, J= 7.8 Hz, 2H), 7.42-7.51 (m, 2H).

4-(4-Bromobutoxy)-1-phenoxybenzene

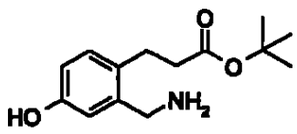


^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83-2.03 (m, 2H), 1.96-2.03 (m, 2H), 3.41 (t, J= 6.6 Hz, 2H), 3.90 (t, J= 6.5 Hz, 2H), 6.76-6.78 (m, 2H), 6.79-6.90 (m, 4H), 6.94-6.97 (m, 1H), 7.19-7.23 (m, 2H).

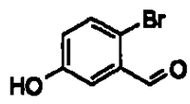
Headpiece Preparations

Preparation 13

3-(2-Aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester

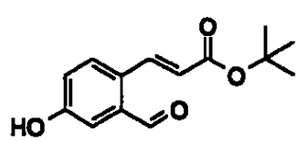


Step A: 2-Bromo-5-hydroxybenzaldehyde



To a suspension of 3-hydroxybenzaldehyde (1 kg, 8.2 mol) in CH_2Cl_2 (10 L) was added a solution of bromine (1.3 kg, 8.2 mol) in CH_2Cl_2 (620 mL) over 1 h. After stirring for about 22 h, the solids were isolated by filtration, washed with CH_2Cl_2 (4 L), and dried under vacuum to afford of 2-bromo-5-hydroxybenzaldehyde as a tan solid (1.05 kg, 63%).

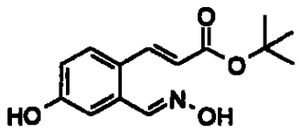
Step B: 3-(2-Formyl-4-hydroxy-phenyl)-acrylic acid tert-butyl ester



To a solution of 2-bromo-5-hydroxybenzaldehyde (200 g, 1.0 mole) in propionitrile (6 L) under N_2 was added tri-o-tolyl phosphine (75.4 g, 0.25 mol) and diisopropylethylamine (350 mL, 260 g, 2.0 mol). The solution was degassed and purged with N_2 three times. To this solution was added tert-butylacrylate (440 mL, 385 g, 3.0 mol) and palladium acetate trimer (27.8 g, 0.12 mol). The mixture was degassed three times and heated to 80°C over 30 min. After 30 min, the reaction was cooled to ambient temperature and filtered. The solids were washed with acetonitrile. The filtrate was transferred to a separatory funnel with acetonitrile (4 L total) and was extracted with hexanes (4 x 5 L). The propionitrile/acetonitrile layer was concentrated by rotary evaporation. The residue was dissolved in toluene (4 L) and washed successively with 1N HCl (1 L), water (1 L), and brine (1 L). The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford crude product as a wet brown solid (293 g). The crude

product was dissolved in CH_2Cl_2 (600 mL) with stirring. To this solution was added hexanes (1.8 L) over ~2 h, and the resulting slurry was stirred at ambient temperature for 1 h. The slurry was cooled in an ice water bath and stirred for 1 h. The product was isolated by filtration, washed with hexanes, and dried under vacuum to afford the product as a tan solid (199.5 g, 80.6%).

Step C: 3-[4-Hydroxy-2-(hydroxyimino-methyl)-phenyl]-acrylic acid tert-butyl ester



A slurry of hydroxylamine hydrochloride (8.33 g, 0.12 mol), pyridine (9.49 g, 0.12 mol), and ethanol (100 mL) was stirred at ambient temperature for 30 min. 3-(2-Formyl-4-hydroxy-phenyl)-acrylic acid tert-butyl ester (14.90 g, 0.06 mol) was added followed by an ethanol (49 mL) rinse. The resulting brown solution was stirred at ambient temperature for 16 h and concentrated. The residue was suspended in water (150 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with saturated NaCl solution (2 x 100 mL), dried (Na_2SO_4), and filtered through a plug of silica gel to remove trace polar impurities. The filtrate was concentrated to give crude product (16.04 g). A 13.56 g sample of the crude material was crystallized from heptane (70 mL) and ethyl acetate (80 mL) to the title compound (7.41 g, 55%), mp 146-149°C. ^{1}H NMR (CD_3OD): δ 1.53 (s, 9H), 4.83 (s, 2H), 6.15-6.23 (d, 1H), 6.82-6.87 (dd, 1H), 7.10-7.12 (d, 1H), 7.52-7.55 (d, 1H), 7.98-8.03 (d, 1H), 8.37 (s, 1H). MS (ES^+) m/z 286.1 ($[M+Na]^+$). MS (ES^-) m/z 262.2 ($[M-H]^-$). Anal. Calculated for $C_{14}H_{17}NO_4$: C: 63.8658; H: 6.5081; N: 5.3198. Found: C: 63.71; H: 6.38; N: 5.51.

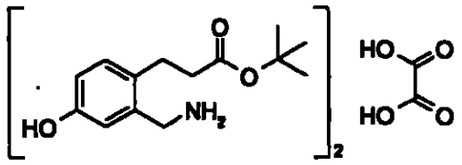
Step D: 3-(2-Aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester

A solution of 3-[4-hydroxy-2-(hydroxyimino-methyl)-phenyl]-acrylic acid tert-butyl ester (0.50 g, 1.9 mmol) in ethanol (50 mL) was treated with 10% palladium on carbon (0.25 g). The resulting suspension was treated with hydrogen using a Parr shaker apparatus at ambient temperature and 50 psi for 16 h. The reaction mixture was filtered through Celite, rinsed with ethanol (20 mL), and concentrated. The residue was dissolved in ethyl acetate (50 mL) and washed with 10% K_2CO_3 solution (2 x 25 mL) and 1N

NaOH (2 x 25 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was crystallized from isopropyl acetate to give the title compound (0.14 g, 40%), mp 154-157°C. ^1H NMR (CD_3OD): δ 1.37 (s, 9H), 2.44-2.50 (t, 2H), 2.80-2.85 (t, 2H), 3.75 (s, 2H), 4.83 (s, 3H), 6.57-6.63 (dd, 1H), 6.75-6.77 (d, 1H), 6.95-7.00 (d, 1H). MS (ES^+) m/z 252.1 ($[M+H]^+$). MS (ES^-) m/z 250.2 ($[M-H]^-$). Anal. Calculated for $C_{14}H_{21}NO_3$: C: 66.9069; H: 8.4222; N: 5.5731. Found: C: 66.57; H: 8.29; N: 5.60.

Preparation 14

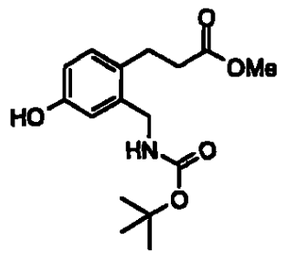
3-(2-Aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester Ethandioate (2: 1)



Alternative to the crystallization of 3-(2-Aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester from isopropyl acetate. The crude tert-butyl-3-[2-(aminomethyl)-4-hydroxyphenyl]propanoate (0.50 g, 0.002 mol) was dissolved in refluxing ethyl acetate (10 mL). A solution of oxalic acid (0.18 g, 0.002 mol) dissolved in ethyl acetate (5 mL) was added and produced a precipitate immediately. The resulting slurry was cooled to 0°C and filtered. The isolated product was slurred in ethanol (5 mL), cooled to 0°C, and filtered to give 3-(2-aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester ethandioate (2:1) (0.41 g, 69%). mp 188-190°C. ^1H NMR (DMSO-d_6): δ 1.36 (s, 18H), 2.39-2.45 (t, 4H), 2.47-2.52 (m, 4H), 2.70-2.76 (t, 4H), 3.83 (s, 4H), 6.61-6.65 (dd, 2H), 6.77-6.82 (d, 2H), 6.97-7.01 (d, 2H). MS (ES^+) m/z 252.1 ($[M+H]^+$). MS (ES^-) m/z 250.2 ($[M-H]^-$). Anal. Calculated for $C_{30}H_{44}N_2O_{10}$: C: 60.80; H: 7.48; N: 4.73. Found: C: 60.79; H: 7.51; N: 4.81.

Preparation 15

3-[2-(tert-Butoxycarbonylamino-methyl)-4-hydroxy-phenyl]-propionic acid methyl ester

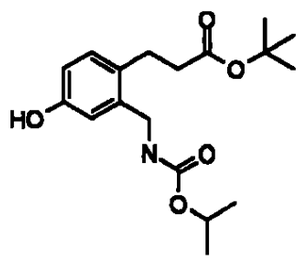


A solution of 3-(2-aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester (1.00 g, 3.98 mmol) in CH_2Cl_2 (10 mL) was treated with water (12 drops) then TFA (10 mL). The solution was stirred at ambient temperature for 6.5 h and concentrated. The residue was diluted with 2,2-dimethoxypropane (40 mL), conc. HCl (4 mL), and then MeOH (10 mL). The solution was stirred for 18 h and concentrated to 3-(2-aminomethyl-4-hydroxy-phenyl)-propionic acid: HCl salt as a tan solid. MS (ES^-) m/z 208 [M-1].

The solid was diluted with THF (20 mL) and saturated aq. $NaHCO_3$ solution (12 mL) and was treated with di-*tert*-butyl dicarbonate (1.09 g, 5.00 mmol). The mixture was stirred for 3 h and concentrated, and the residue was partitioned between EtOAc (75 mL) and 1N HCl (30 ml). The organic layer was dried (Na_2SO_4), and concentrated to give the title compound (1.16 g, 94 %). MS (ES^-) m/z 308 [M-1].

Preparation 16

3-[4-hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester

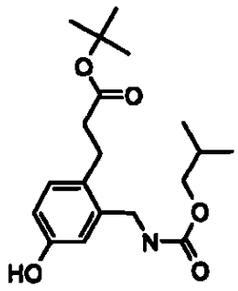


A slurry of 3-(2-aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester (75.4 g, 0.3 mol) in CH_2Cl_2 (900 mL) at 1°C was treated with triethylamine (60.7 g,

0.6 mol). Isopropyl chloroformate (300 mL, 0.3 mol, 1M in toluene) was added while maintaining the temperature less than 12°C. The resulting solution was stirred 16 h at ambient temperature. After 16 h, additional isopropyl chloroformate (15 mL, 0.015 mol, 1.0M in toluene) was added, and the reaction was stirred for 1 h. The reaction mixture was washed with 1N HCl (2 x 200 mL) and saturated $NaHCO_3$ solution (2 x 200 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by filtration through Merck silica gel 62 (750 grams, CH_2Cl_2/MeOH 100/0 to 96/4) to give the title compound (95.48 g, 94.3%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.20-1.24 (d, 6H), 1.40 (s, 9H), 2.46-2.52 (t, 2H), 2.81-2.86 (t, 2H), 4.29-4.32 (d, 2H), 4.86-4.97 (m, 1H), 5.19-5.28 (m, 1H), 6.67-6.72 (dd, 2H), 6.76 (s, 1H), 6.97-7.00 (d, 1H). MS (ES^-) m/z 336.1 $[M-H]^-$.

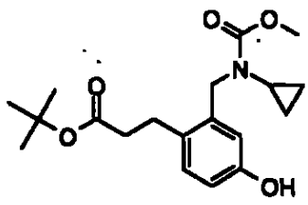
The following intermediate compounds are prepared by a substantially similar manner as described in Preparation 16.

3-[4-Hydroxy-2-(isobutoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester



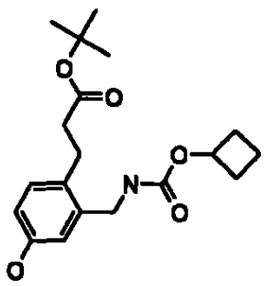
MS (ES^-) m/z 350 $[M-H]^-$.

3-[2-(Cyclopropylmethoxycarbonylamino-methyl)-4-hydroxy-phenyl]-propionic acid tert-butyl ester



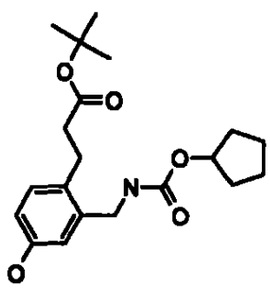
HRMS Calculated for $C_{19}H_{26}NO_5$: m/z 348.1811. Found: 348.1817.

3-[2-(Cyclobutoxycarbonylamino-methyl)-4-hydroxy-phenyl]-propionic acid *tert*-butyl ester



HRMS Calculated for $C_{19}H_{26}NO_5$: m/z 348.1811. Found: 348.1817.

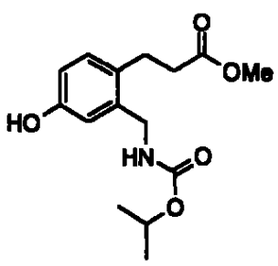
3-[2-(Cyclopentyloxycarbonylamino-methyl)-4-hydroxy-phenyl]-propionic acid tert-butyl ester



MS (ES$^-$) m/z 362 $[M-H]^-$.

Preparation 17

3-[4-Hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid methyl ester

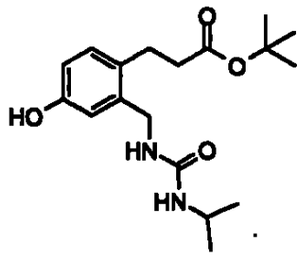


A solution of 3-[4-hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (3.0 mmol, 1.0g) in CH_2Cl_2 (10 mL) was treated with 90% CF_3CO_2H/H_2O (20 mL) at ambient temperature. The mixture was stirred for 3 h and concentrated. The residue was dissolved in MeOH (20 mL), treated with conc. H_2SO_4 (1

mL), and heated at reflux for 14 h. The mixture was cooled and concentrated. The residue was dissolved in water/ethyl acetate and neutralized with K_2CO_3. The organic layer was dried (Na_2SO_4), and concentrated to give the title compound (0.76 g, 86 %). HRMS Calculated for $C_{15}H_{22}NO_5$: m/z 296.1498. Found: 296.1504.

Preparation 18

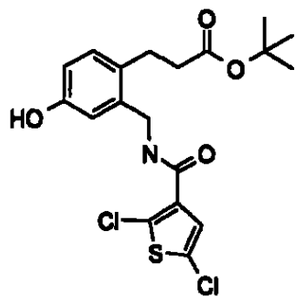
3-[4-Hydroxy-2-(3-isopropyl-ureidomethyl)-phenyl]-propionic acid tert-butyl ester



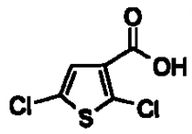
A slurry of 3-(2-aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester (2.24 g, 8.91 mmol) in CH_2Cl_2 (30 mL) was treated with isopropyl isocyanate (1.1 mL, 11 mmol). The reaction mixture was diluted with water, the CH_2Cl_2 was removed under reduced pressure, and the aqueous layer was extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated to the title compound as a white solid (2.6 g, 87%). MS (ES^+) m/z 337 $[M+H]^+$.

Preparation 19

3-(2-{[(2,5-dichloro-thiophene-3-carbonyl)-amino]-methyl}-4-hydroxy-phenyl)-propionic acid tert-butyl ester



Step A: 2,5-Dichloro-thiophene-3-carboxylic acid



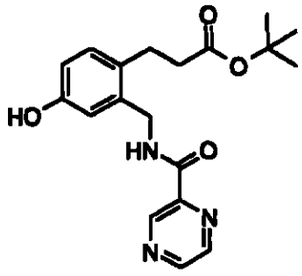
A mixture of the 1-(2,5-dichloro-thiophen-3-yl)-ethanone (10 g, 51.26 mmol) and 9.5% NaOCl (150 mL, 230 mmol, 4.5 eq., commercial bleach) was treated with 5N NaOH (1 mL, 5 mmol, 0.1 eq.). The mixture was stirred vigorously and heated to 55 °C. The internal temperature was monitored closely and heat was removed to control the exotherm. After 6 h at 61°C, starting material was completely consumed. The mixture was cooled to 0°C and carefully quenched with 20 % aq. $NaHSO_3$ solution(20 mL). At 0°C, 6M HCl (12 mL) was added to adjust the pH to 1.5. The mixture was extracted with EtOAc (300 mL and 3 x 50 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), and concentrated to a white solid (8.8 g).

Step B: 3-(2-{[(2,5-dichloro-thiophene-3-carbonyl)-amino]-methyl}-4-hydroxy-phenyl)-propionic acid tert-butyl ester

A solution of the 2,5-dichloro-thiophene-3-carboxylic acid (12.9g, 65.5 mmol) and 4-methylmorpholine (7.17 mL, 65.2 mmol) in dry THF (400 mL) was cooled to -15°C. Isobutyl chloroformate (8.46 mL, 65.2 mmol) was added. The mixture was stirred 3 min and triethylamine (9.1 mL, 65 mmol) was added. A solution of 3-(2-aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester (16.4 g, 65.3 mmol) in DMF (130 mL) pre-cooled to -15°C was added via cannula over 15 min. After stirring 1 h, TLC indicated complete reaction. The reaction mixture was allowed to warm to ambient temperature. Solids were removed by filtration and washed with THF (100 mL). The filtrate was diluted with Et_2O (500 mL) and washed with water (250 mL) then brine (150 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude brown oil was purified by silica gel chromatography (hexanes/EtOAc 2/1) and recrystallization (toluene) to afford the title compound as a white crystalline solid (22.3 g, 79.6%). MS (ES^+) m/z 430.1 $[M+H]^+$.

Preparation 20

3-(4-Hydroxy-2-{[(pyrazine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid tert-butyl ester

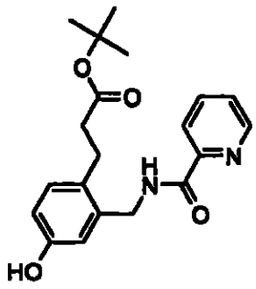


To a solution of pyrazine-2-carboxylic acid (0.570 g, 4.60 mmol) in CH_2Cl_2 (50 mL) was added EDC (0.960 g, 5.01 mmol) and HOBt (0.620 g, 4.60 mmol) at room temperature. The mixture was stirred for 10 min, and 3-(2-aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester (1.05 g, 4.18 mmol) was added. The reaction mixture was stirred for 18 h at room temperature, treated with water (50 mL), and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by silica gel chromatography (EtOAc/hexanes, 1:1

to 1:0) to obtain the title compound (1.05 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.52 (t, 2 H, J = 7.6 Hz), 2.91 (t, 2H, J = 7.6 Hz), 4.66 (d, 2H, J = 6.4 Hz), 6.73 (dd, 1H, J = 2.9, 7.8 Hz), 6.83 (d, 1H, J = 2.4 Hz), 7.07 (d, 1H, J = 8.3 Hz), 8.17 (br s, 1H), 8.49 (dd, 1H, J = 1.5, 2.4 Hz), 8.73 (d, 1H, J = 2.4 Hz), 9.41 (d, 1H, J = 1.5 Hz). MS (ES) m/z 356.1 ([M-H]$^-$).

The following intermediate compounds are prepared by a substantially similar manner as described in Preparation 20.

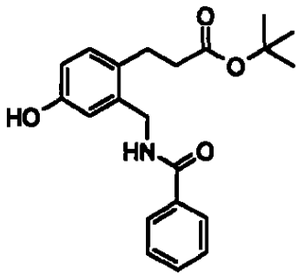
3-(4-Hydroxy-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid tert-butyl ester



^{1}H-NMR($CDCl_3$): 1.40 (s, 9H), 2.51 (t, J=7.6 Hz, 2H), 2.91 (t, J=7.6 Hz, 2H), 4.64 (d, J=5.9 Hz, 2H), 6.72 (d, J=7.8 Hz, 1H), 6.85 (s, 1H), 7.06 (d, J=8.2 Hz, 1H), 7.41 (t, J=7.6 Hz, 1H), 7.84 (t, J=7.0 Hz, 1H), 8.20 (d, J=7.4 Hz, 1H), 8.38 (br s, 1H), 8.50 (d, J=3.5 Hz, 1 H); MS (ES) m/z 348 (M+H).

Preparation 21

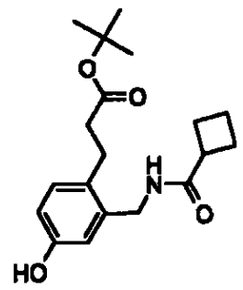
3-[2-(benzoylamino-methyl)-4-hydroxy-phenyl]propionic acid *tert*-butyl ester



A slurry of 3-(2-aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester (0.36 g, 1.43 mmol) in CH_2Cl_2 (10 mL) was cooled in an ice-water bath and treated with triethyl amine (0.40 mL, 0.28 mmol) then dropwise with benzoyl chloride (0.18 mL, 1.55 mmol). The resulting solution was stirred 30 min, and the cooling bath was removed. After 30 min, the solution was concentrated, and the residue was partitioned between EtOAc (50 mL) and 1N HCl (10 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), and concentrated to a solid. The crude mixture was purified by radial chromatography (hexanes:EtOAc 3:1 to 2:1) to give the title compound as a white solid (325 mg, 64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.26 (s, 9H), 2.54 (t, J= 7.1 Hz, 2H), 2.81 (t, J= 6.8 Hz, 2H), 4.55 (d, J= 2H), 6.68 (dd, J= 8.3, 2.4 Hz, 1H), 6.86 (d, J= 2.9 Hz, 1H), 6.96 (d, J= 8.3 Hz, 1H), 7.25-7.29 (m, 2H), 7.34-7.37 (m, 1H), 7.49 (br s, 1H), 7.16-7.79 (m, 2H); MS (ES) m/z 356.2 (M+H).

The following intermediate compound is prepared by a substantially similar manner as described in Preparation 21.

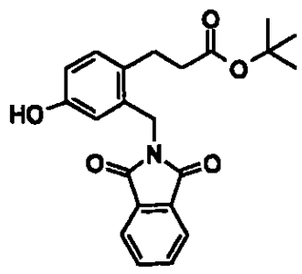
3-{2-[(Cyclobutanecarbonyl-amino)-methyl]-4-hydroxy-phenyl}-propionic acid tert-butyl ester



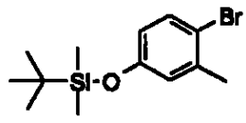
MS (ESI) m/z 334.2 $(M+H)^+$.

Preparation 22

3-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxy-phenyl]-propionic acid tert-butyl ester



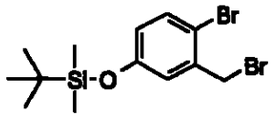
Step A: (4-Bromo-3-methyl-phenoxy)-tert-butyl-dimethyl-silane



A 12 L flask was charged with 4-bromo-3-methyl phenol (428 g, 2.29 mol), CH_2Cl_2 (7.5 L), triethylamine (480 mL, 3.45 mol), and tert-butyldimethylsilyl chloride (324 g, 2.15 mol). To the solution was added 4-dimethylaminopyridine (15.0 g, 0.123 mol). The reaction mixture was stirred at ambient temperature overnight. The reaction was washed with saturated ammonium chloride (2.2 L) and then DI water (0.9

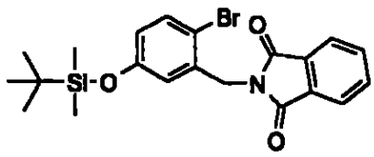
L). The organic layer was dried (Na_2SO_4), filtered, and concentrated to crude product (699 g). This material was purified by silica gel chromatography (heptane) to give the title compound (637 g, 98.5%).

Step B: (4-Bromo-3-bromomethyl-phenoxy)-tert-butyl-dimethyl-silane



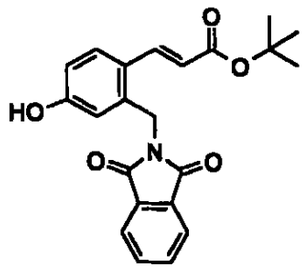
(4-Bromo-3-methyl-phenoxy)-tert-butyl-dimethyl-silane (255 g, 0.846 mol), dichloroethane (2.5 L), N-bromosuccinimide (165 g, 0.927 mol) and 2,2'-azobisisobutyronitrile (19.0 g, 0.116 mol) were combined in a 5 L flask. The mixture was degassed by evacuating and purging with N_2 (5x). The reaction mixture was heated to 47°C, and the heat was shut off. An exotherm to 76°C occurred. GC analysis showed 6.5% unreacted starting material. The heat was applied again, and the reaction was held at reflux (83°C) for 15 min. After cooling to 8°C, heptane (1.0 L) was added. The resulting slurry was stirred at 4 °C for 30 min and filtered. The filtrate was evaporated to dryness. The residue was treated with heptane (1 L), placed in the freezer overnight, and filtered. The filtrate was concentrated to the title compound (326 g, 101%).

Step C: 2-[2-Bromo-5-(tert-butyl-dimethyl-silanyloxy)-benzyl]-isoindole-1,3-dione



A 12 L flask was charged with (4-bromo-3-bromomethyl-phenoxy)-tert-butyl-dimethyl-silane (568 g 1.49 mol), DMF (3.1 L), and potassium phthalimide (316 g 1.71 mol). An exotherm to 34 °C occurred. After 40 min, the reaction mixture was cooled to 18°C. Ether (6.2 L) and DI water (4.9 L) were added, and the layers were separated. The organic layer was washed with saturated NaCl solution (2 L), dried (Na_2SO_4), filtered, and concentrated. The residue was recrystallized from heptane (1.5 L) to give the title compound (454 g, 68%).

Step D: 3-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxy-phenyl]-acrylic acid tert-butyl ester



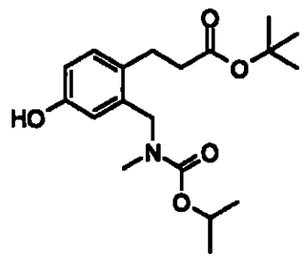
A 12 L flask was charged with 2-[2-bromo-5-(tert-butyl-dimethyl-silanyloxy)-benzyl]-isoindole-1,3-dione (461 g, 1.03 mol), propionitrile (7 L), tri-*ortho*-tolyl phosphine (76.0 g, 0.250 mol) and diisopropyl ethyl amine (365 mL, 2.10 mol). The reaction mixture was degassed/purged with N_2 (3x), and tert-butyl acrylate (465 mL, 3.17 mol) was added. After degassing/purging one time, palladium (II) acetate (28.0 g, 0.125 mol) was added. The stirred mixture was degassed/purged with N_2 three times and heated to 95°C for 20 h. The mixture was filtered through a hyflo cake, washed with acetonitrile, and concentrated to a brown oil (841 g). The residue was dissolved in THF (3.5 L), and tetrabutylammonium fluoride (TBAF, 650 mL, 0.65 mol, 1M in THF) was added. After 1 h, additional TBAF (95 mL) was added. The mixture was rotated on the rotary evaporator for 10 min and was concentrated to crude product (987 g). This material was purified by silica gel chromatography (toluene/ethyl acetate, 100/0 to 75/25) to give the title compound (340 g, 86.8%).

Step E: 3-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxy-phenyl]-propionic acid tert-butyl ester

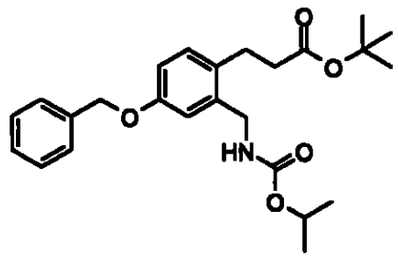
A 1 gallon autoclave was charged with 3-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxy-phenyl]-acrylic acid tert-butyl ester (196 g, 0.517 mol), ethyl acetate (2.6 L) and 5 % palladium on carbon (75 g). The autoclave was kept at 25°C under 60 psi of hydrogen for 21 h. The temperature of the reaction was increased to 40 °C, and the pressure was increased to 75 psi for 5 h. The mixture was filtered through a pad of hyflo and concentrated to the title compound (186 g, 94.4 %): MS (ESI) m/z 380.2 $(M-H)^-$.

Preparation 23

3-{4-Hydroxy-2-[(isopropoxycarbonyl-methyl-amino)-methyl]-phenyl}-propionic acid tert-butyl ester



Step A: 3-[5-Benzyloxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester



To a solution of 3-[5-hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (14.8 mmol) in DMF (100 mL) was added Cs_2CO_3 (29.6 mmol) and benzyl bromide (16.3 mmol). The reaction mixture was stirred overnight at ambient temperature and diluted with EtOAc (200 mL). The mixture was washed with brine (100 mL) and water (100 mL). The organic layer was dried (Na_2SO_4) and concentrated to a yellow oil (6.8 g). MS [ES] m/z 428 $(M+H)^+$.

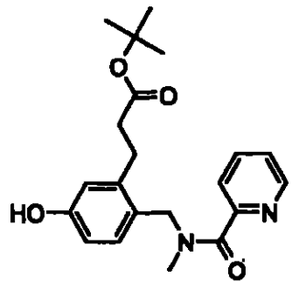
Step B: 3-{5-Hydroxy-2-[(isopropoxycarbonyl-methyl-amino)-methyl]-phenyl}-propionic acid tert-butyl ester

To a solution of 3-[5-benzyloxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (6.3 g, 0.015mol) in DMF (100 mL) was added NaH (29.4 mmol, 60% oil dispersion). The reaction mixture was stirred at 0°C for 15 min, treated with methyl iodide (4.18 g, 29.4 mmol), and stirred overnight under N_2 at ambient temperature. The mixture was concentrated and triturated with hexanes (200 mL). The residue was diluted with EtOAc (200 mL), and the solution was washed with

water (200 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated to a yellow oil (5.2 g). The material was dissolved in EtOAc (100 mL), and 5% Pd/C (0.725 g) was added. The reaction mixture was shaken under a hydrogen atmosphere in a Parr apparatus at 60psi overnight at 40°C. The mixture was filtered and concentrated to give the title compound (2.1 g). MS [ES] m/z 352 $(M+H)^+$.

The following intermediate compound is prepared by a substantially similar manner as described in Preparation 23.

3-(5-Hydroxy-2-{[methyl-(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid tert-butyl ester



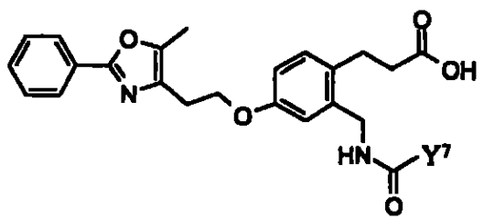
MS [ES] m/z 371 $(M+H)^+$.

The following General Procedures are used to prepare the compounds of present invention as illustrated below.

General Procedures I and II

General Procedure I

General Procedure for the Parallel Synthesis of Carboxamides from Carboxylic Acids

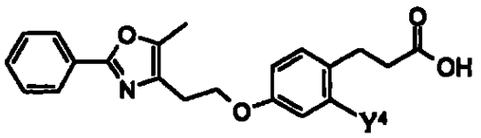


3-{2-Aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester: acetic acid salt (704 mg, 1.4 mmol) was

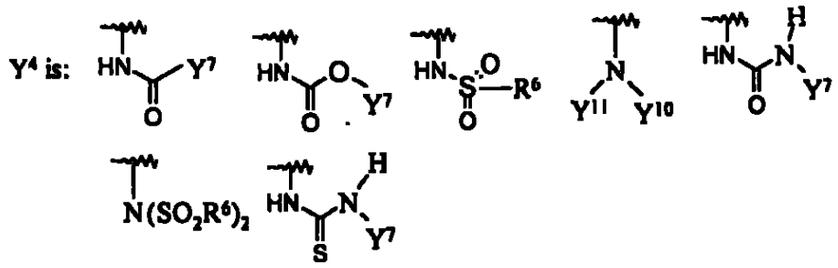
dissolved in CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ solution (15 mL). The organic layer was dried ($NaSO_4$), filtered, and concentrated to 3-{2-aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester (636 mg, 1.4 mmol). This amine (0.1 mmol, 0.1 M in CH_2Cl_2) was added to a carboxylic acid (1.4 eq) in a 1 dram vial. N-Hydroxybenzotriazole hydrate (1.4eq, 0.17 M in CH_2Cl_2/DMF 10/1; HOBt) and EDC (1.4 eq, 0.18 M CH_2Cl_2) were added, and the vials were capped and shaken for 18 h. DMF (0.5 mL) and triethylamine (0.5 mL) were added and the vials were shaken for 72 h. Brine (1 mL) was added, and the mixtures were transferred to a ChemElute cartridge and eluted with CH_2Cl_2. The solvent was removed under a stream of N_2. The residue was treated with a mixture of CH_2Cl_2/TFA/water 60/35/5 (1 mL), agitated briefly, and allowed to stand at ambient temperature for 2 h. The solvent was removed under a stream of N_2. The residue was treated with 10% CCl_4/CH_2Cl_2 (1 mL) and concentrated under a stream of N_2 (2x). The crude products were dried under vacuum and purified by mass-directed HPLC.

General Procedure II

General Procedure for the Parallel Synthesis of Carboxamides, Carbamates, Sulfonamides, Ureas, and Thioureas from Carboxylic Acid Chlorides, Chloroformates, Sulfonyl Chlorides, Isocyanates, and Isothiocyanates



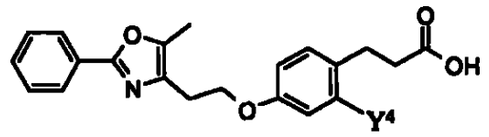
Y^4 is:



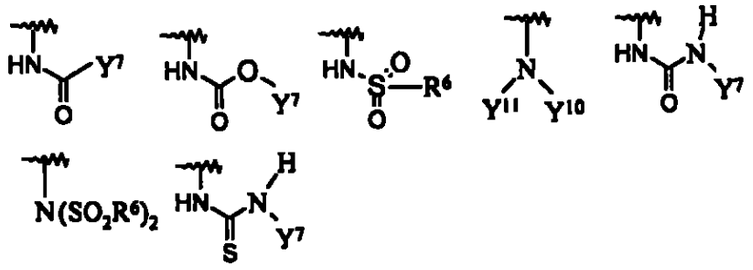
3-{2-Aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester: acetic acid salt (720 mg, 1.4 mmol) was dissolved in CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ solution (15 mL). The organic layer was dried ($NaSO_4$), filtered, and concentrated to 3-{2-aminomethyl-4-[2-(5-

methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester (586 mg, 92%). This amine (0.1 mmol, 0.1 M in CH_2Cl_2) and carboxylic acid chloride, chloroformate, sulfonyl chloride, isocyanate, or thioisocyanate (1 eq), and triethylamine (0.2 mL) were placed in a 1 dram vial. The vials were capped and shaken for 18 h. DMF (0.5 mL) was added to incomplete reaction mixtures, and the vials were shaken for 2 h. Brine (1 mL) was added, and the mixtures were transferred to a ChemElute cartridge and eluted with CH_2Cl_2. The solvent was removed under a stream of N_2. The residue was treated with a mixture of CH_2Cl_2/TFA/water 60/35/5 (1 mL), agitated briefly, and allowed to stand at ambient temperature for 2 h. The solvent was removed under a stream of N_2. The residue was treated with 10% CCl_4/CH_2Cl_2 (1 mL) and concentrated under a stream of N_2 (2x). The crude products were dried under vacuum and purified by mass-directed HPLC.

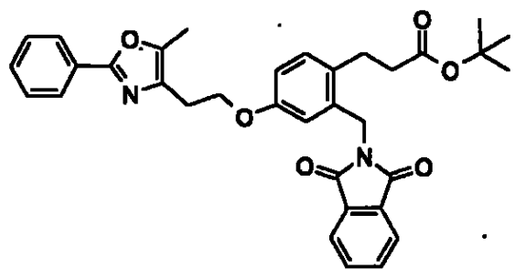
Example 1



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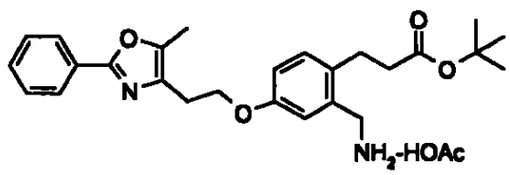


Step A: 3-{2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester



A 2 L 3-neck flask was charged with 3-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxy-phenyl]-propionic acid tert-butyl ester (67.9 g, 0.178mol), toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl ester (76.6 g, 0.214 mol) and DMF (680 mL). Cesium carbonate (75.4 g, 0.231 mol) was added, and the reaction mixture was heated at 55 °C for 18 h. After cooling, ethyl acetate (890 mL) and DI water (1200 mL) were added, the mixture was agitated, and the layers were separated. The aqueous layer was back-extracted with ethyl acetate (740 mL). The organic layers were combined and washed with 1N NaOH (375 mL) then saturated NaCl solution (2 x 375 mL). The organic solution was dried (Na_2SO_4), filtered, and concentrated to an oil (107 g). The crude oil was dissolved in toluene (50 mL), and heptane was added (~100 mL) until cloudiness remained even with agitation. The mixture was warmed to 50 °C on a rotary evaporator to yield a solution. Seed crystals were added, and rotation was continued at ambient temperature overnight. The product slurry was placed in the freezer overnight and filtered. The title compound was dried in a vacuum oven at 35 °C (71.4 g, 70.8 %).

Step B: 3-{2-Aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester: acetic acid salt

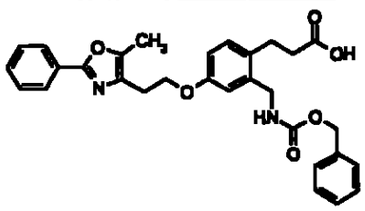
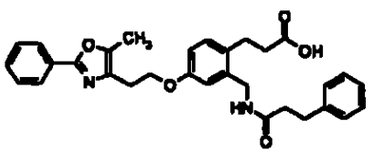
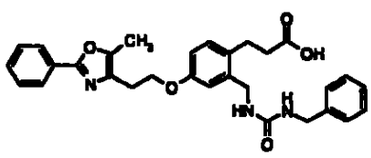


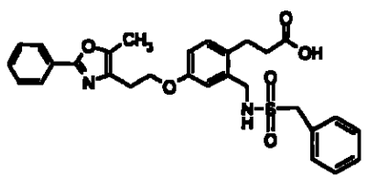
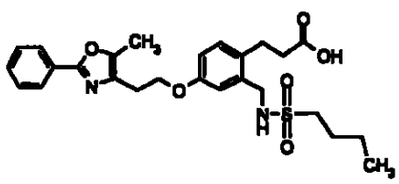
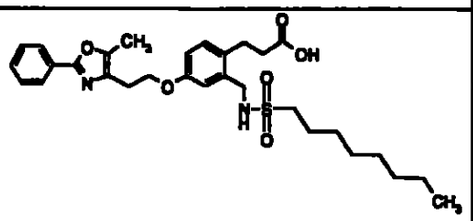
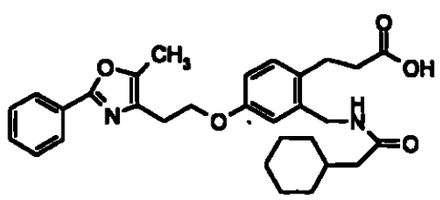
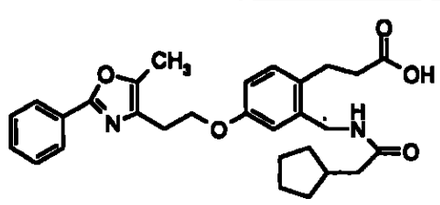
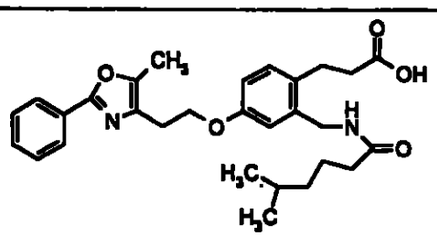
A 3 L 3-neck flask was charged with 3-{2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester (71.0 g, 0.125 mol) and isopropanol (IPA, 1.35 L). After warming to 40 °C and adding IPA (250 mL), a solution was still not obtained. After cooling to <30 °C, sodium borohydride (25.6 g, 0.677 mol) was added carefully in portions. Tap water was added to the bath, and the reaction was allowed to stir overnight. A spatula was used to break up the solids in the thick slurry, and IPA (200 mL) was added. Glacial acetic acid (130 mL, 2.27 mol) was added dropwise over 2 h. The reaction mixture was heated at reflux for 10 h, allowed to cool over the weekend, and concentrated to crude product (237 g). CH_2Cl_2 (100 mL) was added to give a thick gel which was poured onto a column

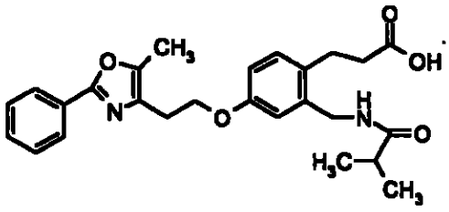
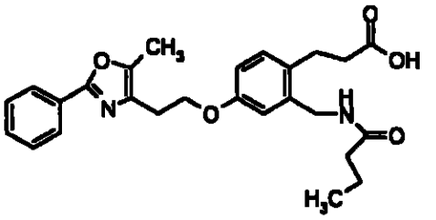
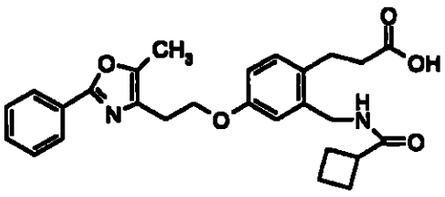
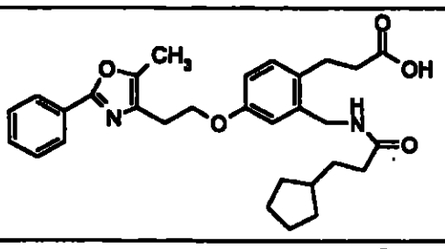
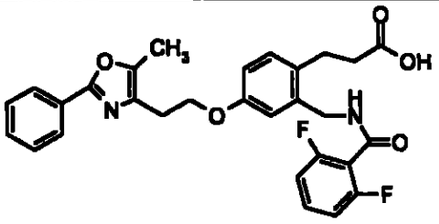
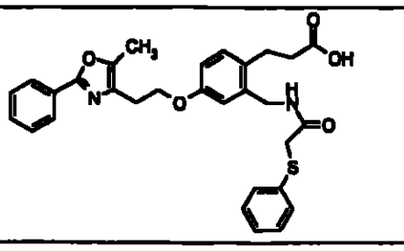
of silica gel 60 equilibrated with CH_2Cl_2. Methanol was used to help dissolve the crude material. Eluting with CH_2Cl_2/MeOH (1/1) gave the product mixture (182 g). Ethyl acetate (200 mL) was added, and a precipitate formed. The mixture was heated to 40 °C, and the solution was cooled to 0 °C. The pure product was filtered, washed with heptane/EtOAc (1:1, 2 x 100 mL), and dried to yield a white fluffy solid (35.4 g, 57%). The filtrate was concentrated (116 g) and purified again by silica gel chromatography (CH_2Cl_2/MeOH 100/0 to 80/20) to give additional product as an amber oil (13.9 g, 22%).

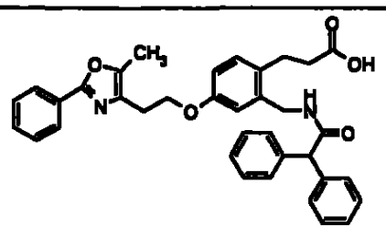
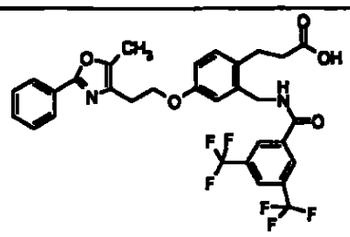
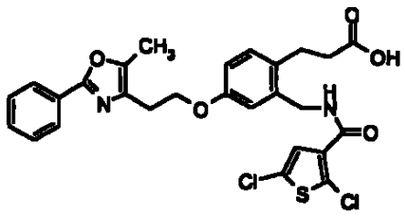
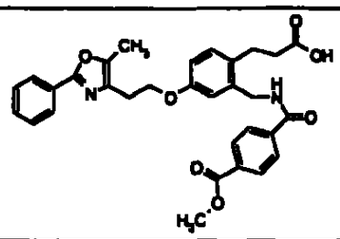
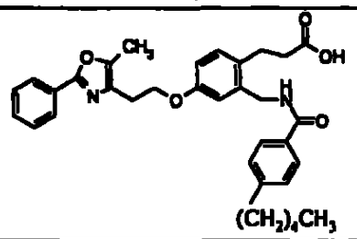
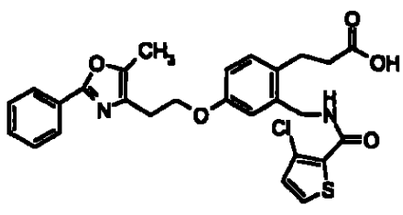
Examples 2- 230

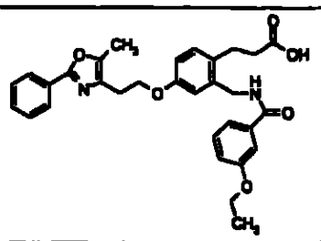
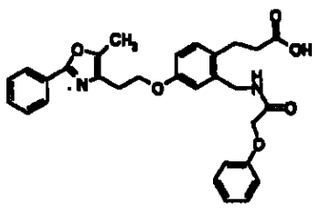
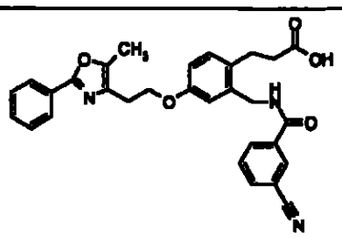
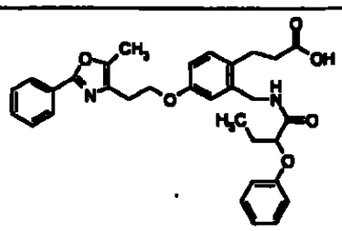
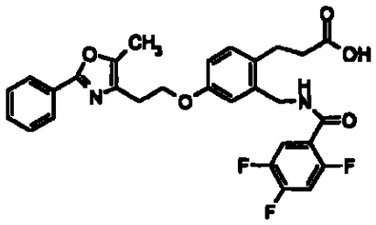
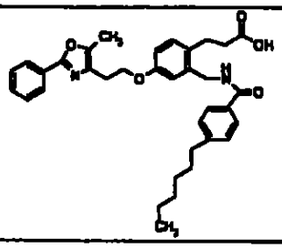
Examples 2-230 are prepared by following a substantially similar procedure as described in Example 1 and General Procedures I and II.

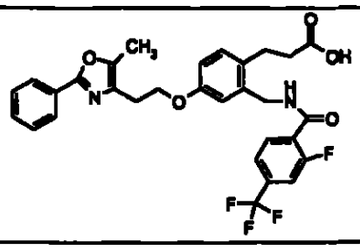
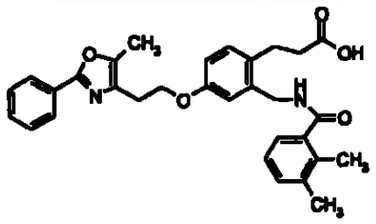
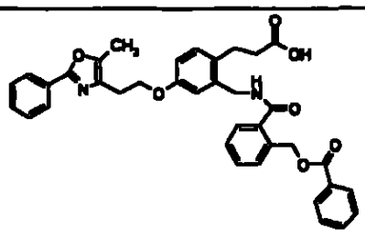
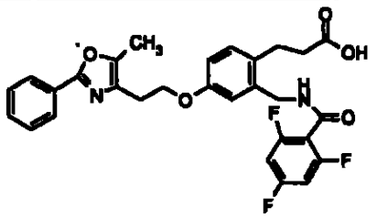
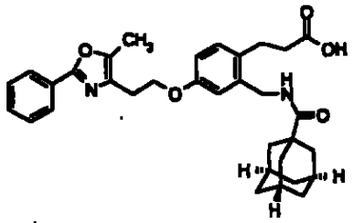
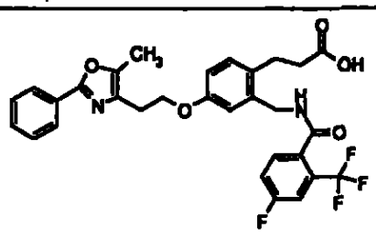
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3		513.5 FIA	I
4		514.4 FIA	II

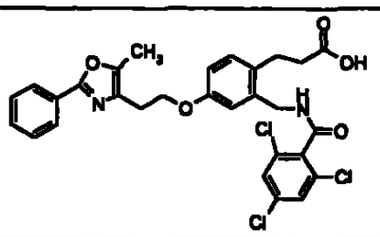
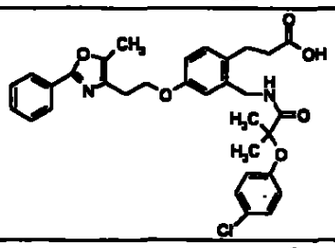
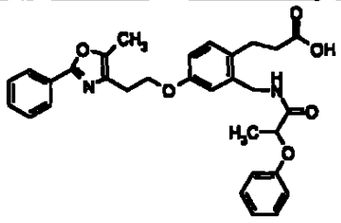
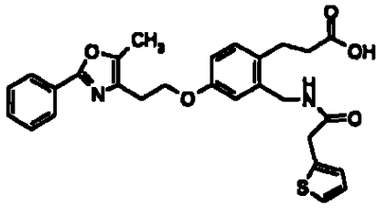
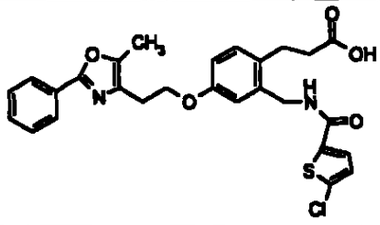
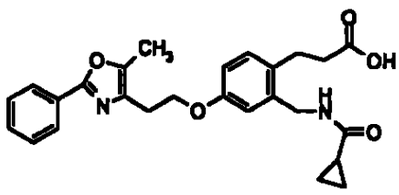
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7		557.1 FIA	II
8		505.3	II
9		491.3	I
10		493.3	I

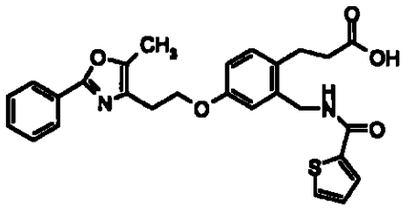
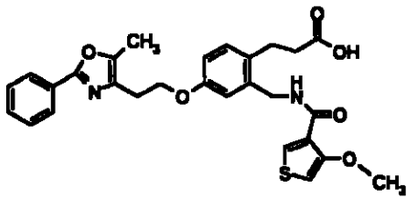
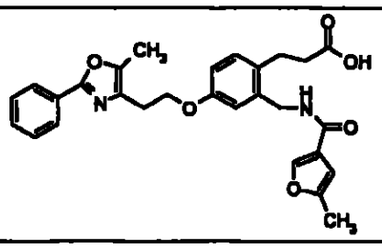
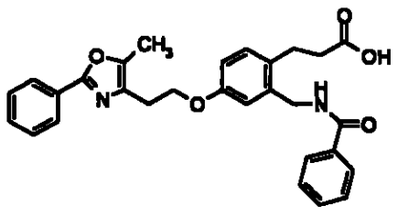
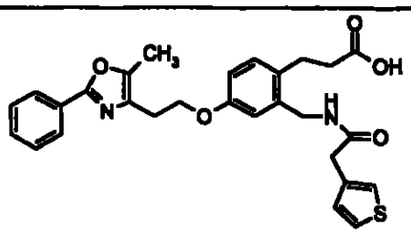
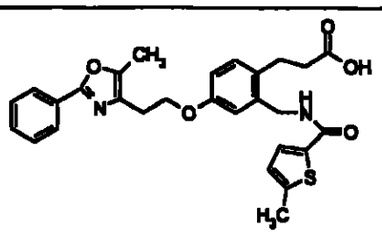
No	Compounds	MS (ES+)	General Procedur e
11		451.2	I
12		451.2	II
13		463.3	II
14		505.3	II
15		521.6	II
16		531.6	II

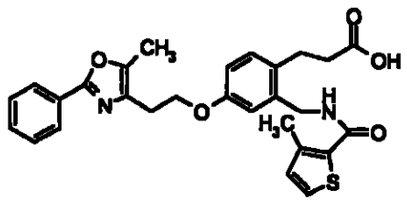
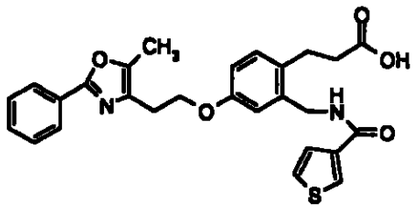
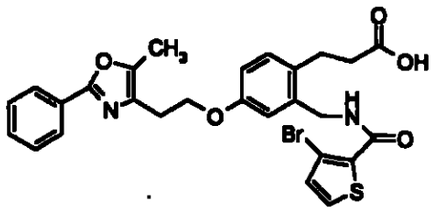
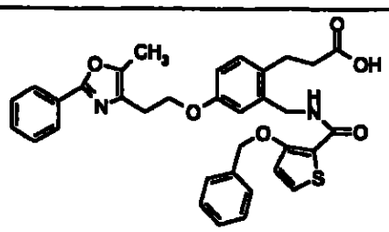
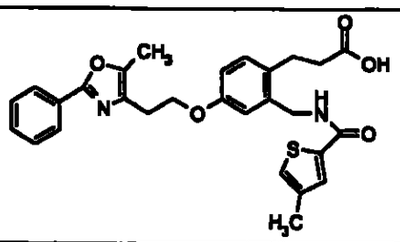
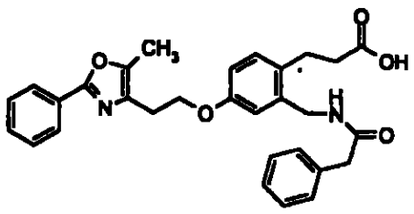
No	Compounds	MS (ES+)	General Procedur
17		575.7	II
18		621.6	II
19		559.8	II
20		543.7	II
21		555.4	II
22		525.2	II

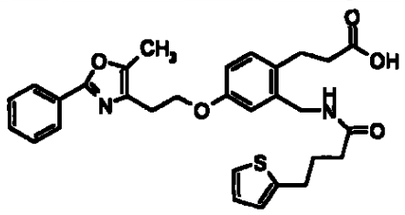
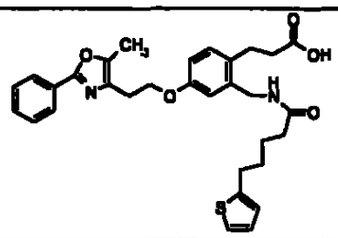
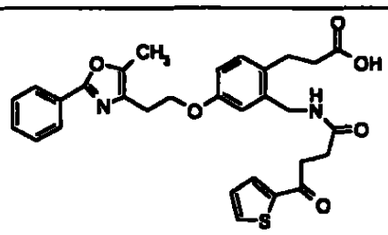
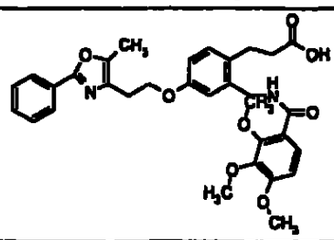
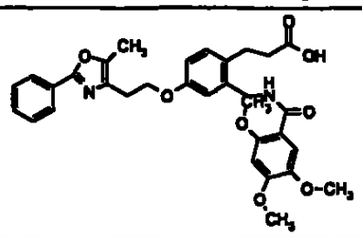
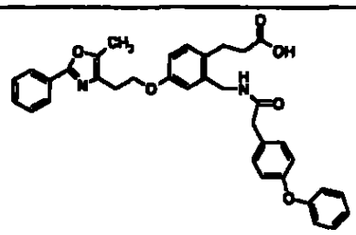
No	Compounds	MS (ES+)	General Procedur
23		529.3	II
24		515.3	II
25		510.6	II
26		543.7	II
27		539.3	II
28		569.4	II

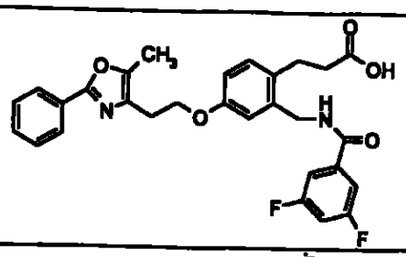
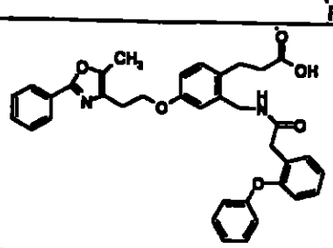
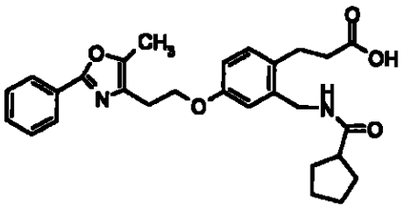
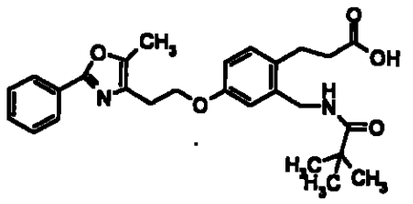
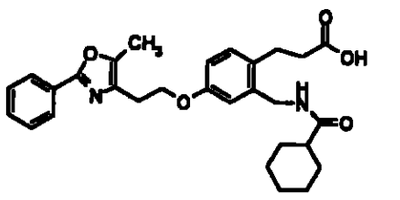
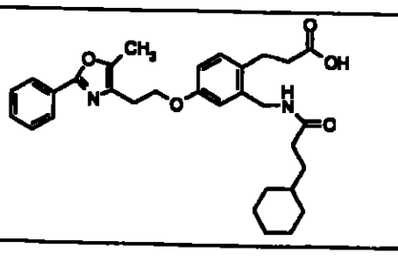
No	Compounds	MS (ES+)	General Procedur
29		571.3	II
30		513.4	II
31		619.4	II
32		539.3	II
33		543.4	II
34		571.3	II

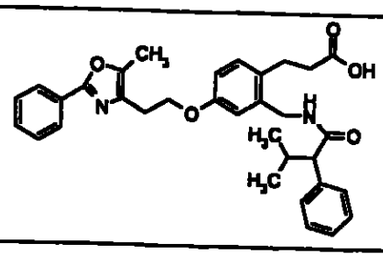
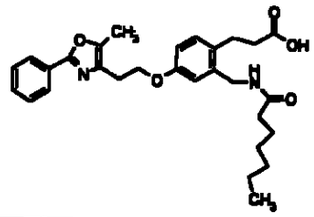
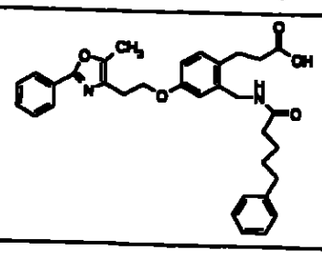
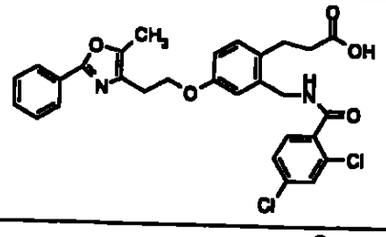
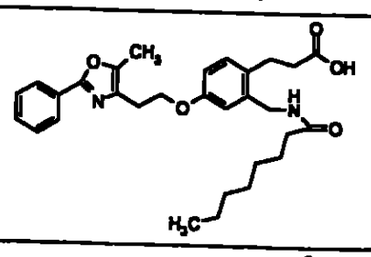
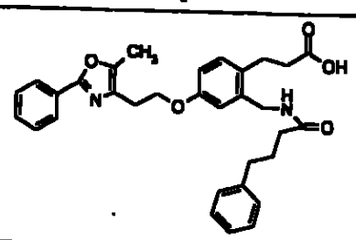
No	Compounds	MS (ES+)	General Procedur
35		589.2	II
36		577.3	II
37		529.7	I
38		505.3	I
39		525.2	I
40		549.3	I

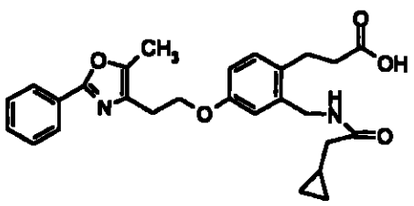
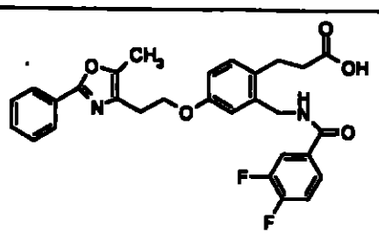
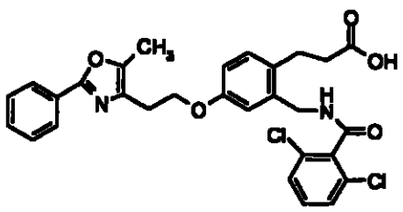
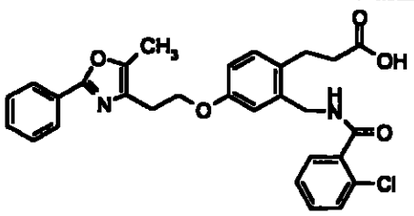
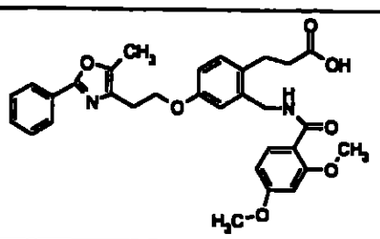
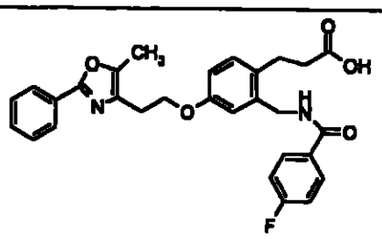
No	Compounds	MS (ES+)	General Procedur
41		491.3	I
42		521.3	I
43		489.3	I
44		485.3	I
45		505.3	I
46		505.3	I

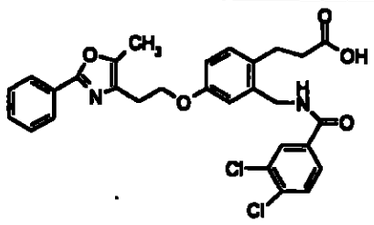
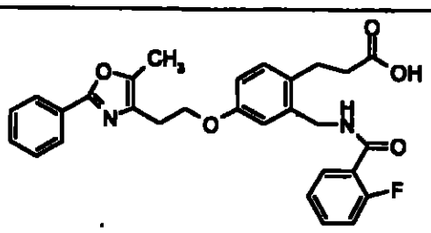
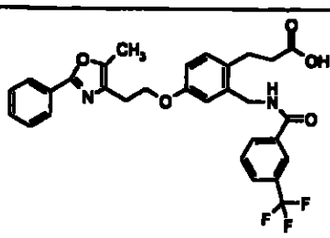
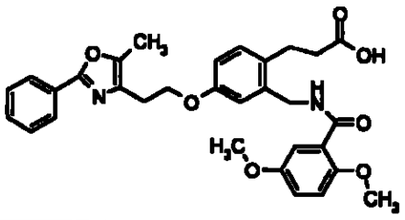
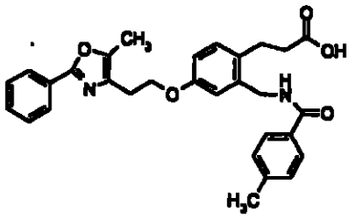
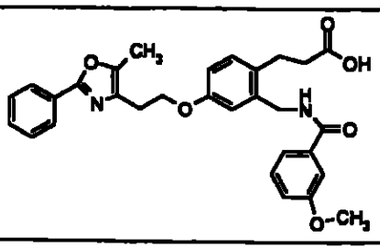
No	Compounds	MS (ES+)	General Procedur e
47		505.3	I
48		491.3	I
49		571.2	I
50		597.4	I
51		505.3	I
52		499.3	I

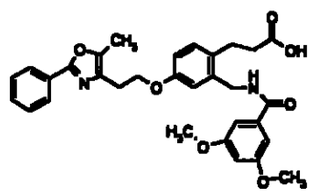
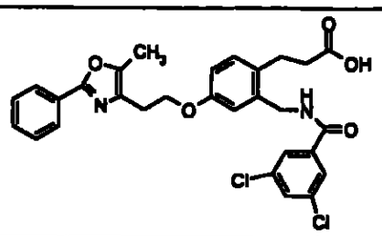
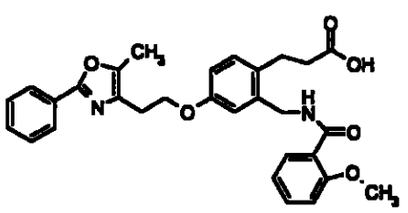
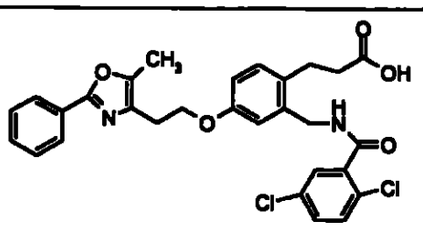
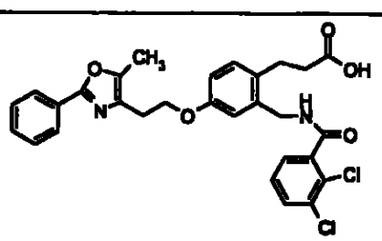
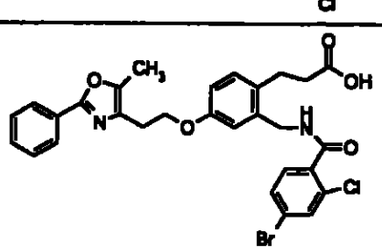
No	Compounds	MS (ES+)	General Procedur
53		533.3	I
54		547.3	I
55		547.3	I
56		575	I
57		575	I
58		591	I

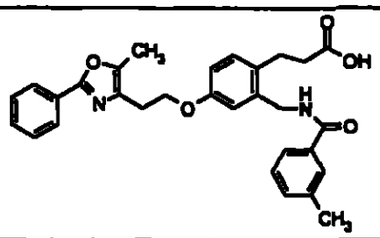
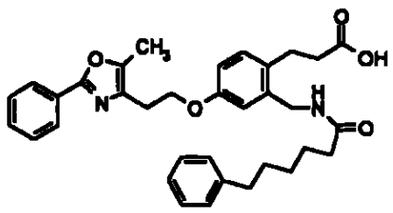
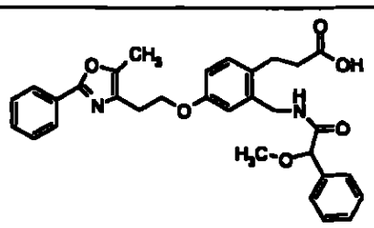
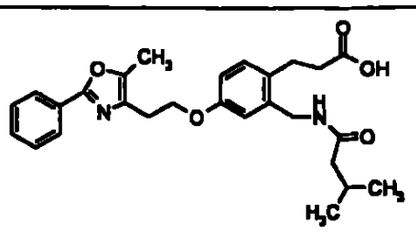
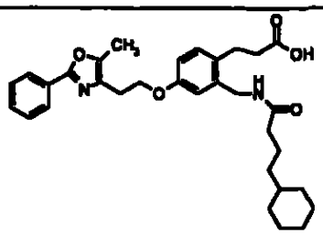
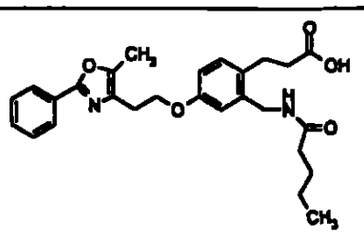
No	Compounds	MS (ES+)	General Procedur
59		521	I
60		591	I
61		477.2	I
62		465	I
63		491	I
64		519	I

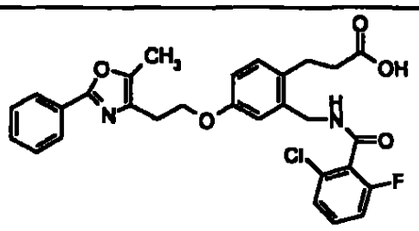
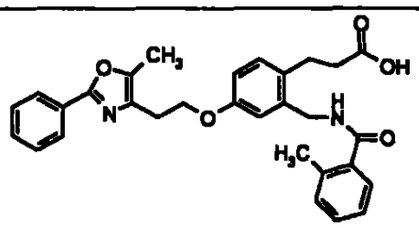
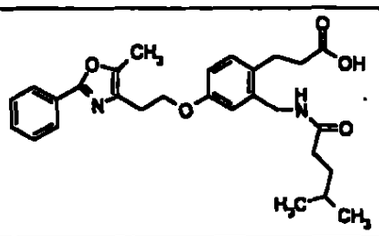
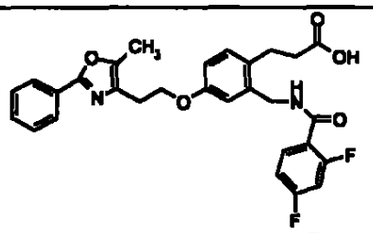
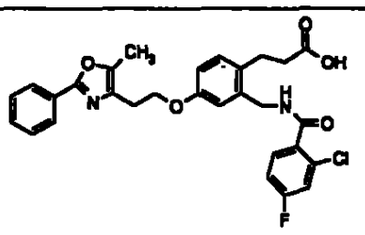
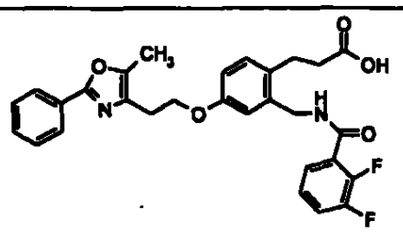
No	Compounds	MS (ES+)	General Procedur
65		541	I
66		493	I
67		541	I
68		554	I
69		507	I
70		527	I

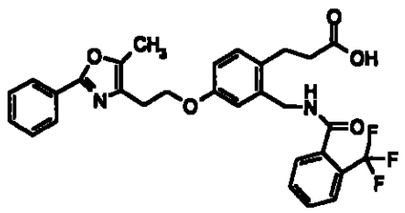
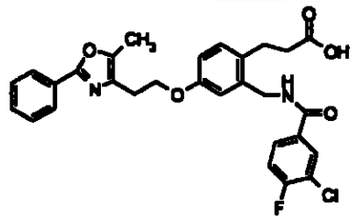
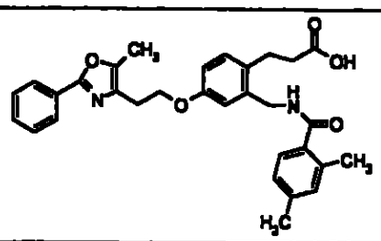
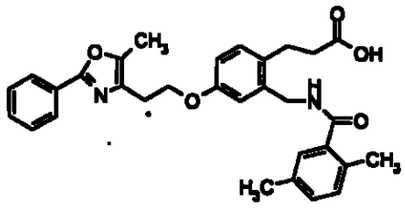
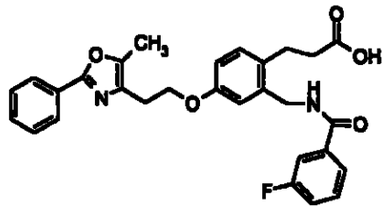
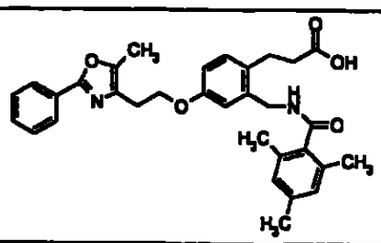
No	Compounds	MS (ES+)	General Procedur
71		463	I
72		521	I
73		554	I
74		520	I
75		545	I
76		503	I

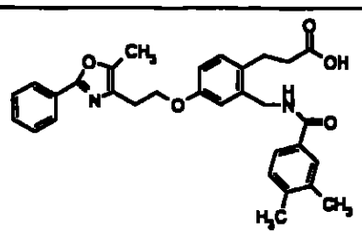
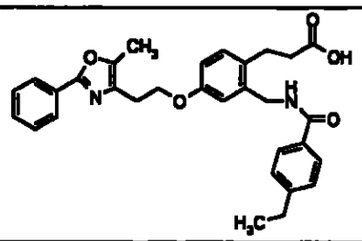
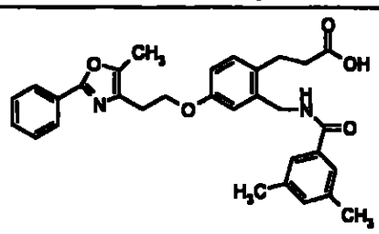
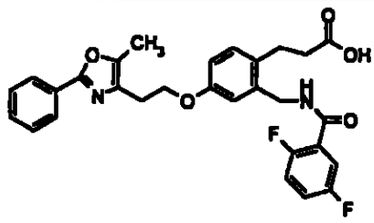
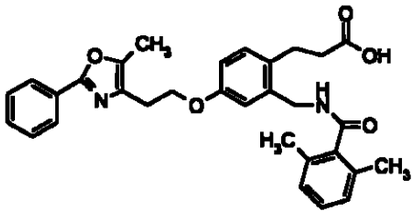
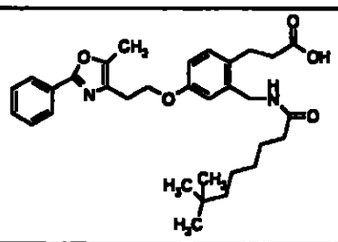
No	Compounds	MS (ES+)	General Procedur
77		554	I
78		503	I
79		553	I
80		545	I
81		499	I
82		515.2	I

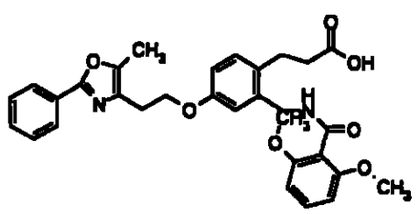
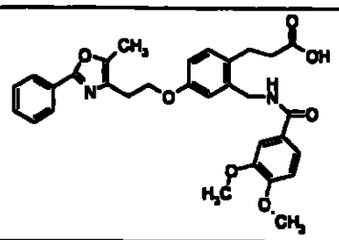
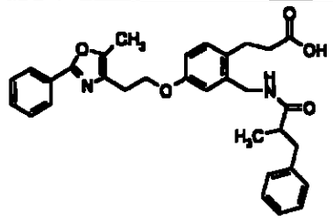
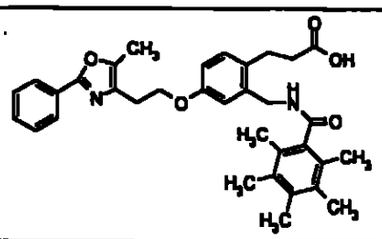
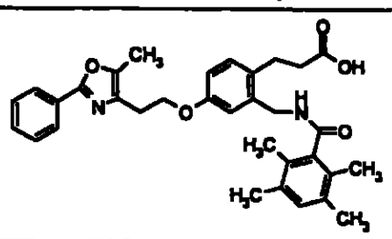
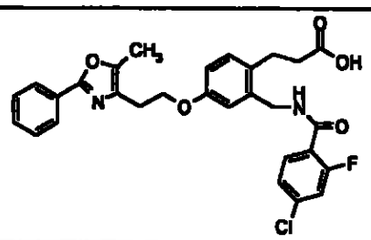
No	Compounds	MS (ES+)	General Procedur
83		545.3	I
84		554	I
85		515	I
86		554	I
87		554	I
88		598	I

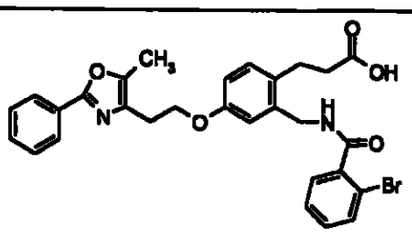
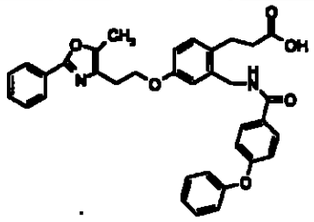
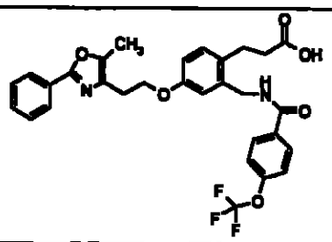
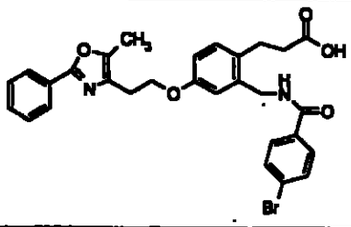
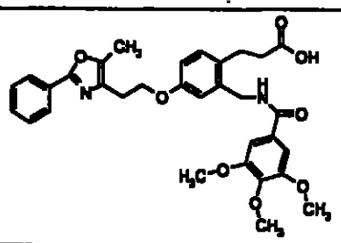
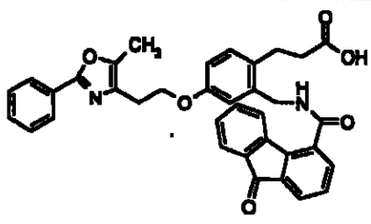
No	Compounds	MS (ES+)	General Procedur
89		499	I
90		555	I
91		529	I
92		465	I
93		533	I
94		465	I

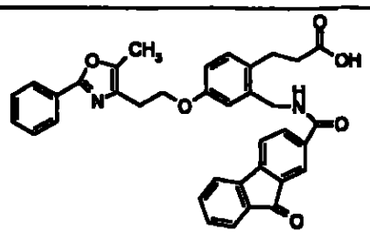
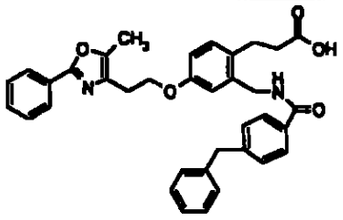
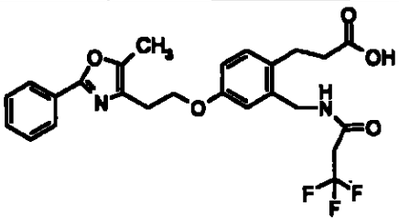
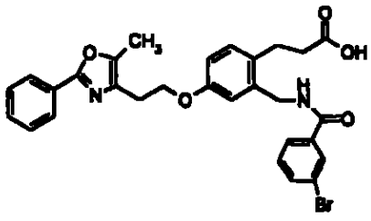
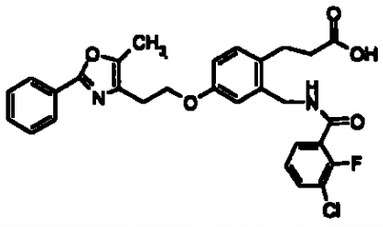
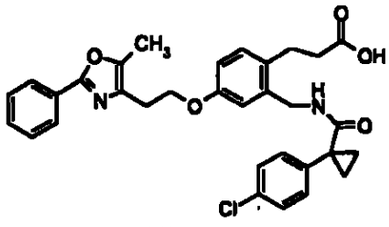
No	Compounds	MS (ES+)	General Procedur
95		538	I
96		499	I
97		479	I
98		521	I
99		538	I
100		521	I

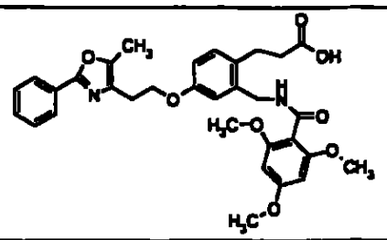
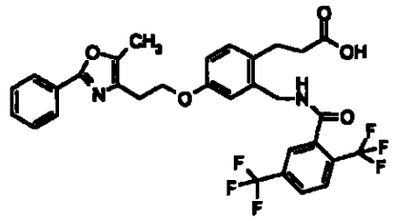
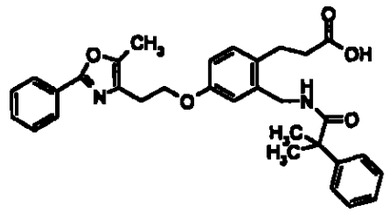
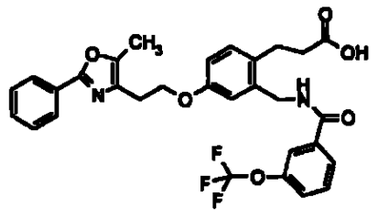
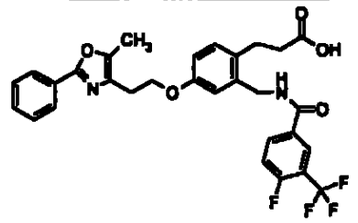
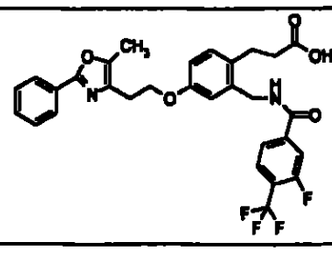
No	Compounds	MS (ES+)	General Procedur
101		553	I
102		538	I
103		513	I
104		513	I
105		503	I
106		527	I

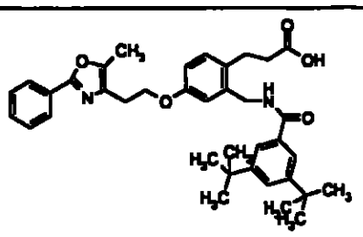
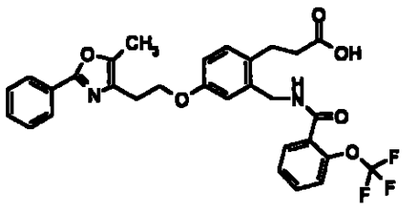
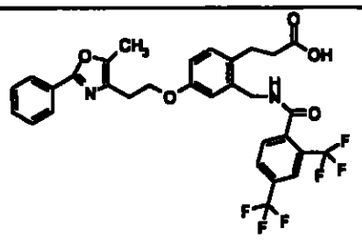
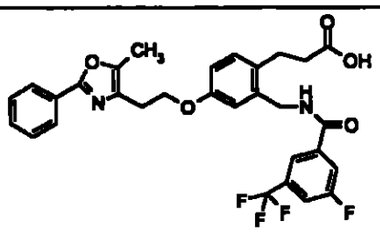
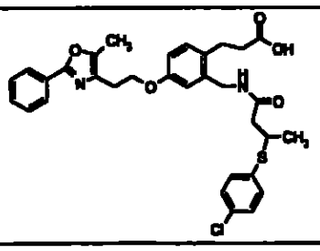
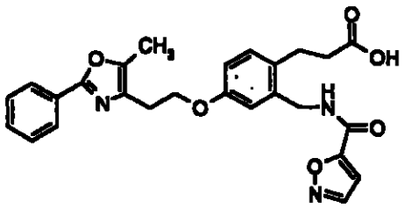
No	Compounds	MS (ES+)	General Procedur e
107		513	I
108		513	I
109		513	I
110		521	I
111		513	I
112		535	I

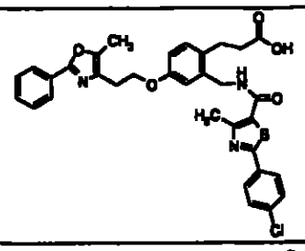
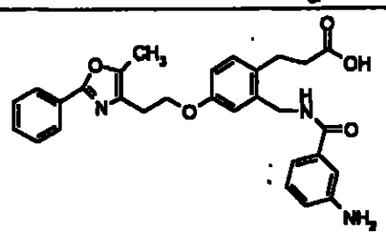
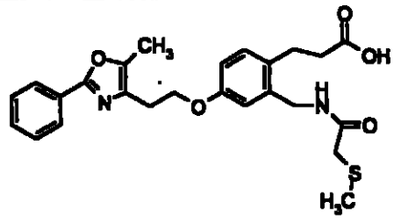
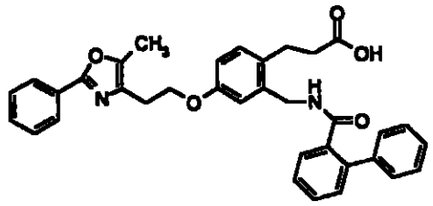
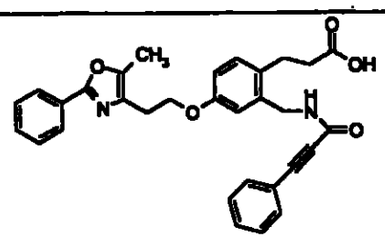
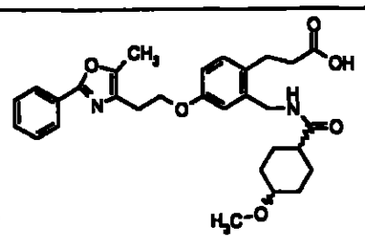
No	Compounds	MS (ES+)	General Procedur
113		545	I
114		545	I
115		527	I
116		555	I
117		541	I
118		538	I

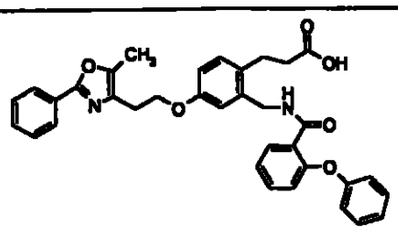
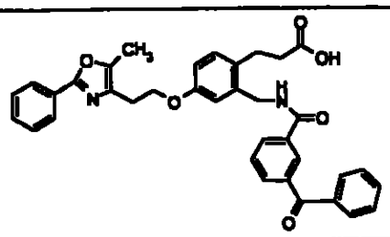
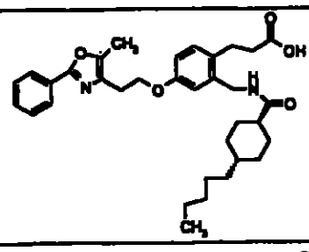
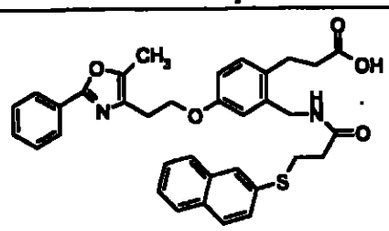
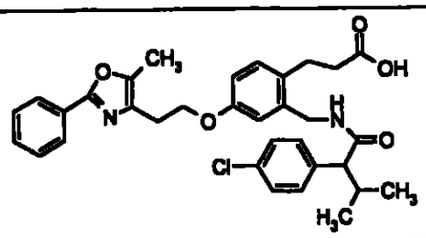
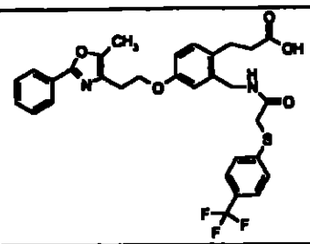
No	Compounds	MS (ES+)	General Procedur
119		564	I
120		577	I
121		569	I
122		564	I
123		575	I
124		587	I

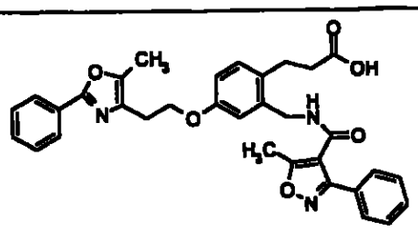
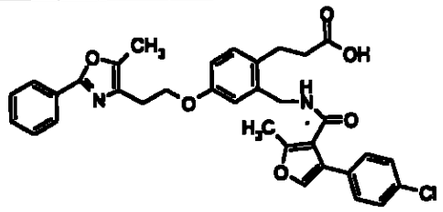
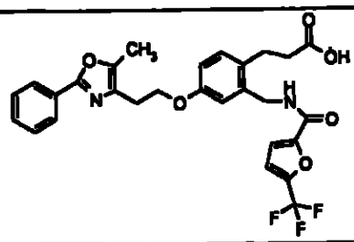
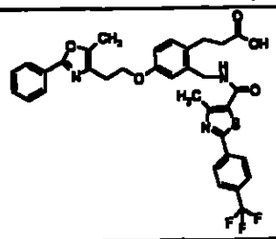
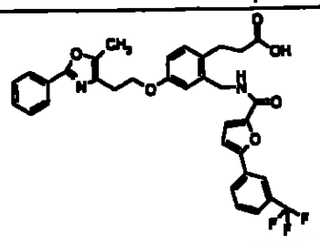
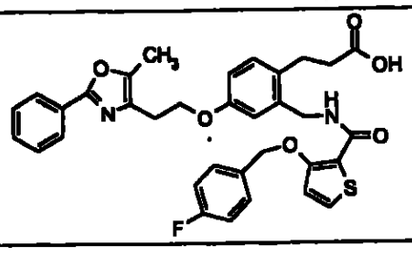
No	Compounds	MS (ES+)	General Procedur
125		587	I
126		575	I
127		491	I
128		564	I
129		538	I
130		560	I

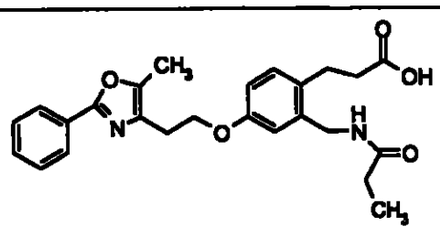
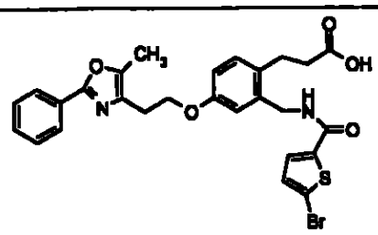
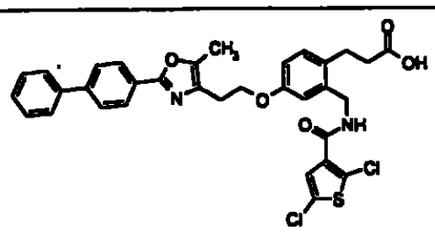
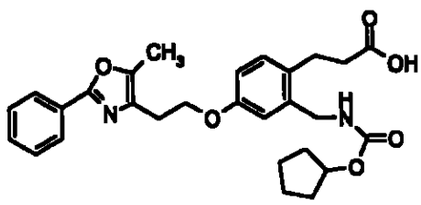
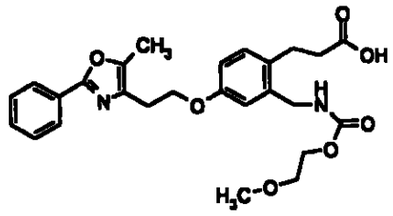
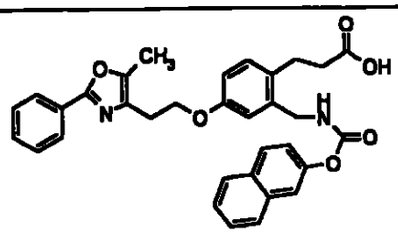
No	Compounds	MS (ES+)	General Procedur
131		575	I
132		621	I
133		527	I
134		569	I
135		571	I
136		571	I

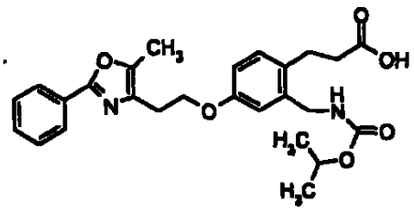
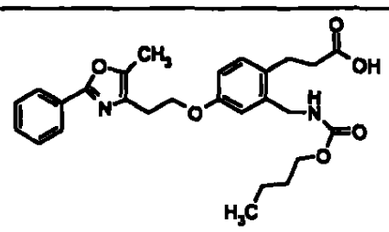
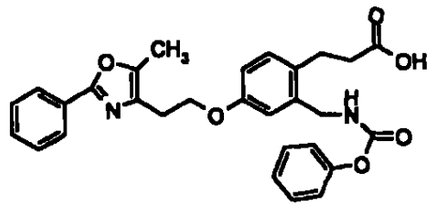
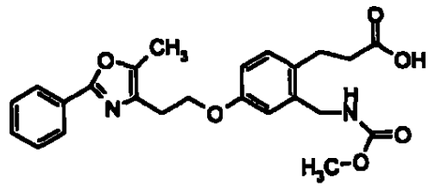
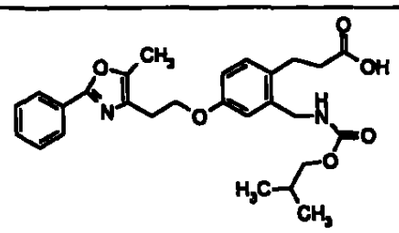
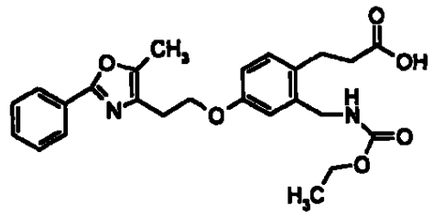
No	Compounds	MS (ES+)	General Procedur
137		597	I
138		569	I
139		621	I
140		571	I
141		594	I
142		476	I

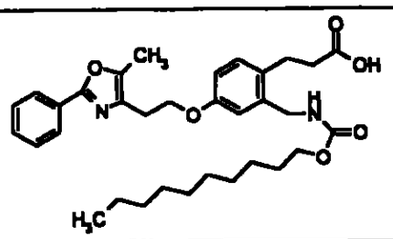
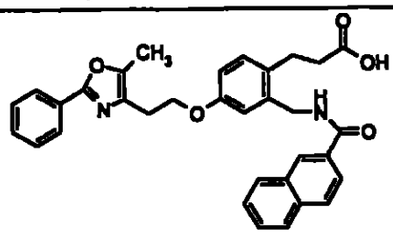
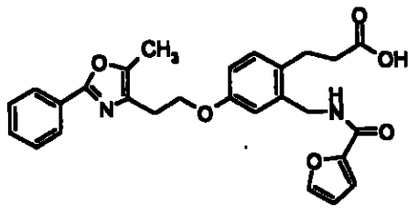
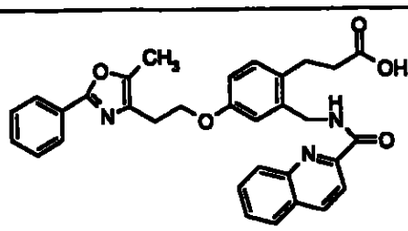
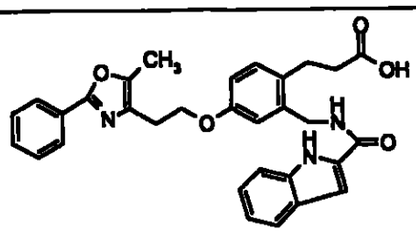
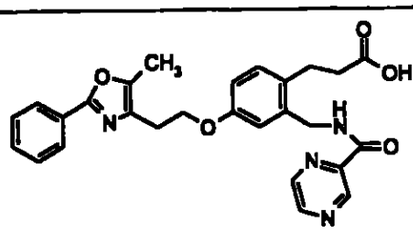
No	Compounds	MS (ES+)	General Procedur e
143		617	I
144		500	I
145		469	I
146		561	I
147		509	I
148		521	I

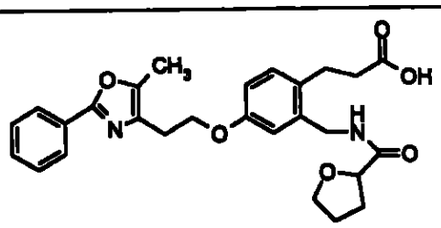
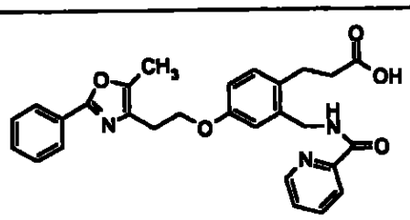
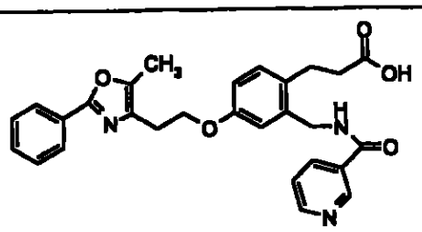
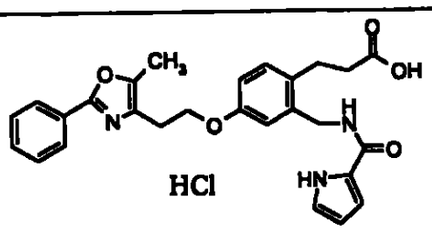
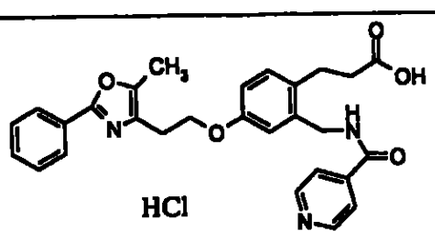
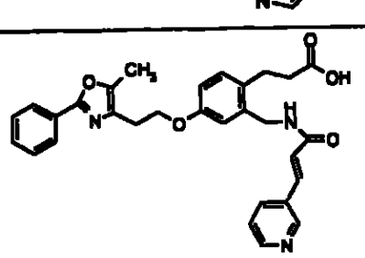
No	Compounds	MS (ES+)	General Procedur
149		577	I
150		589	I
151		561	I
152		595	I
153		575	I
154		599	I

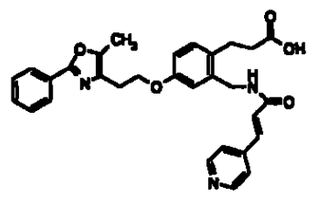
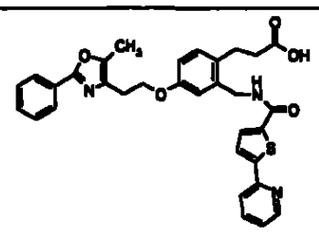
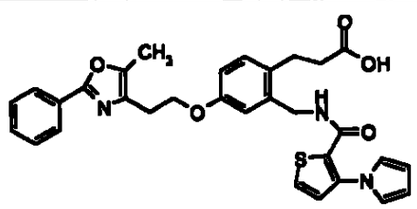
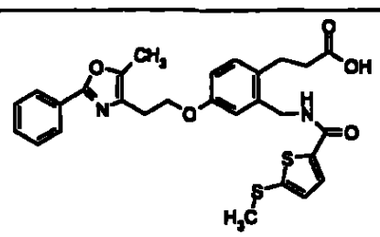
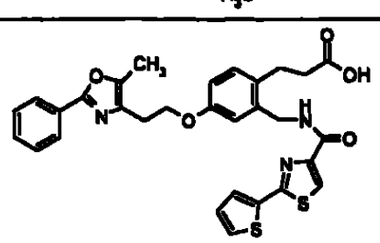
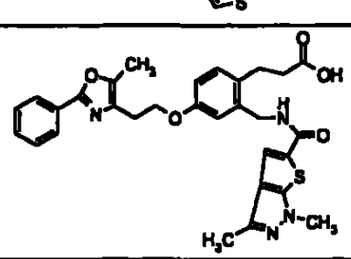
No	Compounds	MS (ES+)	General Procedur
155		566	I
156		599	I
157		543	I
158		650	I
159		619	I
160		615	I

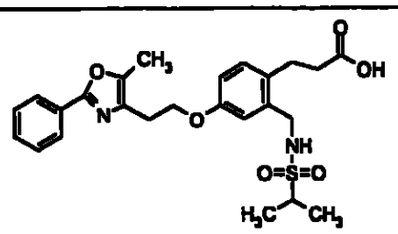
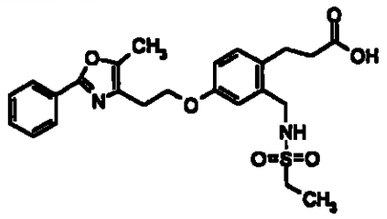
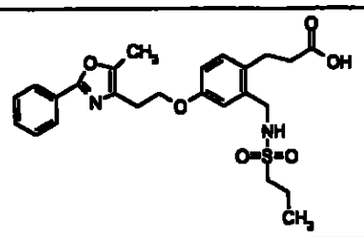
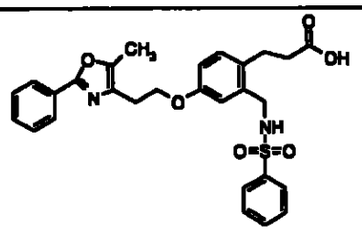
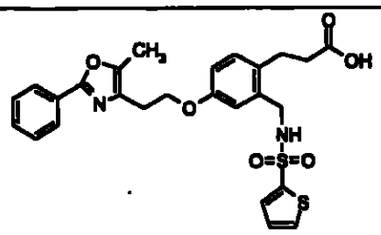
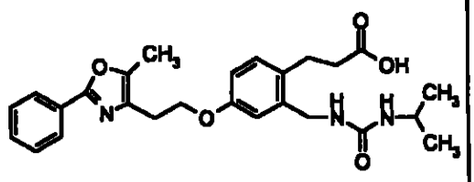
No	Compounds	MS (ES+)	General Procedur
161		437.2	I
162		571.2	I
163		see text	I
164		493.2	II
165		483.2	II
166		551.2	II

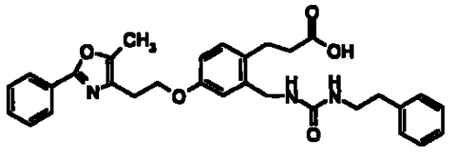
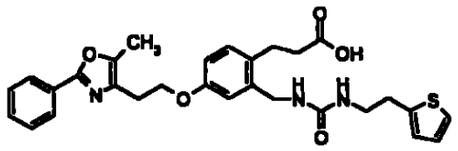
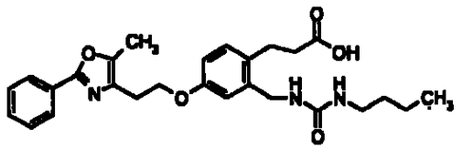
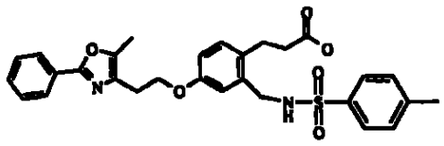
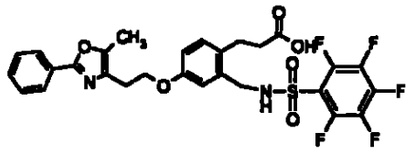
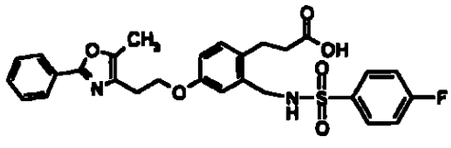
No	Compounds	MS (ES+)	General Procedur
167		467.2	II
168		481.2	II
169		501.2	II
170		439.2	II
171		481.3	II
172		453.2	II

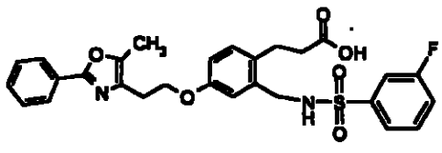
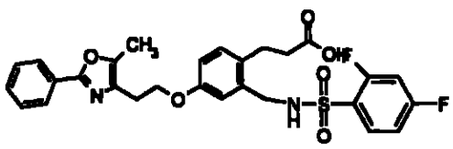
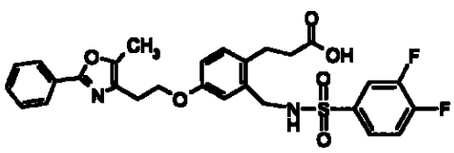
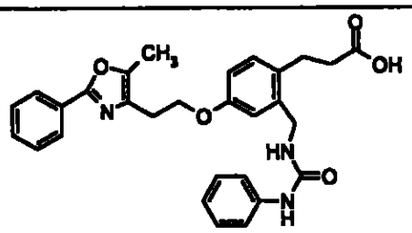
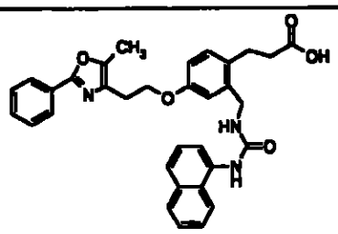
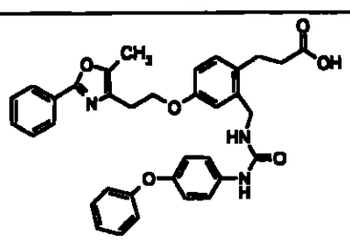
No	Compounds	MS (ES+)	General Procedur
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174		535.2	II
175		475.2	I
176		536.2	I
177		524.2	I
178		487.2	I

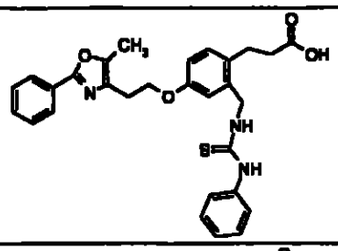
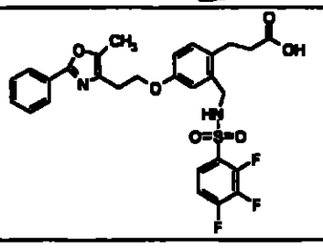
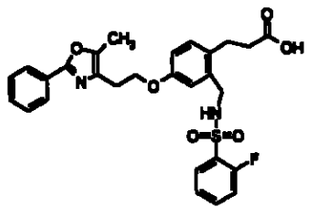
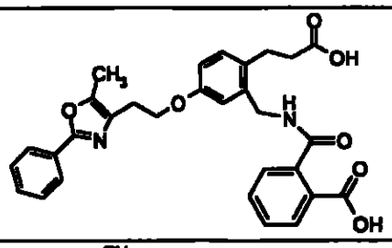
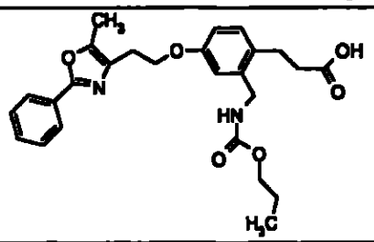
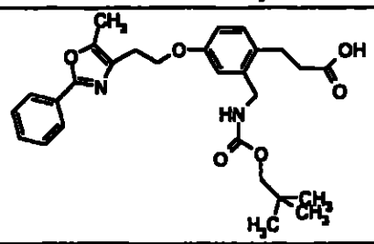
No	Compounds	MS (ES+)	General Procedur
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180		486.2	I
181		486.2	I
182	 HCl	474.2	I
183	 HCl	486.2	I
184		512	I

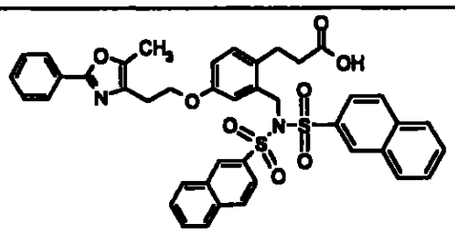
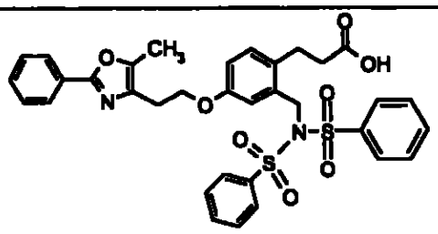
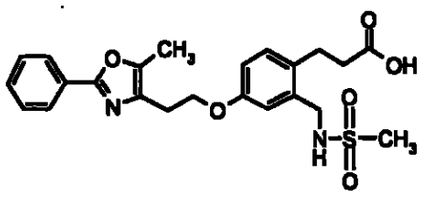
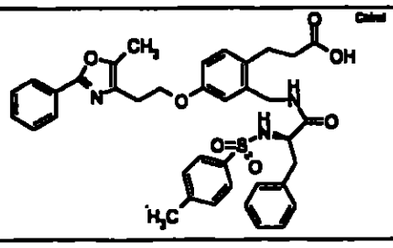
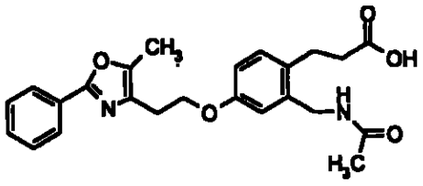
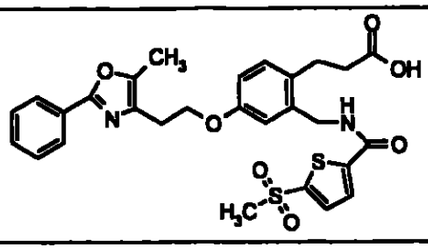
No	Compounds	MS (ES+)	General Procedur
185		512.2	I
186		568.1	I
187		556.1	I
188		537.1	I
189		574.1	I
190		559.1	I

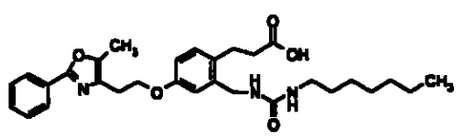
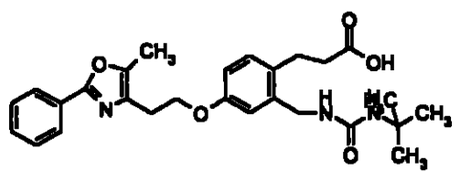
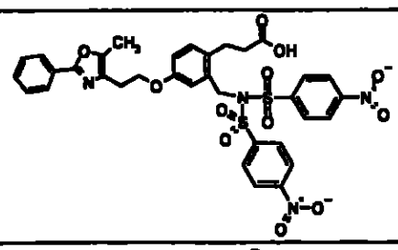
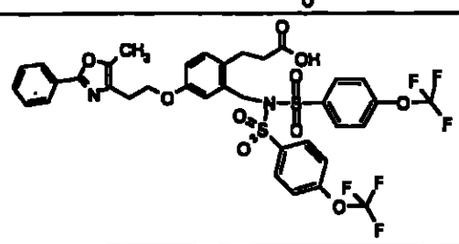
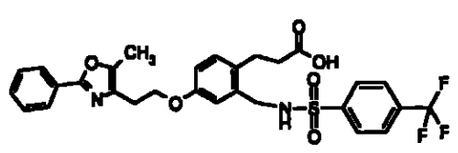
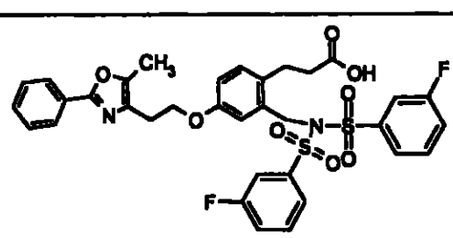
No	Compounds	MS (ES+)	General Procedur
191		487.3	II
192		473.0	II
193		487.3	II
194		521.3	II
195		527.2	II
196		466.3	II

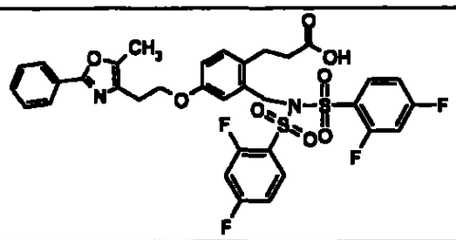
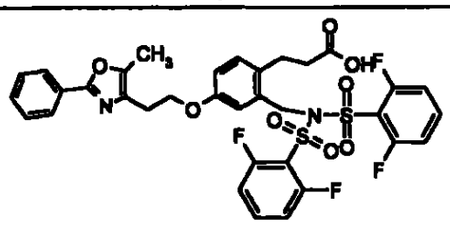
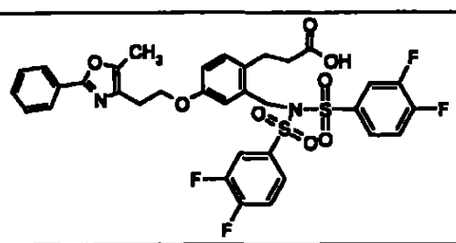
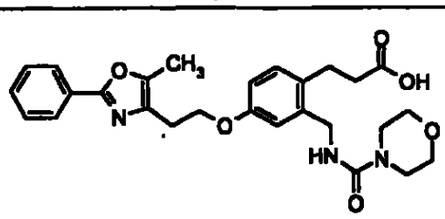
No	Compounds	MS (ES+)	General Procedur
197		528.3	II
198		534.3	II
199		480.3	II
200		535.2	II
201		611.1	II
202		539.2	II

No	Compounds	MS (ES+)	General Procedur
203		539.1	II
204		557.1	II
205		557.1	II
206		500.2	II
207		550.2	II
208		592.2	II

No	Compounds	MS (ES+)	General Procedur
209		516.1	II
210		575.1	II
211		539.2	II
212		529	II
213		467.3	II
214		495.3	II

No	Compounds	MS (ES+)	General Procedur
215		761.2 (FIA)	II
216		661.1 (FIA)	II
217		459.4 (FIA)	II
218		682	II
219		423	I
220		569	I

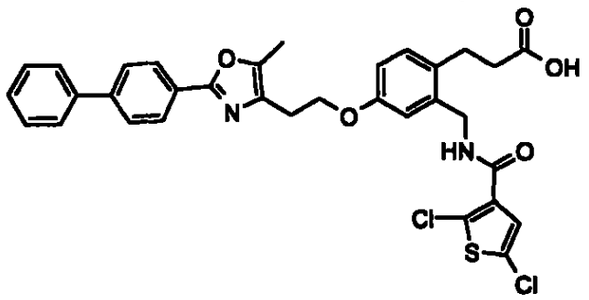
No	Compounds	MS (ES+)	General Procedur
221		552	II
222		480	II
223		751	II
224		829	II
225		589	II
226		697	II

No	Compounds	MS (ES+)	General Procedur
227		733	II
228		733	II
229		733	II
230		494.1	II

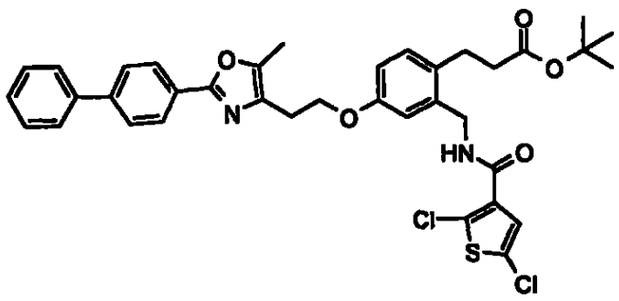
5

Example 231

3-(4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-{[(2,5-dichloro-thiophene-3-carbonyl)-amino]-methyl}-phenyl)-propionic acid



Step A: 3-(4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-{[(2,5-dichloro-thiophene-3-carbonyl)-amino]-methyl}-phenyl)-propionic acid tert-butyl ester



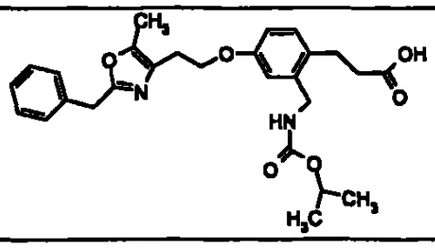
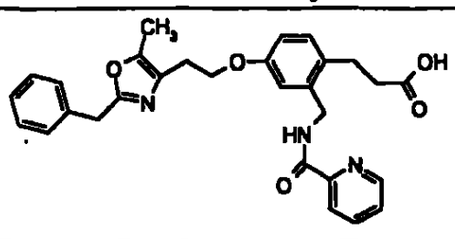
A mixture of 3-(2-{[(2,5-dichloro-thiophene-3-carbonyl)-amino]-methyl}-4-hydroxy-phenyl)-propionic acid tert-butyl ester (280 mg, 0.651 mmol) and toluene-4-sulfonic acid 2-(2-biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethyl ester (498 mg, 1.15 mmol), were reacted according to Standard procedure A to give, after radial chromatography (hexanes/ EtOAc 98:2 to 90:10), the title compound as a white solid (367 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ1.36 (s, 9 H), 2.37 (s, 3 H), 2.55 (t, 2H, J = 7.3 Hz), 2.87 (t, 2H, J = 7.3 Hz), 2.96 (t, 2 H, J = 6.6 Hz), 4.22 (t, 2H, J = 6.8 Hz), 4.58 (d, 2H, J = 5.4 Hz), 6.80 (dd, 1H, J = 8.3 Hz, J = 2.4 Hz), 6.88 (d, 1H, J = 2.9 Hz), 6.97 (t, 1H, J = 5.9 Hz), 7.10 (d, 1 H, J = 8.8 Hz), 7.13 (s, 1 H), 7.36 (t, 1H, J = 7.3 Hz), 7.45 (t, 2H, J = 7.8 Hz), 7.63 (d, 2 H, J = 8.3 Hz), 7.65 (d, 2H, J = 6.3 Hz), 8.02 (d, 2H, J = 7.8 Hz). MS (ES) m/e 691.2 [M+1].

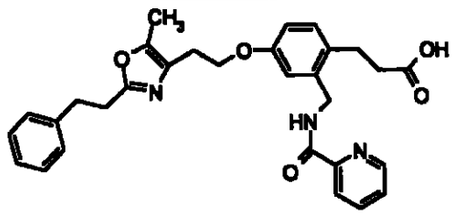
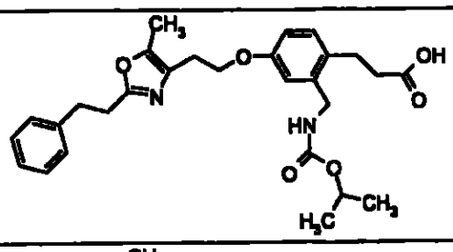
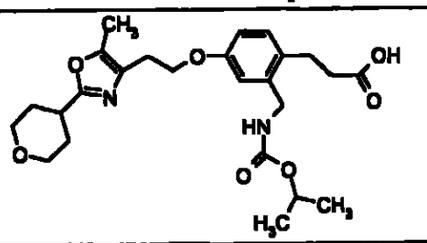
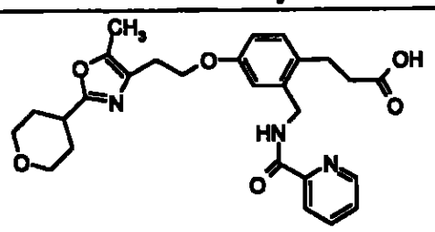
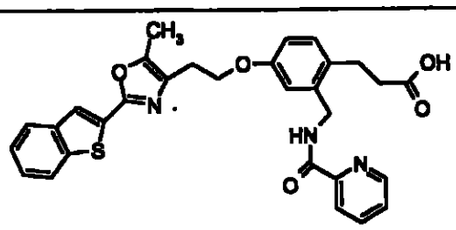
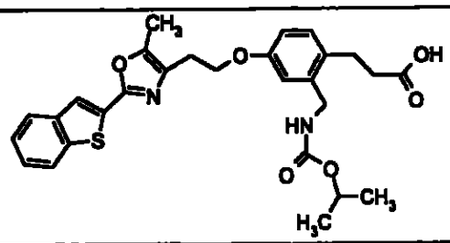
Step B: 3-(4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-{[(2,5-dichloro-thiophene-3-carbonyl)-amino]-methyl}-phenyl)-propionic acid

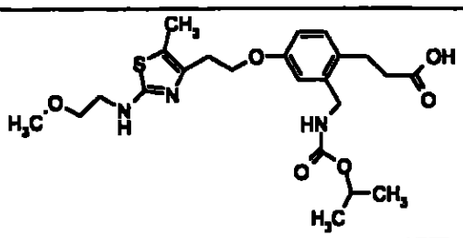
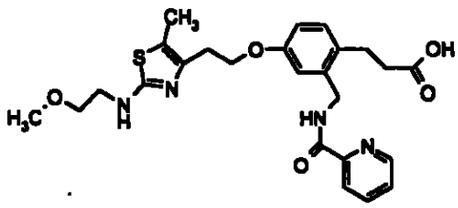
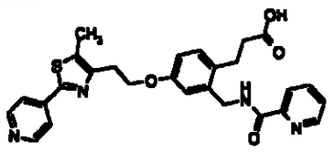
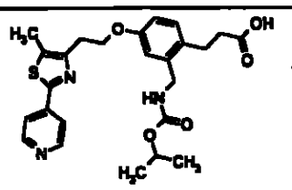
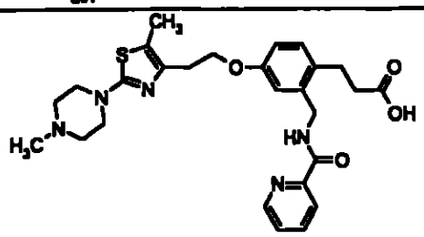
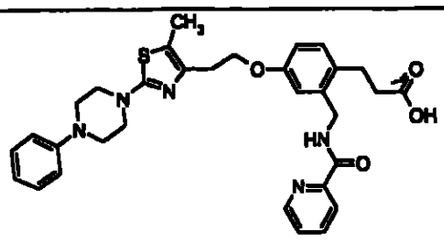
A solution of the 3-(4-[2-(2-biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-{[(2,5-dichloro-thiophene-3-carbonyl)-amino]-methyl}-phenyl)-propionic acid tert-butyl ester (367 mg, 0.531 mmol) in CH_2Cl_2 (20 mL) was treated with anisole (2.0 mL) then TFA (6.0 mL). The mixture was stirred at room temperature for 2 h and concentrated. The residue was co-evaporated with CCl_4 three times, dried under vacuum, triturated with ether, and filtered to obtain the title compound as a white solid (301 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d6): δ 2.25 (s, 3 H), 2.38 (t, 2H, J = 8.3 Hz), 2.71 (t, 2H, J = 7.3 Hz), 2.82 (t, 2H, J = 6.3 Hz), 4.07 (t, 2H, J = 6.6 Hz), 4.28 (d, 2H, J = 4.9 Hz), 6.68 (d, 1H, J = 9.3 Hz), 6.77 (s, 1H), 7.00 (d, 1H, J = 8.3 Hz), 7.24 (s, 1H), 7.29 (t, 1 H, J = 5.9 Hz), 7.39 (t, 2H, J = 7.8 Hz), 7.63 (t, 2H, J = 7.8 Hz), 7.71 (d, 2 H, J = 8.3 Hz), 7.88 (d, 2H, J = 8.3 Hz), 8.69 (t, 2H, J = 5.9 Hz). MS (ES) m/e 635.1 [M+1].

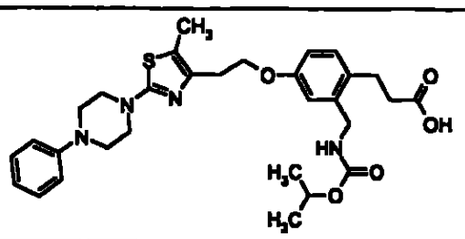
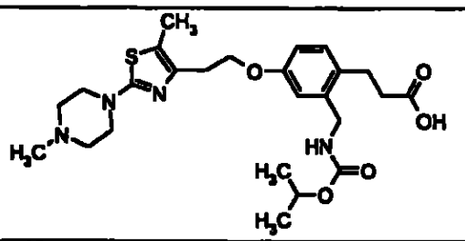
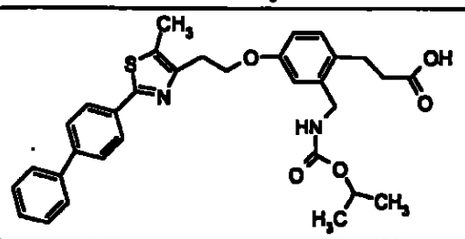
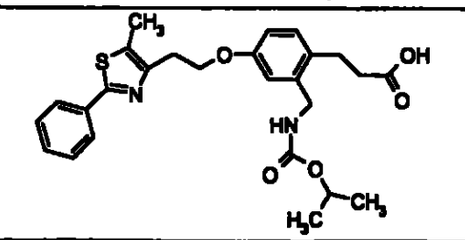
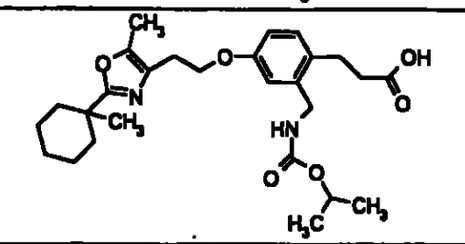
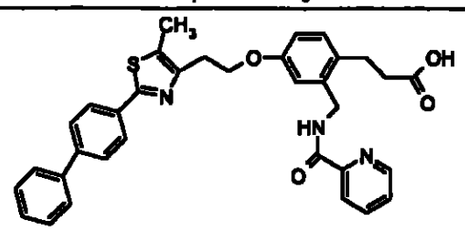
Examples 232-318

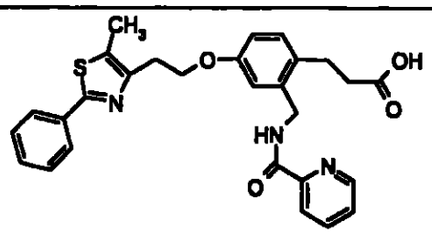
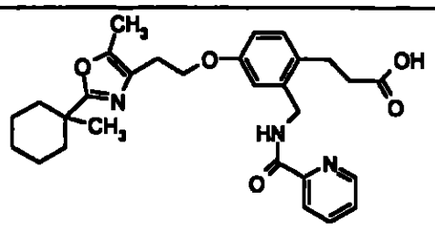
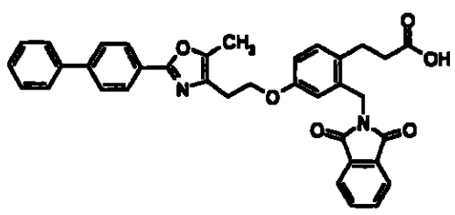
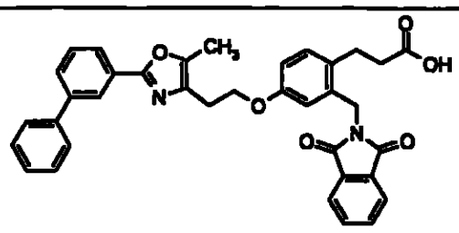
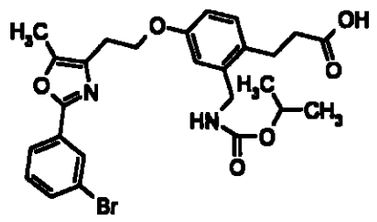
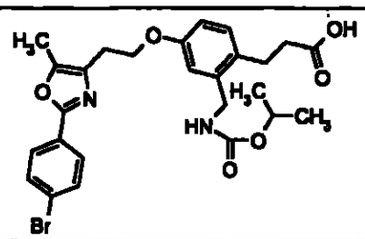
Examples 232-318 are prepared by following a substantially similar procedure as described in Example 231 and Standard coupling procedure A and Standard hydrolysis procedures C to E.

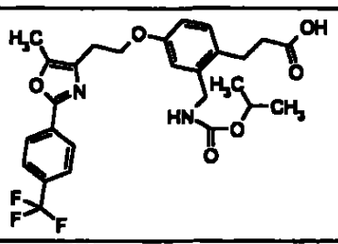
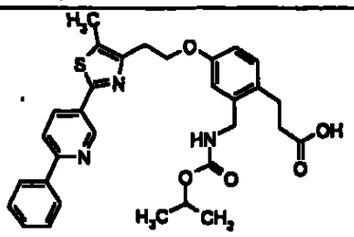
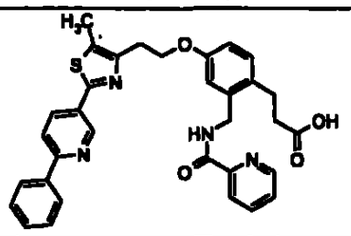
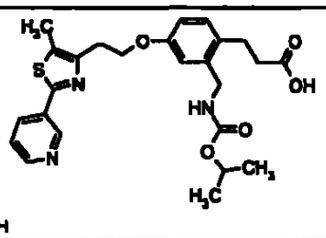
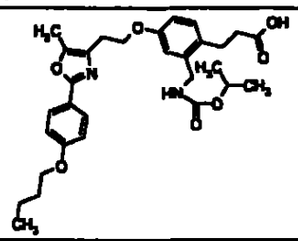
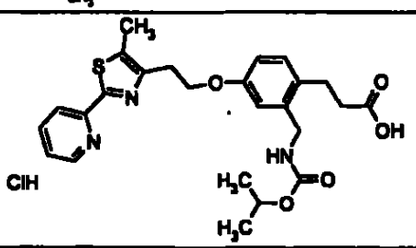
No.	Compounds	MS (ES+)
232		481.3
233		500.3

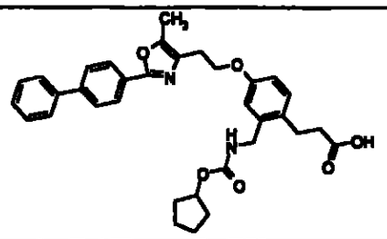
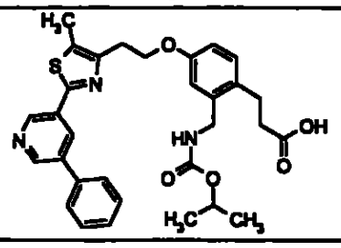
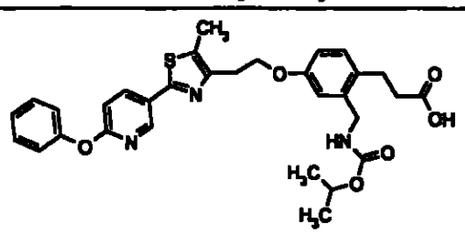
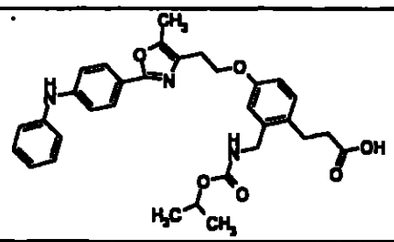
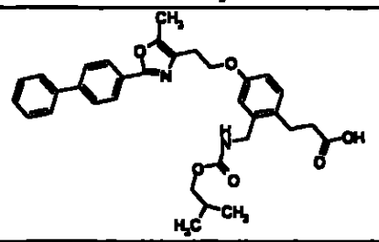
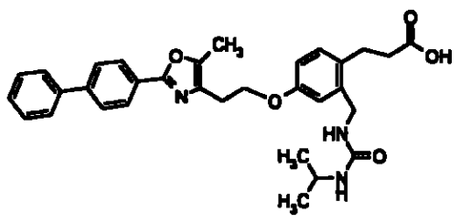
No.	Compounds	MS (ES+)
234		514.3
235		495.3
236		475.1
237		494.3
238		542.2
239		523.3

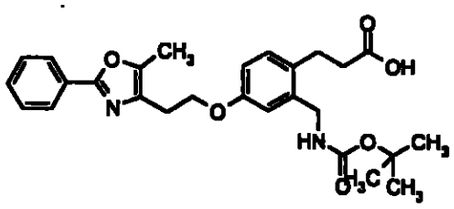
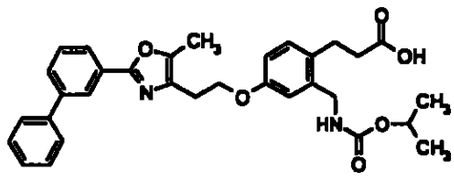
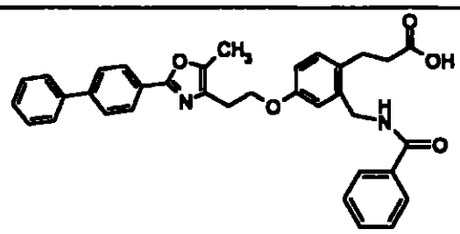
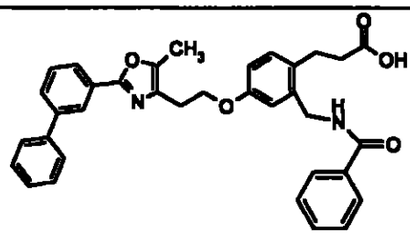
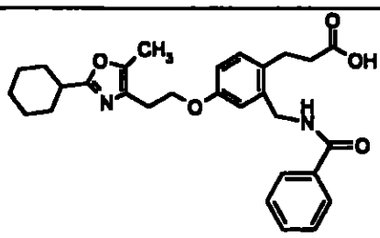
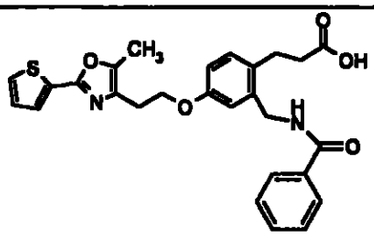
No.	Compounds	MS (ES+)
240		480.3
241		499.2
242		503
243		484
244		524.4
245		586.3

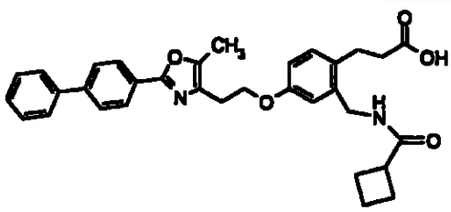
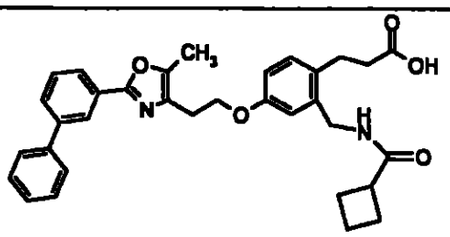
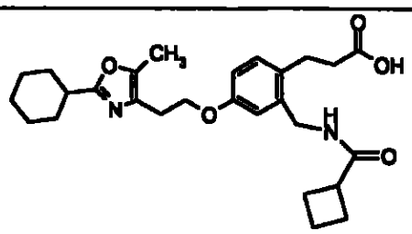
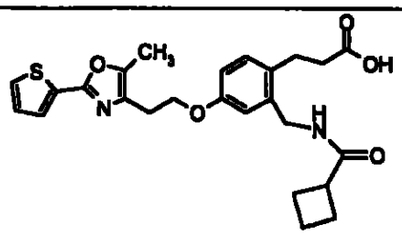
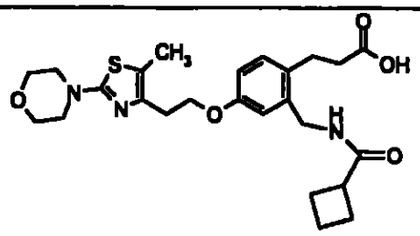
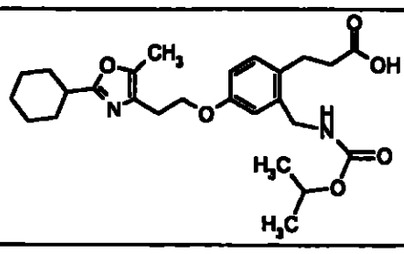
No.	Compounds	MS (ES+)
246		567.3
247		505.3
248		559.2
249		483.2
250		487.3
251		578.3

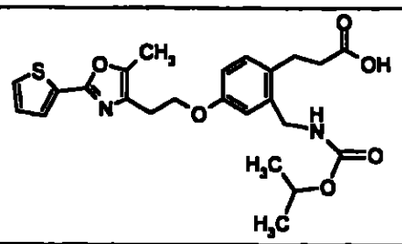
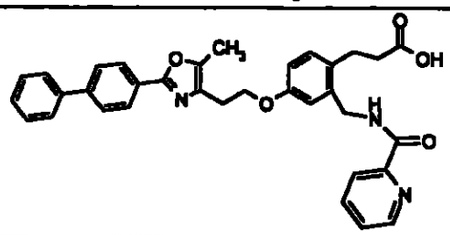
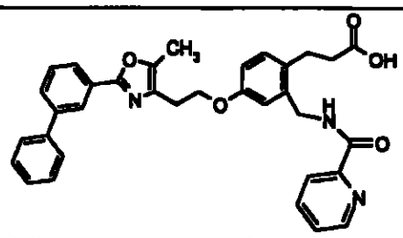
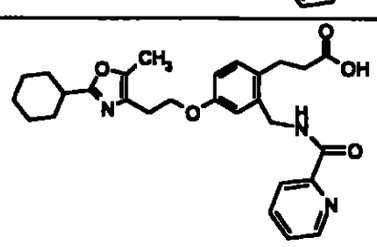
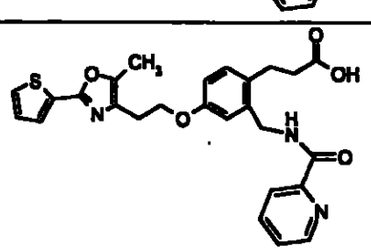
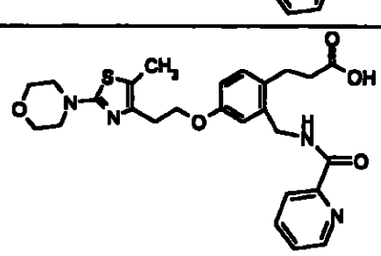
No.	Compounds	MS (ES+)
252		502.2
253		503.3
254		587.2
255		587.2
256		545/547
257		545/547

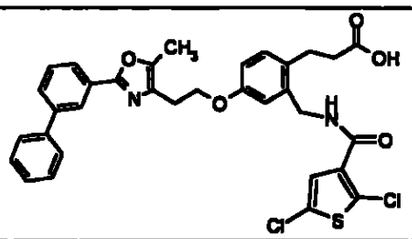
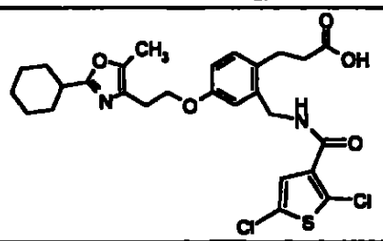
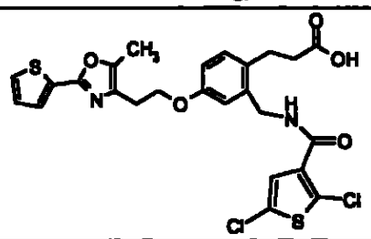
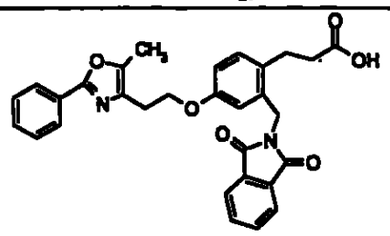
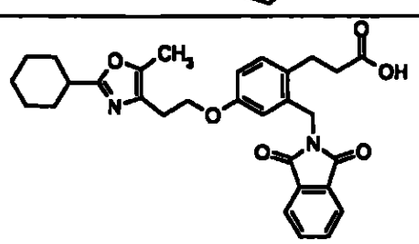
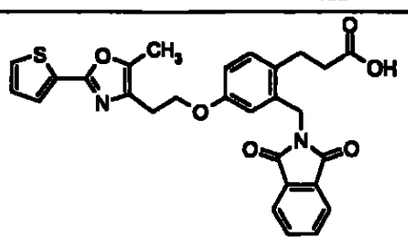
No.	Compounds	MS (ES+)
258		535
259		560
260		579
261		484
262		539
263		484

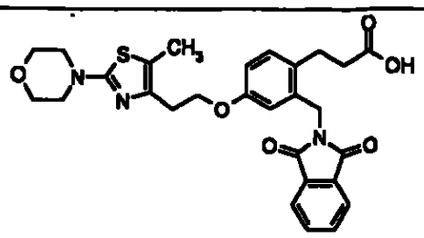
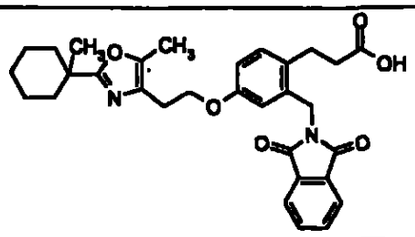
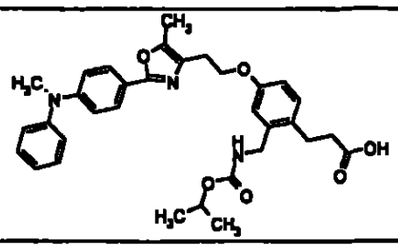
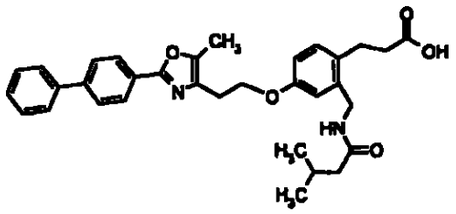
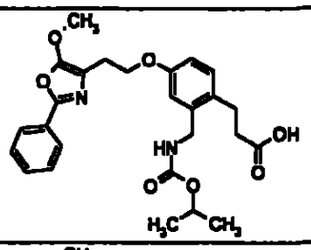
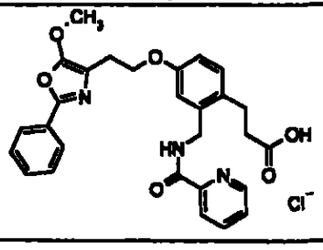
No.	Compounds	MS (ES+)
264		569
265		560
266		576.1
267		558.4
268		557.2
269		542

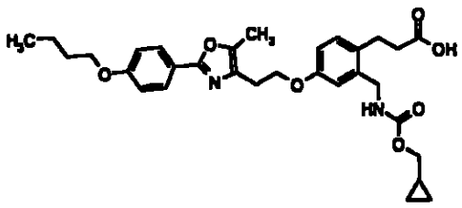
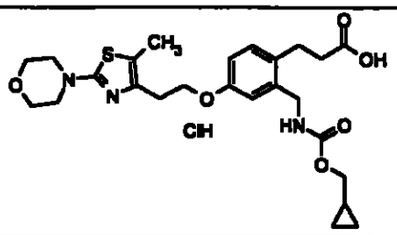
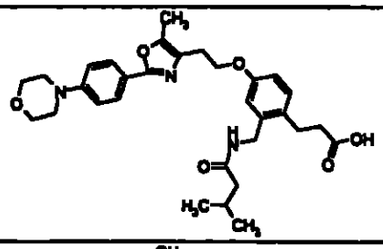
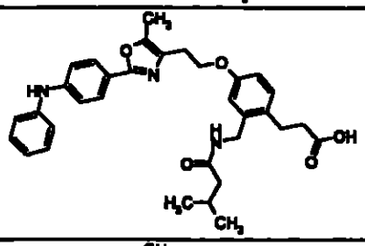
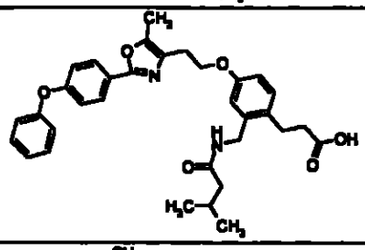
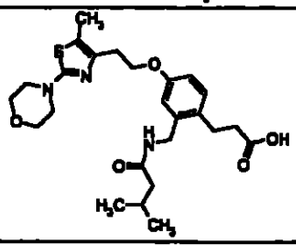
No.	Compounds	MS (ES+)
270		481.3
271		543.2
272		561.3
273		561.3
274		491.3
275		491.2

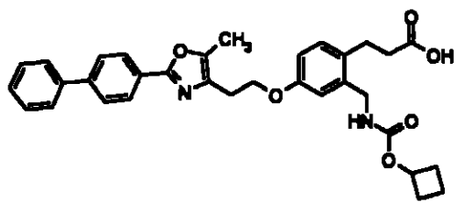
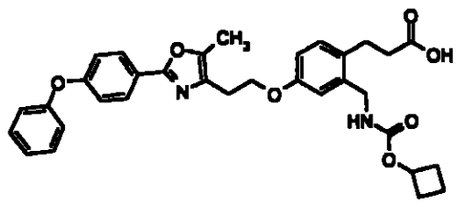
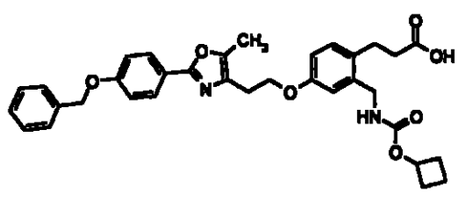
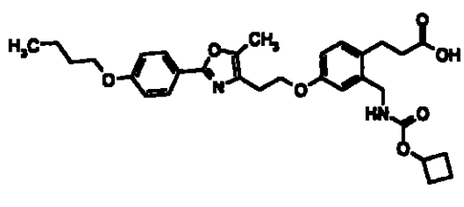
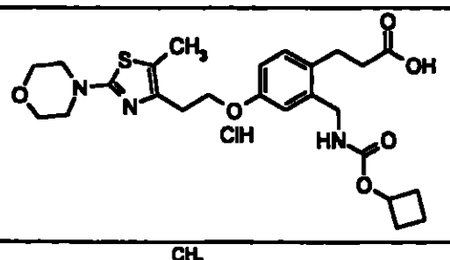
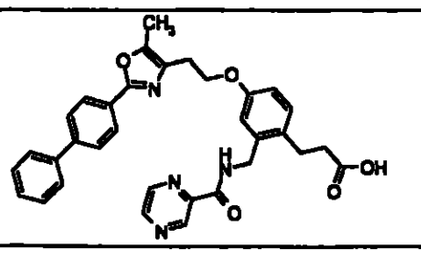
No.	Compounds	MS (ES+)
276		539.3
278		539.3
279		469.3
280		469.3
281		488.1
282		473.3

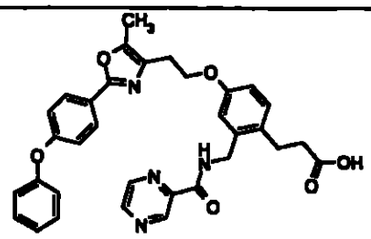
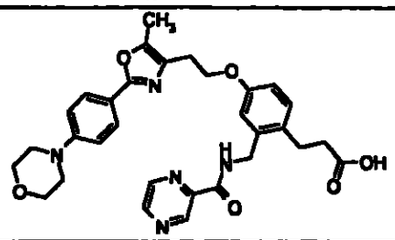
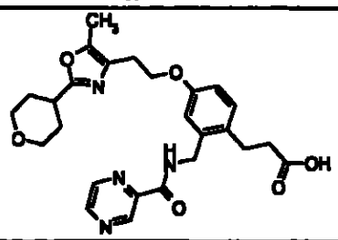
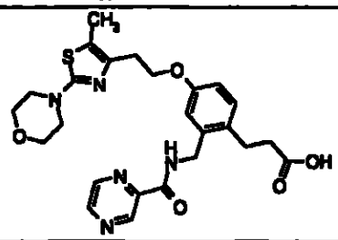
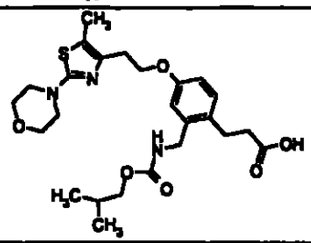
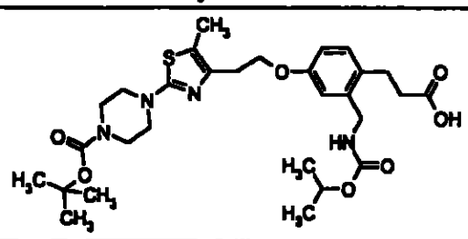
No.	Compounds	MS (ES+)
283		473.2
284		562.2
285		562.3
286		492.2
287		492.2
288		511.2

No.	Compounds	MS (ES+)
289		635.2
290		565.2
291		565
292		511
293		517
294		517

No.	Compounds	MS (ES+)
295		536
296		531
297		572.2
298		541
299		483
300		502

No.	Compounds	MS (ES+)
301		551.2770 (HRMS)
302		504.2171 (HRMS)
303		550.2
304		554
305		557.2
306		490.2

No.	Compounds	MS (ES+)
307		555.2426 (HRMS)
308		571.2436 (HRMS)
309		585.2595 (HRMS)
310		551.2753 (HRMS)
311		504.2144 (HRMS)
312		563.2

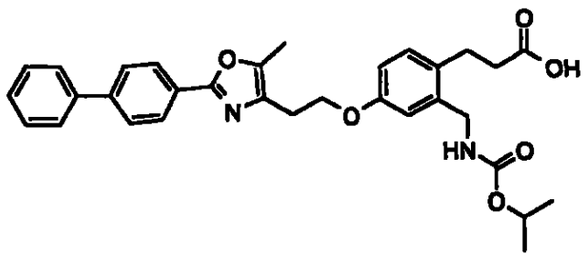
No.	Compounds	MS (ES+)
313		579.2
314		572.2
315		495.2
316		512.2
317		506.2
318		^{1}H NMR

^{1}H NMR data for Example 318:

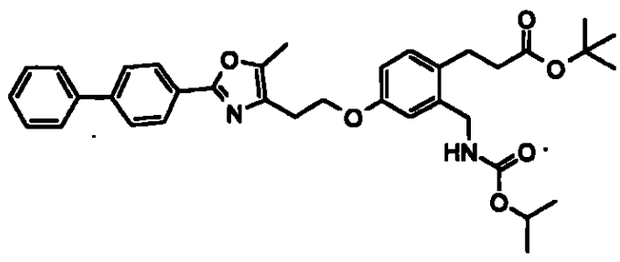
(400 MHz, $CDCl_3$): d 6.98 (1H, d, J=7.9 Hz), 6.71 (1H, s), 6.68 (1H, d, J=7.9 Hz), 4.97 (1H, m), 4.86 (2H, m), 4.31 (2H, bs), 4.08 (2H, t, J=6.5 Hz), 3.45 (4H, m), 3.27 (4H, m), 2.86 (4H, m), 2.55 (2H, bs), 2.18 (3H, s), 1.42 (9H, s), 1.16 (6H, d, J=7.2 Hz).

Example 319

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



Step A: {4-[2-(5-Methyl-2-(4-phenyl)phenyl-oxazol-4-yl)-ethoxy]-2-(isopropylcarbamate)methyl}-propionic acid tert-butyl ester



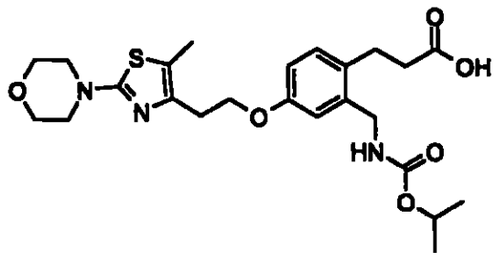
3-[4-hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (258 mg, 0.763 mmol) and toluene-4-sulfonic acid 2-(2-biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethyl ester (654 mg, 1.51 mmol) were reacted according to Standard procedure A. Purification by radial chromatography (CH_2Cl_2/EtOAc 98/2 to 90/10) gave the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, 6H, J = 5.9 Hz), 1.31 (s, 9 H), 2.30 (s, 3 H), 2.39 (t, 2H, J = 7.6 Hz), 2.89 (t, 2H, J = 6.6 Hz), 4.14 (t, 2H, J = 6.6 Hz), 4.25 (d, 2H, J = 5.4.Hz), 4.85 (heptet, 1H, J = 5.8 Hz), 6.67 (dd, 1H, J = 8.3 Hz, J= 2.4 Hz), 6.75 (d, 1H, J = 2.4 Hz), 6.99 (d, 1H, J = 8.3 Hz), 7.26-7.30 (m, 1 H), 7.37 (t, 2H, J = 7.6 Hz), 7.53-7.58 (m, 4 H), 7.95 (d, 2H, J = 8.3 Hz). MS (ES) m/e 599.4 [M+1].

Step B: {4-[2-(5-Methyl-2-(4-phenyl)phenyl-oxazol-4-yl)-ethoxy]-2-(isopropylcarbamate)methyl}-propionic acid

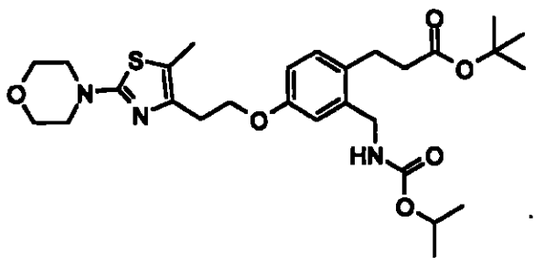
A solution of {4-[2-(5-methyl-2-(4-phenyl)phenyl-oxazol-4-yl)-ethoxy]-2-(isopropylcarbamate)methyl}-propionic acid (414 mg, 0.763 mmol) in CH_2Cl_2 (10 mL) was treated with anisole (1.0 mL) then trifluoroacetic acid (TFA, 3.0 mL). The solution was stirred at room temperature for 2 h and concentrated. The residue was co-evaporated with CCl_4 twice, dried under vacuum, triturated with ether, and filtered to obtain the title compound as a white solid (287 mg, 69%). ^{1}H NMR (400 MHz, CDCl3) δ 1.11 (d, 6H, J = 5.9 Hz), 2.28 (s, 3 H), 2.46 (t, 2H, J = 7.6 Hz), 2.79 (t, 2H, J = 7.6 Hz), 2.86 (t, 2H, J = 6.6 Hz), 4.11 (t, 2H, J = 6.8 Hz), 4.24 (d, 2H, J = 5.4 Hz), 4.82 (heptet, 1H, J = 6.1 Hz), 5.05 (bs, 1 H), 6.66 (dd, 1H, J = 2.4, 8.3 Hz), 6.73 (d, 1H, J = 2.4 Hz), 6.99 (d, 1H, J = 8.3 Hz), 7.24-7.28 (m, 1 H), 7.35 (t, 2H, J = 7.6 Hz), 7.51-7.56 (m, 4 H), 7.98 (d, 2H, J = 8.3 Hz). MS (ES) m/e 543.1 [M+1].

Example 320

3-{2-(Isopropoxycarbonylaminomethyl)-4-[2-(5-methyl-2-morpholin-4-yl-thiazol-4-yl)ethoxy]-phenyl}propionic acid



Step A: 3-{2-(Isopropoxycarbonylamino-methyl)-4-[2-(5-methyl-2-morpholin-4-yl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester



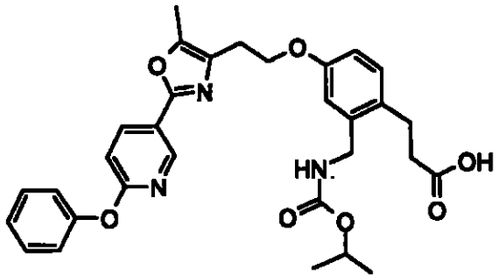
3-[4-hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (272 mg, 0.806 mmol) and toluene-4-sulfonic acid 2-(5-methyl-2-morpholin-4-yl-thiazol-4-yl)-ethyl ester (522 mg, 1.36 mmol) were reacted according to Standard procedure A. Purification using radial chromatography (CH_2Cl_2/EtOAc 98:2 to 75:25) gave the title compound as a white solid (387 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, 6H, J = 5.9 Hz), 1.32 (s, 9 H), 2.16 (s, 3 H), 2.39 (t, 2H, J = 7.6 Hz), 2.77 (t, 2H, J = 7.6 Hz), 2.84 (t, 2H, J = 7.1 Hz), 3.28 (t, 4H, J = 4.9 Hz), 3.70 (t, 4H, J = 4.9 Hz), 4.08 (t, 2H, J = 7.1 Hz), 4.25 (d, 2H, J = 5.4 Hz), 4.83 (heptet, 1H, J = 4.9 Hz), 6.66 (dd, 1H, J = 2.4, 8.3 Hz), 6.72 (d, 1H, J = 2.4 Hz), 6.98 (d, 1H, J = 8.3 Hz). MS (ES) m/e 548.3 [M+1].

Step B: 3-{2-(Isopropoxycarbonylaminomethyl)-4-[2-(5-methyl-2-morpholin-4-yl-thiazol-4-yl)ethoxy]-phenyl}propionic acid

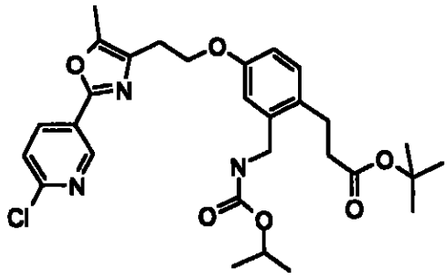
A solution of 3-{2-(isopropoxycarbonylamino-methyl)-4-[2-(5-methyl-2-morpholin-4-yl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester (387 mg, 0.706 mmol) in CH_2Cl_2 (10 mL) was treated with anisole (1 mL) then TFA (3 mL). The solution was stirred at room temperature for 2 h and concentrated. The residue was co-evaporated with CCl_4 twice, dried under vacuum, triturated with ether, and filtered to obtain the title compound as a white solid (236 mg, 60%), isolated as the trifluoracetic acid salt: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, 6H, J = 6.4 Hz), 2.16 (s, 3H), 2.47 (t, 2H, J = 7.6 Hz), 2.79 (t, 2H, J = 7.6 Hz), 2.87 (t, 2H, J = 6.4 Hz), 3.35 (t, 4H, J = 4.9 Hz), 3.70 (t, 4H, J = 4.9 Hz), 4.07 (t, 2H, J = 6.6 Hz), 4.23 (d, 2H, J = 5.4 Hz), 4.82 (heptet, 1H, J = 6.1 Hz), 5.07 (bs, 1H), 6.63 (dd, 1H, J = 2.7, 8.6 Hz), 6.69 (d, 1H, J = 2.9 Hz), 6.98 (d, 1H, J = 8.3 Hz). MS (ES) m/e 492.1 [M+1].

Example 321

3-(2-(2-Isopropoxycarbonyl-ethyl)-4-{2-[5-methyl-2-(6-phenoxy-pyridin-3-yl)-oxazol-4-yl]ethoxy}-phenyl)-propionic acid



Step A: 3-(2-(2-Isopropoxycarbonyl-ethyl)-4-{2-[5-methyl-2-(6-chloro-pyridin-3-yl)-oxazol-4-yl]ethoxy}-phenyl)-propionic acid t-butyl ester



Toluene-4-sulfonic acid 2-[2-(6-chloro-pyridn-3-yl)-5-methyl-oxaxol-4-yl]-ethyl ester tosylate (290 mg, 0.74 mmol) and 3-[4-hydroxy-2-(2-isopropoxycarbonyl-ethyl)-phenyl]-propionic acid t-butyl ester (274 mg, 0.81 mmol) were converted to the title compound (183 mg, 44 %) according to Standard procedure A. MS (ESI) m/z 559 $(M+H)^+$.

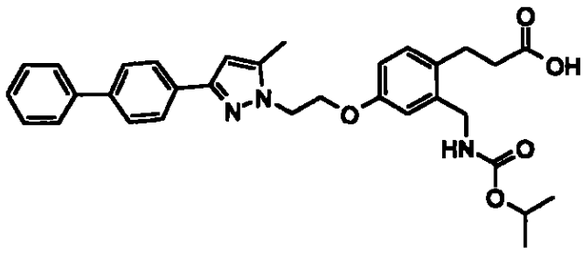
Step B: 3-(2-(2-Isopropoxycarbonyl-ethyl)-4-{2-[5-methyl-2-(6-phenoxy-pyridin-3-yl)-oxazol-4-yl]ethoxy}-phenyl)-propionic acid

To a suspension of NaH (20 mg, 0.48 mmol) in DMF (10 mL) at ambient temperature was added phenol (45 mg, 0.48 mmol). The mixture was stirred at 60°C for 20 min, and 3-(2-(2-isopropoxycarbonyl-ethyl)-4-{2-[5-methyl-2-(6-chloro-pyridin-3-yl)-oxazol-4-yl]ethoxy}-phenyl)-propionic acid t-butyl ester (180 mg, 0.32 mmol) was added. The resulting mixture was stirred at 60°C overnight, cooled, diluted with EtOAc, and washed with water/brine (4x). The organic layer was dried ($MgSO_4$), filtered and

concentrated. The residue was purified by silica gel chromatography (hexanes/EtOAc 3/1 to 1/1) to afford the intermediate ester as an oil (60 mg, 30%). The title compound was generated using Standard hydrolysis procedure C. MS (ESI) m/z 560 $(M+H)^+$. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25 (d, J=0.5 Hz, 6H), 2.42 (s, 3H), 2.65 (m, 2H), 2.96 (m, 4H), 4.38 (m, 2H), 4.18 (m, 2H), 4.38 (m, 1H), 5.00 (m, 2H), 6.82 (m, 3H), 6.96 (m, 1H), 7.12 (m, 1H), 7.20 (m, 2H), 7.45 (m, 2H), 8.28 (m, 1H), 8.80 (m, 1H).

Example 322

3-[4-[2-(3-Biphenyl-4-yl-5-methyl-pyrazol-1-yl)-ethoxy]-2-(isopropoxycarbonyl-amino-methyl)-phenyl]-propionic acid

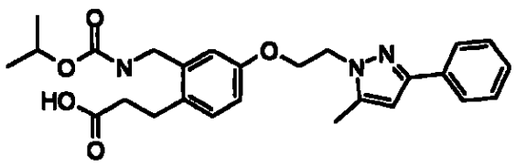


The title compound was prepared from 3-[4-hydroxy-2-(isopropoxycarbonyl-amino-methyl)-phenyl]-propionic acid tert-butyl ester (Prep 16) and 2-(3-biphenyl-4-yl-5-methyl-pyrazol-1-yl)-ethanol (Prep 11) using Standard coupling procedure B followed by Standard hydrolysis procedure C. MS [ES] m/e 542 $(M+1)^+$.

The following Examples 323 to 333 are prepared by following a substantially similar procedure as described in Example 322.

Examples 323

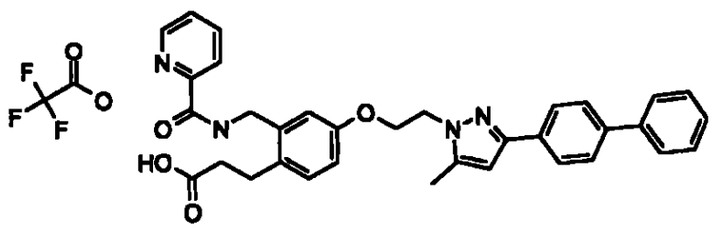
3-{2-(Isopropoxycarbonylamino-methyl)-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethoxy]-phenyl}-propionic acid



HRMS Calculated for $C_{26}H_{32}N_3O_5$: m/z 466.2342. Found: 466.2331.

Examples 324

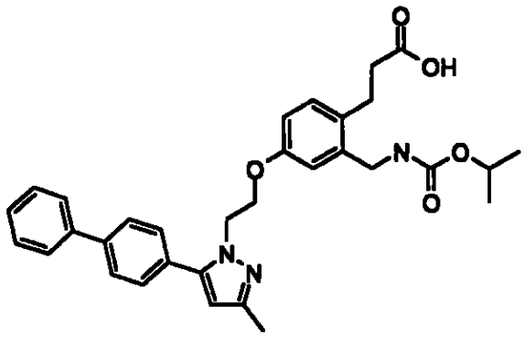
3-(4-[2-(3-Biphenyl-4-yl-5-methyl-pyrazol-1-yl)-ethoxy]-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid trifluoroacetate



HRMS Calculated for $C_{28}H_{30}N_4O_4$: m/z 486.2267. Found: 486.2233.

Examples 325

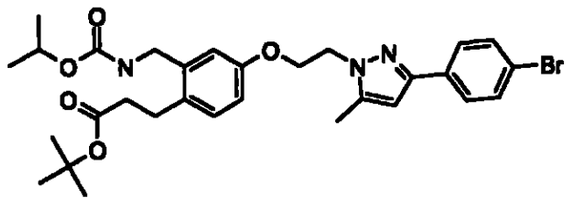
3-[4-[2-(5-Biphenyl-4-yl-3-methyl-pyrazol-1-yl)-ethoxy]-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



HRMS Calculated for $C_{32}H_{36}N_3O_5$: m/z 542.2655. Found: 542.2678

Examples 326

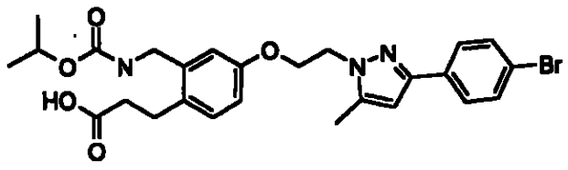
3-[4-{2-[3-(4-Bromo-phenyl)-5-methyl-pyrazol-1-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester



HRMS Calculated for $C_{30}H_{39}BrN_3O_5$: m/z 600.2073. Found: 600.2064;

Examples 327

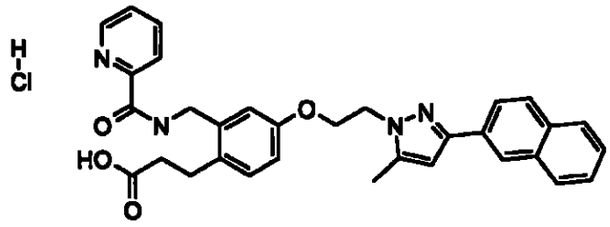
3-[4-{2-[3-(4-Bromo-phenyl)-5-methyl-pyrazol-1-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



HRMS Calculated for $C_{26}H_{31}BrN_3O_5$: m/z 544.1447. Found: 544.1456.

Examples 328

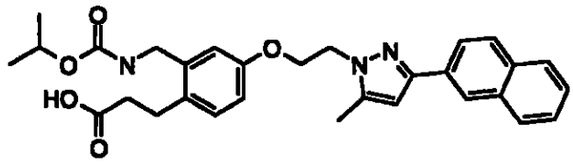
3-(4-[2-(5-Methyl-3-naphthalen-2-yl-pyrazol-1-yl)-ethoxy]-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid hydrochloride



The above compound is prepared by using Standard hydrolysis procedure D. HRMS Calculated for $C_{32}H_{31}N_4O_4$: m/z 535.2345. Found: 535.2343

Examples 329

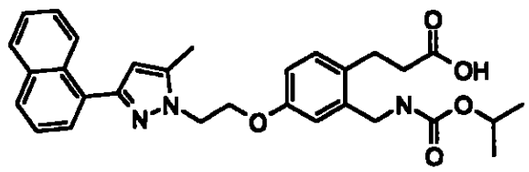
3-{2-(Isopropoxycarbonylamino-methyl)-4-[2-(5-methyl-3-naphthalen-2-yl-pyrazol-1-yl)-ethoxy]-phenyl}-propionic acid



HRMS Calculated for $C_{30}H_{34}N_3O_5$: m/z 516.2498. Found: 516.2485.

Examples 330

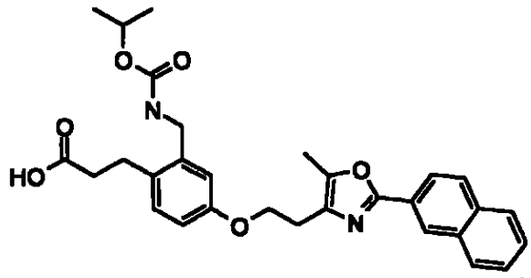
3-{2-(Isopropoxycarbonylamino-methyl)-4-[2-(5-methyl-3-naphthalen-1-yl-pyrazol-1-yl)-ethoxy]-phenyl}-propionic acid



HRMS Calculated for $C_{30}H_{34}N_3O_5$: m/z 516.2498. Found: 516.2529.

Examples 331

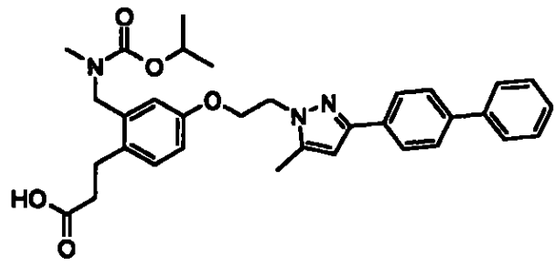
3-{2-(Isopropoxycarbonylamino-methyl)-4-[2-(5-methyl-2-naphthalen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



HRMS Calculated for $C_{30}H_{33}N_2O_6$: m/z 517.2339. Found: 517.2328.

Examples 332

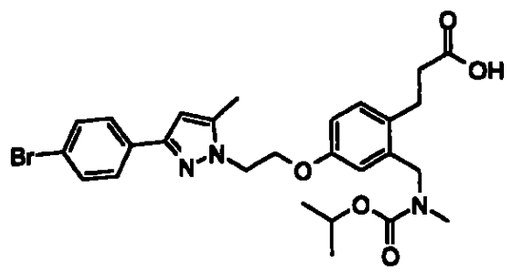
3-{4-[2-(3-Biphenyl-4-yl-5-methyl-pyrazol-1-yl)-ethoxy]-2-[(isopropoxy-carbonyl-methyl-amino)-methyl]-phenyl}-propionic acid



HRMS Calculated for $C_{33}H_{38}N_3O_5$: m/z 556.2811. Found: 556.2819

Examples 333

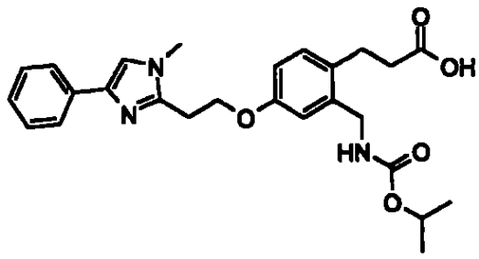
3-{4-{2-[3-(4-Bromo-phenyl)-5-methyl-pyrazol-1-yl]-ethoxy}-2-[(isopropoxy-carbonyl-methyl-amino)-methyl]-phenyl}-propionic acid



HRMS Calculated for $C_{27}H_{33}BrN_3O_5$: m/z 558.1604. Found: 558.1608

Example 334

3-{2-(Isopropoxycarbonylamino-methyl)-4-[2-(1-methyl-4-phenyl-1H-imidazol-2-yl)-ethoxy]-phenyl}-propionic acid

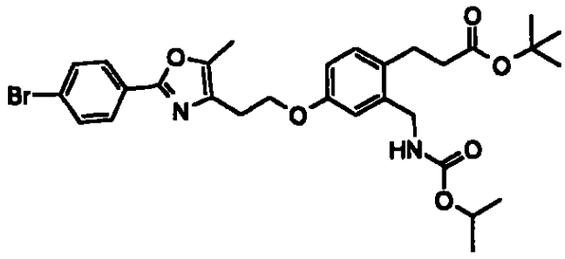


The title compound was prepared from 3-[4-hydroxy-2-(isopropoxycarbonyl-amino-methyl)-phenyl]-propionic acid tert-butyl ester (Prep 16) and 2-(1-Methyl-4-phenyl-1H-imidazol-2-yl)-ethanol (*J. Med. Chem.* 1998, *41*(25), 5037-5054) using Standard coupling procedure B followed by Standard hydrolysis procedure D affording an off-white finely-crystalline solid. HRMS Calculated for C26H31N3O5: m/z 466.2342. Found: 466.2355.

Tail Piece Aryl Ring Modifications

Example 335

3-[4-{2-[2-(4-Bromo-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonyl-amino-methyl)-phenyl]-propionic acid tert-butyl ester

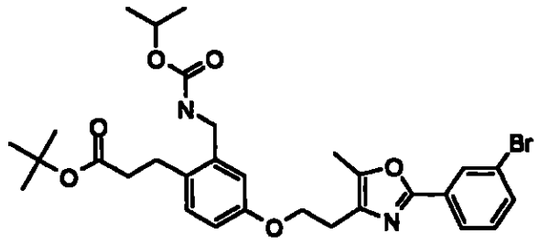


Toluene-4-sulfonic acid 2-[2-(4-bromo-phenyl)-5-methyl-oxazol-4-yl]-ethyl ester (5.06g, 11.6mmol) and 3-[4-hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (3.01g, 8.92mmol) were coupled using Standard procedure A to give the title compound as a white solid (3.41 g, 64%). MS [ES] m/z 601,603 (M+H).

The following Examples 336 to 337 are prepared by following a substantially similar procedure as described in Example 335.

Example 336

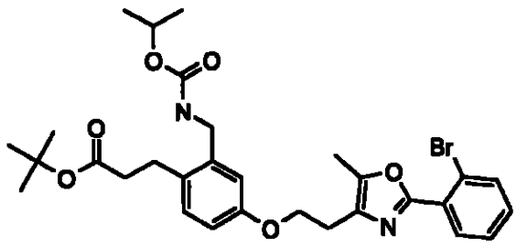
3-[4-{2-[2-(3-Bromo-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxy-carbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester



MS [ES] m/z 601,603 (M+H).

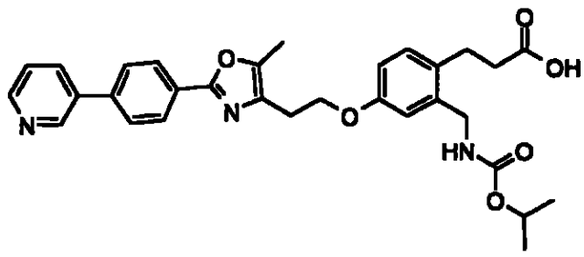
Example 337

3-[4-{2-[2-(2-Bromo-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxy-carbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester.



Example 338

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



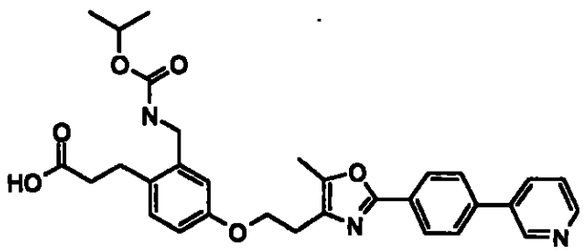
Suzuki Coupling Using Aryl Boronic Acids: A mixture of 3-[4-{2-[2-(4-bromo-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (450 mg, 0.75 mmol), 3-pyridineboronic acid (120 mg, 0.97 mmol), triphenylphosphine (6 mg, 0.024 mmol), 2M aqueous sodium carbonate (3mL) in n-propanol (15mL) was sparged with nitrogen for 5 min. Palladium acetate (2 mg, 0.008 mmol) was added, and the reaction was heated to reflux under a blanket of nitrogen for 4 h. The reaction mixture was concentrated and then partitioned between water/EtOAc. The organic layer was dried ($MgSO_4$) and concentrated to crude product (290 mg). This material was purified by silica gel column chromatography to yield 3-(2-(isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-pyridin-3-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid tert-butyl ester was obtained as a white solid (230 mg, 51%). ^{1}H NMR (CDCl3) δ1.25 (d, 6H), 1.42 (s, 9H), 2.42 (s, 3H), 2.51 (t, 2H), 2.89 (t, 2H), 3.05 (t, 2H), 4.26 (t, 2H), 4.36 (d, 2H), 4.96 (m, 2H), 6.78 (dd, 1H), 6.87 (d, 1H), 7.21 (d, 1H), 7.47 (dd, 1H), 7.67 (d, 2H), 8.00 (dt, 1H), 8.12 (d, 2H), 8.65 (dd, 1H),8.94 (s, 1H). MS [EI+] m/z 600 (M+H).

This ester (225 mg, 0.375 mmol) was dissolved in THF (15mL) and treated with 1N HCl (1mL). The mixture was heated at reflux for 7 h, cooled, and concentrated. The residue was azeotroped twice with acetonitrile and dried in a vacuum oven to give the title compound, isolated as the HCl salt (140 mg, 64%). ^{1}H NMR (DMSO-d_6) δ1.15 (d, 6H), 2.41 (s, 3H), 2.45 (t, 2H), 2.76 (t, 2H), 2.95 (t, 2H), 4.17 (overlapping t and d, 4H), 4.75 q, 1H), 6.77 (m, 2H), 7.07 (dd, 1H), 7.55 (t, 1H), 8.02 (m, 4H), 8.73 (d, 1H), 8.85 (d, 1H), 9.25 (s, 1H). MS [EI+] m/z 544 (M+H).

The following Examples 339 to 367 are prepared by following a substantially similar procedure as described in Example 338

Example 339

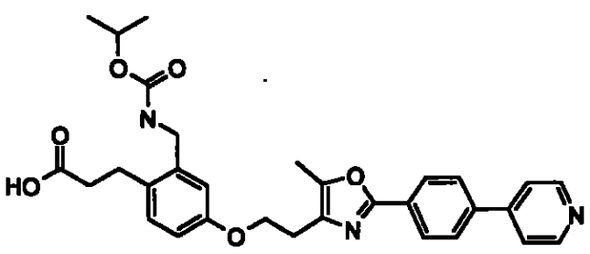
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(4-pyridin-3-ylphenyl)oxazol-4-yl]ethoxy} phenyl) propionic acid



MS (ES) m/z 544 (M+1).

Example 340

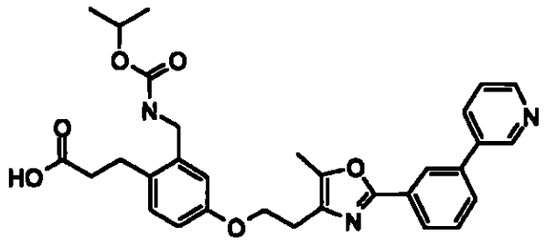
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(4-pyridin-4-yl-phenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 544 (M+1).

Example 341

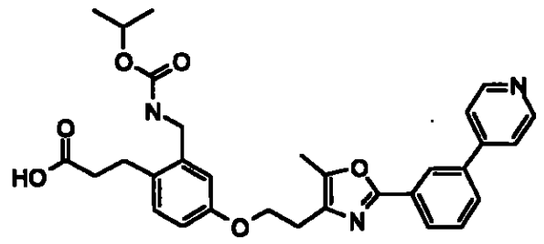
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(3-pyridin-3-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 544 (M+1).

Example 342

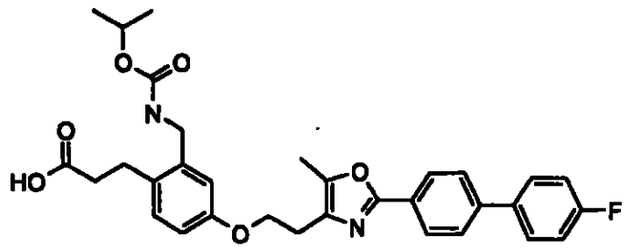
3-(2-(Isopropoxycarbonylaminmethyl)-4-{2-[5-methyl-2-(3-pyridin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 544 (M+1).

Example 343

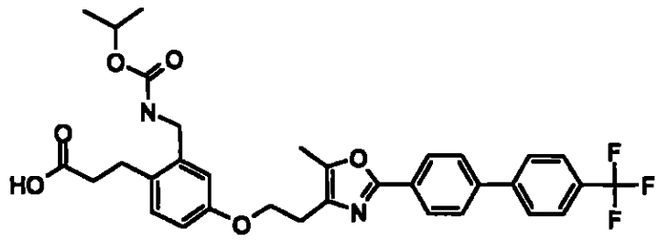
3-[4-{2-[2-(4'-Fluorobiphenyl-4-yl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 559 (M+1).

Example 344

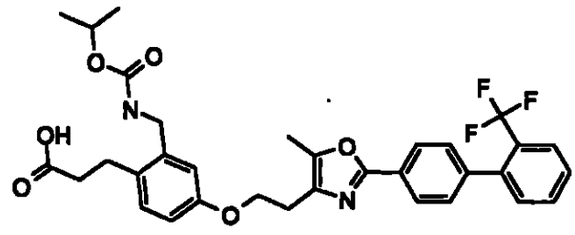
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(4'-trifluoromethylbiphenyl-4-yl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 609 (M+1).

Example 345

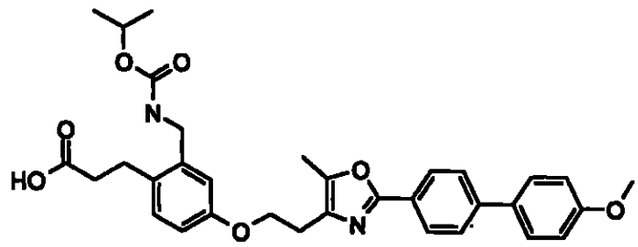
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(2'-trifluoromethylbiphenyl-4-yl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 609 (M+1).

Example 346

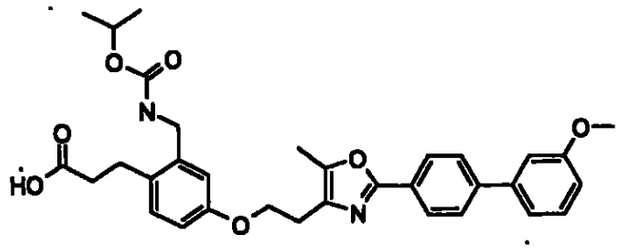
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[2-(4'-methoxybiphenyl-4-yl)-5-methyloxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 571 (M+1).

Example 347

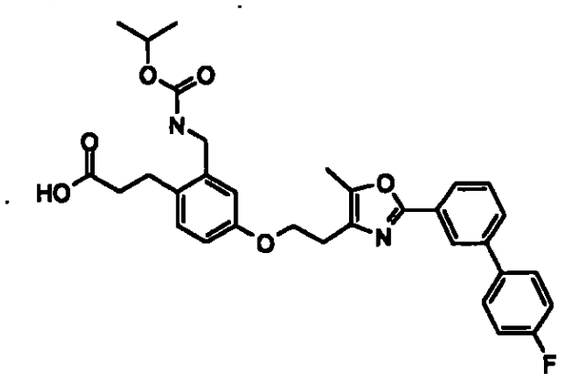
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[2-(3'-methoxybiphenyl-4-yl)-5-methyloxazol-4-yl]ethoxy}phenyl) propionic acid



^{1}H-NMR (DMSO-d6) δ 1.16 (d, 6H), 2.39 (s, 3H), 2.45 (t, 2H), 2.76 (t, 2H), 2.95 (t, 2H), 3.85 s, 3H), 4.17 (m, 4H), 4.77 (m, 1H), 6.74-7.55 (m, 7H, 7.83 (d, 2H), 7.99 (d, 2H).

Example 348

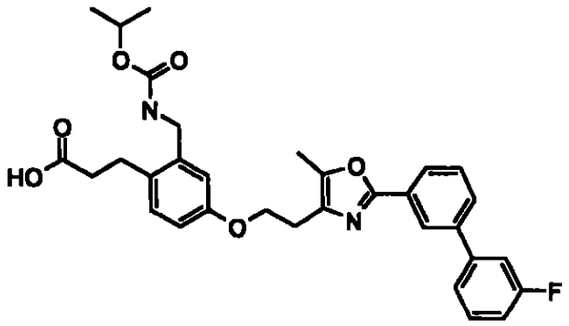
3-[4-{2-[2-(4'-Fluorobiphenyl-3-yl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 559 (M+1).

Example 349

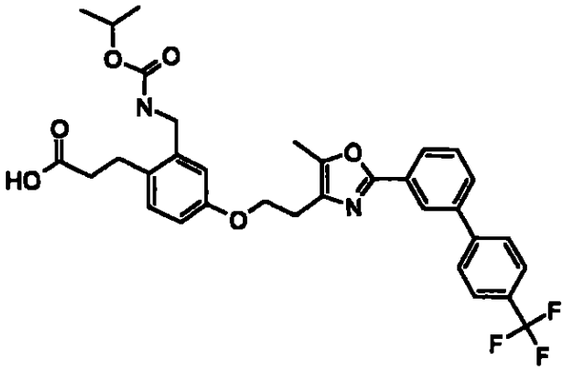
3-[4-{2-[2-(3'-Fluorobiphenyl-3-yl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 546 (M+1).

Example 350

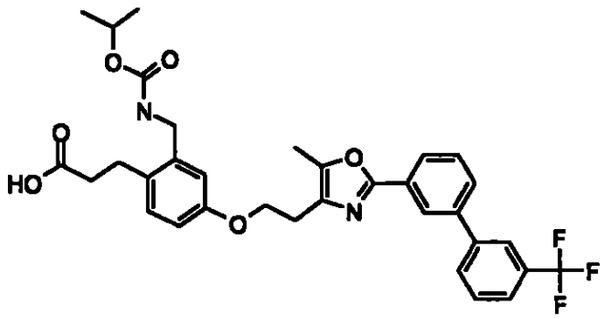
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(4'-trifluoromethylbiphenyl-3-yl)oxazol-4-yl]ethoxy}phenyl) propionic acid



^{1}H-NMR (DMSO-d6) δ 1.15 (d, 6H), 2.40 (s, 3H), 2.45 (t, 2H), 2.79 (t, 2H), 2.96 (t, 2H), 4.17 (m, 4H), 4.75 (m, 1H), 6.77 (m, 2H), 7.08 (d, 1H), 7.53 (m, 1H), 7.66 (m, 1H), 7.83-8.05 (m, 5H), 8.20 (s, 1H).

Example 351

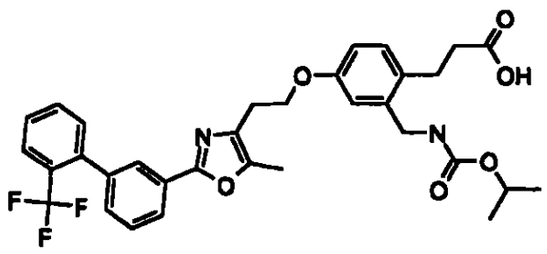
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(3'-trifluoromethylbiphenyl-3-yl)oxazol-4-yl]ethoxy}phenyl) propionic acid



^{1}H-NMR (DMSO-d6) δ 1.14 (d, 6H), 2.40 (s, 3H), 2.45 (t, 2H), 2.67 (t, 2H), 2.95 (t, 2H), 4.16 (m, 4H), 4.74 (m, 1H), 6.77 (m, 2H), 7.09 d, 1H), 7.47-8.20 (m, 8H).

Example 352

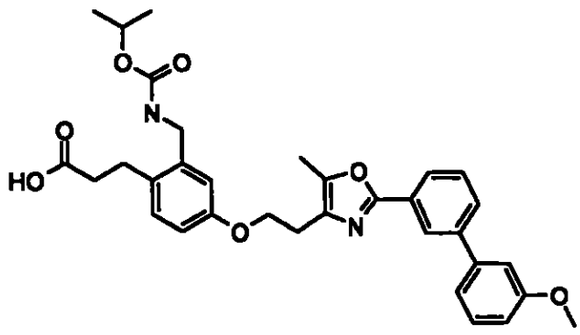
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(2'-trifluoromethylbiphenyl-3-yl)oxazol-4-yl]ethoxy}phenyl) propionic acid



^{1}H-NMR (DMSO-d6) δ 1.13 (d, 6H), 2.36 (s, 3H), 2.44 (t, 2H), 2.77 (t, 2H), 2.93 (t, 2H), 4.15 (m, 4H), 4.74 (m, 1H), 6.76 (m, 2H), 7.06 (d, 1H), 7.40-8.00 (m, 8H).

Example 353

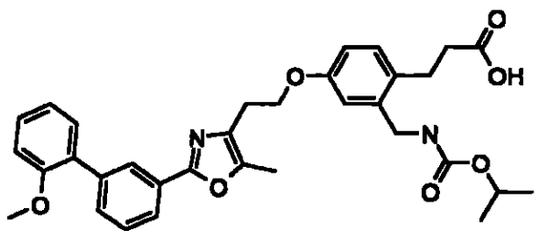
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[2-(3'-methoxybiphenyl-3-yl)-5-methyloxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 573 (M+1).

Example 354

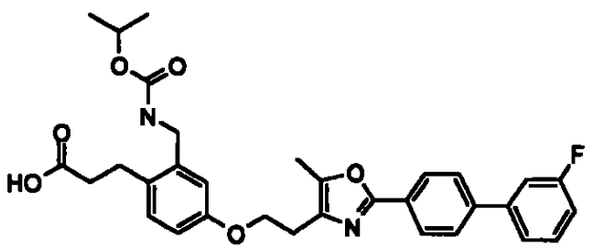
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[2-(2'-methoxybiphenyl-3-yl)-5-methyloxazol-4-yl]ethoxy}phenyl) propionic acid



^{1}H-NMR (DMSO-d6) δ 1.13 (d, 6H), 2.40 (s, 2H), 2.45 (t, 2H), 2.78 (t, 2H), 2.93 (t, 2H), 3.80 (s, 3H), 4.16 (m, 4H), 4.75 (m, 1H), 6.76 (m, 2H), 7.07 (m, 2H), 7.16 (d, 1H), 7.32-8.05 (m, 6H).

Example 355

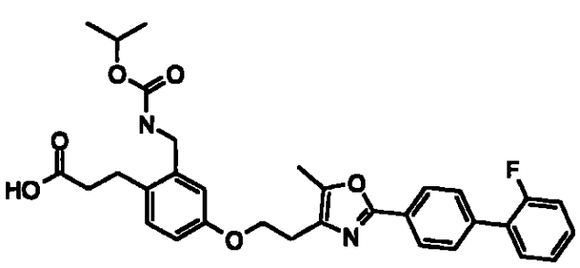
3-[4-{2-[2-(3'-Fluorobiphenyl-4-yl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 559 (M+1).

Example 356

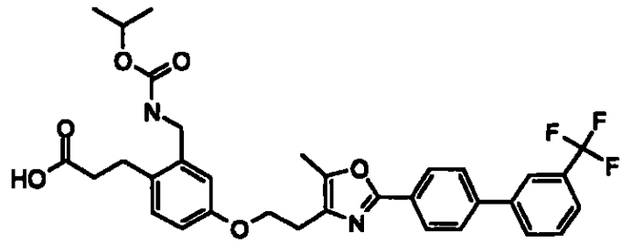
3-[4-{2-[2-(2'-Fluoro-biphenyl-4-yl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylaminomethyl)-phenyl]-propionic acid



^{1}H-NMR (CDCl3) δ 1.25 (d, 6H), 2.41 (s, 3H), 2.65 (t, 2H), 2.95 (t, 2H), 3.01 (t, 2H), 4.24 (t, 2H), 4.38 (br d, 2H), 4.96 (m, 1H), 5.03 (br s, 1H), 6.78 (dd, 1H), 6.84 (d, 1H), 7.19-7.55 (m, 6H), 7.65 (dd, 2H), 8.06 dd, 2H).

Example 357

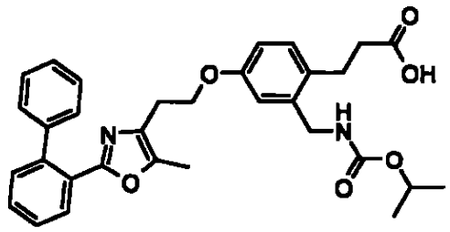
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(3'-trifluoromethylbiphenyl-4-yl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 561 (M+1).

Example 358

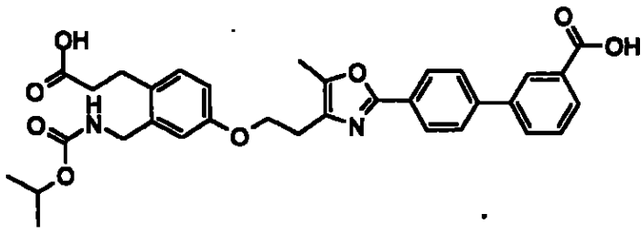
3-[4-[2-(2-Biphenyl-2-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 543.2 $(M+1)^+$.

Example 359

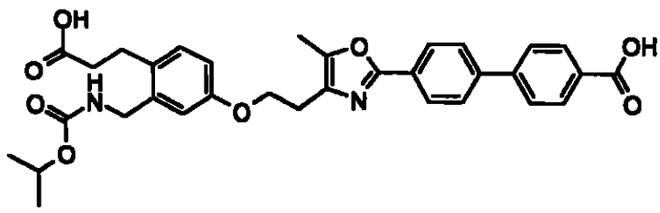
4'-(4-{2-[4-(2-Carboxy-ethyl)-3-(isopropoxycarbonylamino-methyl)-phenoxy]-ethyl}-5-methyl-oxazol-2-yl)-biphenyl-3-carboxylic acid



The above compound is prepared after an additional hydrolysis step using Standard procedure E. MS (ES) m/z 587.3 $(M+1)^+$.

Example 360

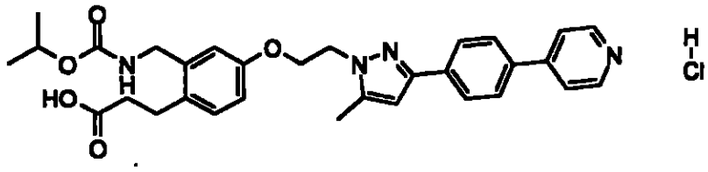
4'-(4-{2-[4-(2-Carboxy-ethyl)-3-(isopropoxycarbonylamino-methyl)-phenoxy]-ethyl}-5-methyl-oxazol-2-yl)-biphenyl-4-carboxylic acid



The above compound is prepared after an additional hydrolysis step using Standard procedure E. MS (ES) m/z 587.2 $(M+1)^+$.

Example 361

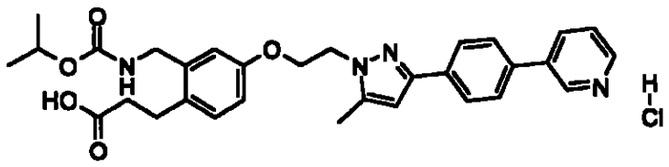
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-3-(4-pyridin-4-yl-phenyl)-pyrazol-1-yl]-ethoxy}-phenyl)-propionic acid hydrochloride



HRMS Calculated for $C_{31}H_{35}N_4O_5$: m/z 543.2607. Found: 543.2614.

Example 362

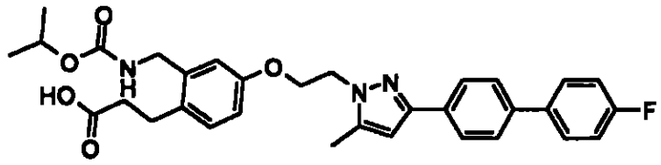
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-3-(4-pyridin-3-yl-phenyl)-pyrazol-1-yl]-ethoxy}-phenyl)-propionic acid hydrochloride



HRMS Calculated for $C_{31}H_{35}N_4O_5$: m/z 543.2607. Found: 543.2612.

Example 363

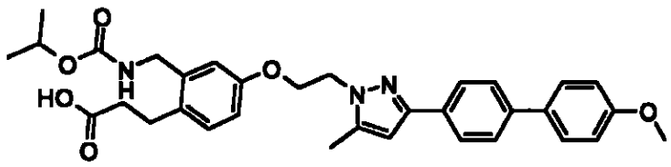
3-[4-{2-[3-(4'-Fluoro-biphenyl-4-yl)-5-methyl-pyrazol-1-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



HRMS Calculated for $C_{28}H_{35}FN_3O_5$: m/z 560.2561. Found: 560.2575.

Example 364

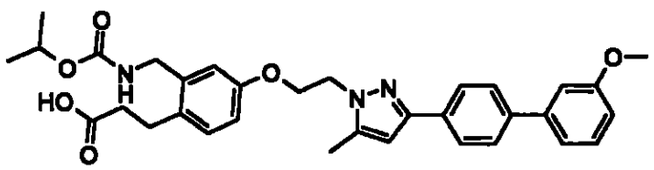
3-[4-{2-[3-(4'-Methoxy-biphenyl-4-yl)-5-methyl-pyrazol-1-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



HRMS Calculated for $C_{33}H_{38}N_3O_6$: m/z 572.2761. Found: 572.2752.

Example 365

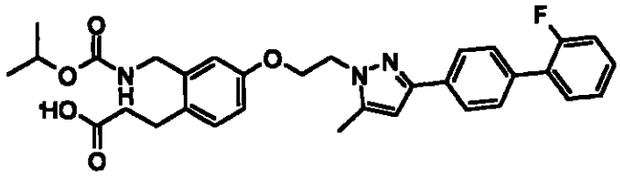
3-[4-{2-[3-(3'-Methoxy-biphenyl-4-yl)-5-methyl-pyrazol-1-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



HRMS Calculated for $C_{33}H_{38}N_3O_6$: m/z 572.2761. Found: 572.2776.

Example 366

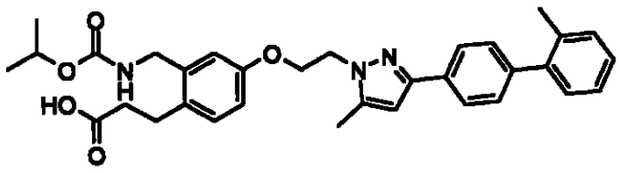
3-[4-{2-[3-(2'-Fluoro-biphenyl-4-yl)-5-methyl-pyrazol-1-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



HRMS Calculated for $C_{32}H_{35}FN_4O_5$: m/z 560.2561. Found: 560.2540.

Example 367

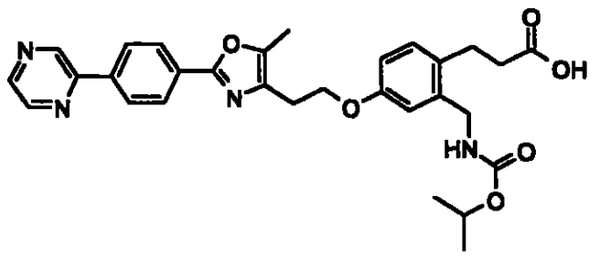
3-[4-{2-[3-(2'-Methyl-biphenyl-4-yl)-5-methyl-pyrazol-1-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



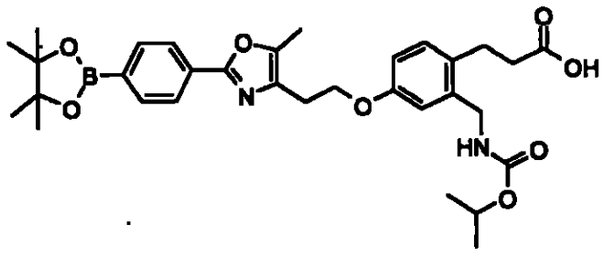
HRMS Calculated for $C_{33}H_{38}N_3O_5$: m/z 556.2811. Found: 556.2802.

Example 368

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



Step A: 3-[2-(Isopropoxycarbonylamino-methyl)-4-(2-{5-methyl-2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid



A solution of 3-[4-{2-[2-(4-bromo-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (4.00 g, 6.65 mmol) in DMSO (50 mL) was treated with bis(pinacolato)diborane (2.20 g, 8.64 mmol) and potassium acetate (1.96 g, 19.95 mmol). The solution was sparged with nitrogen for 10min, $Pd(dppf)Cl_2$ (980 mg, 1.20 mmol; 1:1 complex with CH_2Cl_2) was added, and the reaction mixture was heated at 80 °C for 4 h. The mixture was partitioned between water and ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (9:1 hexanes:ethyl acetate) yielded the title compound as a yellow oil (2.81 g). ^1H NMR (300MHz $CDCl_3$) δ 1.25 (d, 6H), 1.26 (s, 9H), 1.37 (s, 12H), 2.40 (s, 3H), 2.51 (t, 2H), 2.88 (t, 2H), 2.98 (t, 2H), 4.26 (t, 2H), 4.35 (d, 2H), 4.97 (br m, 2H), 6.77 (dd, 1H), 6.85 (d, 1H), 7.10 (d, 1H), 7.87 (d, 2H), 7.99 (d, 2H). MS [EI+] 649 (M+H).

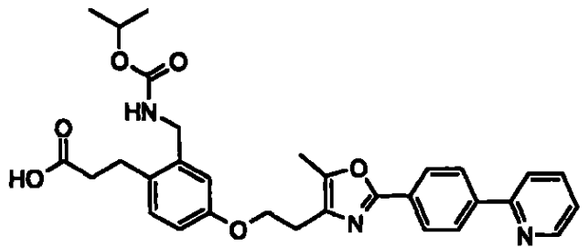
Step B: 3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-pyrazin-2-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid

Suzuki coupling using haloaryl compounds: 3-[2-(Isopropoxycarbonylamino-methyl)-4-(2-{5-methyl-2-[4-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-phenyl]-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid (500 g, 0.771 mmol), CsF (258 g, 1.69 mmol), $PdCl_2$(dppf) (0.057 g, 0.07 mmol), and 2-chloropyrazine (.0971g, 0.85 mmol) were added to a 3-neck flask and were dissolved in anhydrous dioxane (25 mL). The reaction mixture was stirred at 100°C under a stream of N_2 for about 12 h. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with saturated NaCl (100 mL) and water (100 mL). The organic layer was filtered through Celite, dried (Na_2SO_4), filtered, and concentrated. The crude product (1.2 g) was purified by radial chromatography (10-70% EtOAc/hexanes) to give the intermediate ester (0.312g): MS (ES) m/z 601 $(M+H)^+$. The ester was dissolved in of 4M HCl/dioxane (10 mL). The mixture was stirred N_2 for 16 h and concentrated to give the title compound (305 mg, 72%): MS (ES) m/z 545 $(M+H)^+$. Anal. Calculated for C 66.16%, H 5.92%, N 10.29%. Found C 65.97%, H 6.07%, N 10.45%.

The following Examples 369 to 382 are prepared by following a substantially similar procedure as described in Example 368.

Example 369

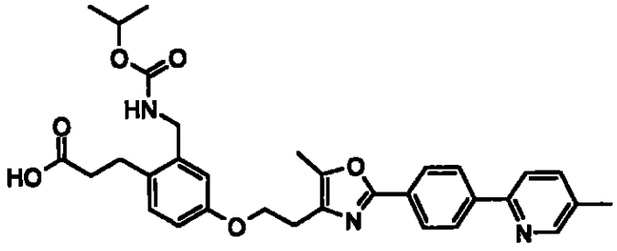
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(4-pyridin-2-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 544 (M+1).

Example 370

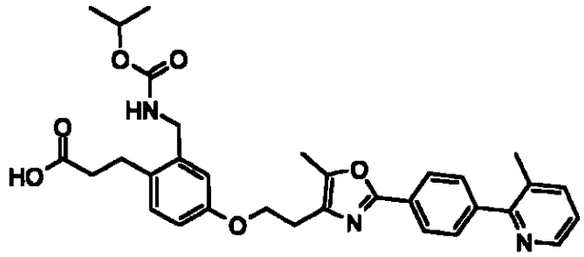
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(5-methylpyridin-2-yl)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 558 (M+1).

Example 371

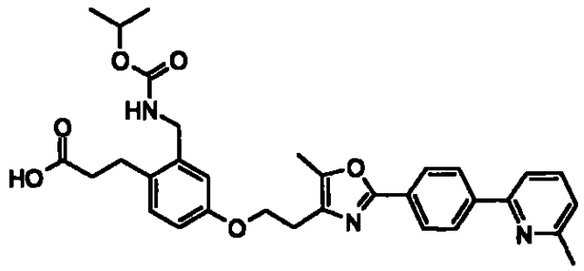
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(3-methylpyridin-2-yl)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 558 (M+1).

Example 372

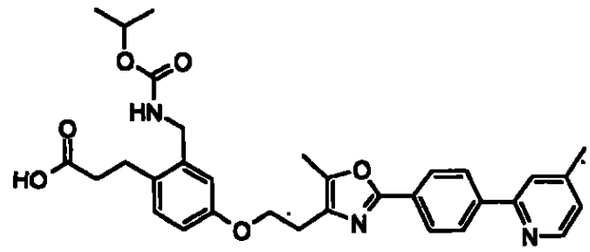
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(6-methylpyridin-2-yl)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 492 (M+1).

Example 373

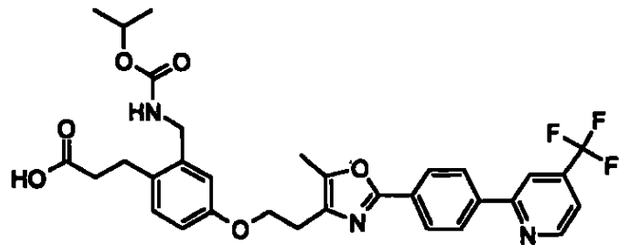
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(4-methylpyridin-2-yl)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 558 (M+1).

Example 374

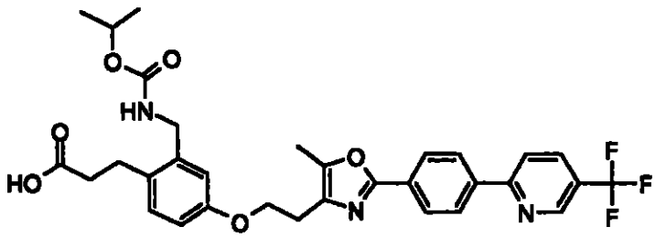
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(4-trifluoromethylpyridin-2-yl)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 612 (M+1).

Example 375

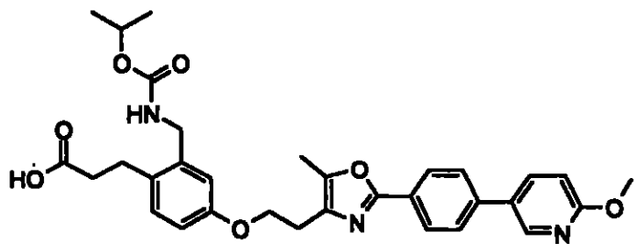
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(5-trifluoromethylpyridin-2-yl)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 612 (M+1).

Example 376

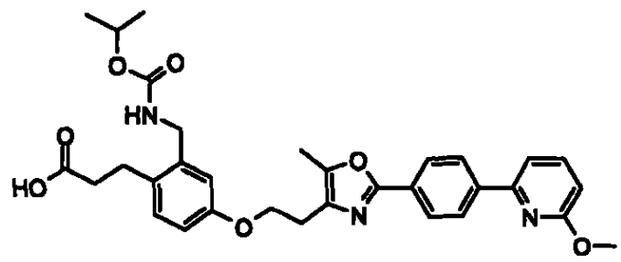
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{2-[4-(6-methoxypyridin-3-yl)phenyl]-5-methyloxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 574 (M+1).

Example 377

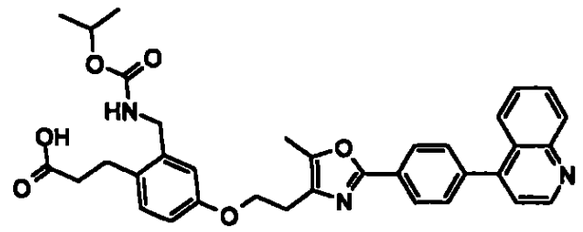
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{2-[4-(6-methoxypyridin-2-yl)phenyl]-5-methyloxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 574 (M+1).

Example 378

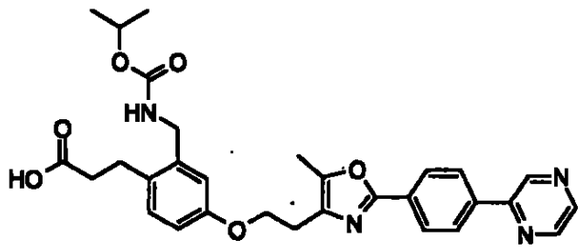
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(4-quinolin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 594 (M+1).

Example 379

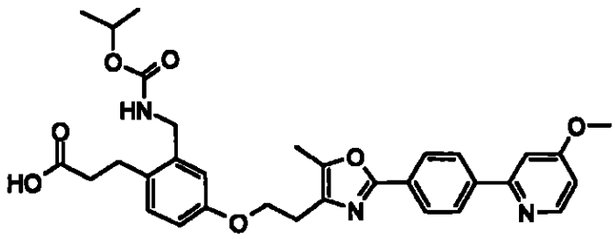
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(4-pyrazin-2-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 545 (M+1).

Example 380

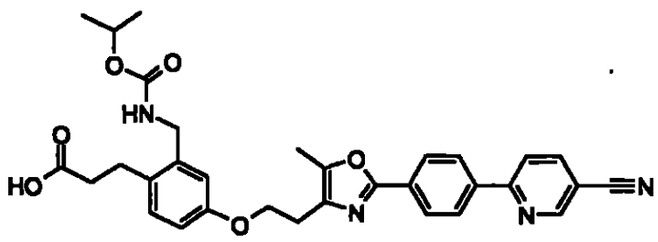
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{2-[4-(4-methoxypyridin-2-yl)phenyl]-5-methyloxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 574 (M+1).

Example 381

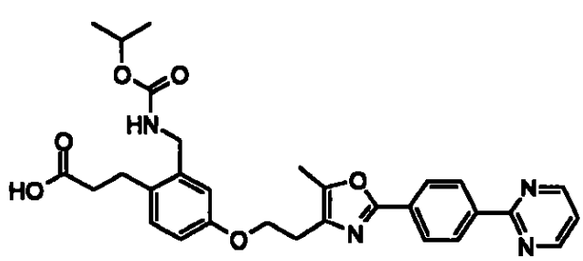
3-[4-(2-{2-[4-(5-Cyanopyridin-2-yl)phenyl]-5-methyloxazol-4-yl}ethoxy)-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 569 (M+1).

Example 382

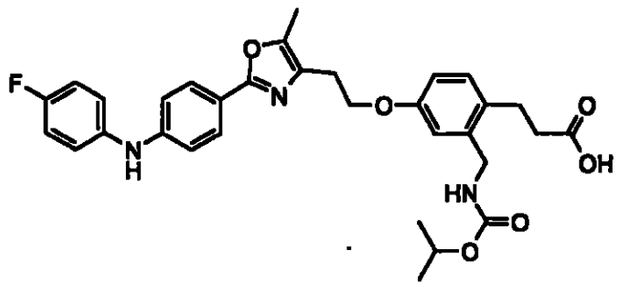
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-pyrimidin-2-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid:



MS (ES) m/z 545 $(M+H)^+$. Anal. Calculated for C 66.16%, H 5.92%, N 10.29%, Found C 65.87%, H 6.17%, N 10.53%.

Example 383

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

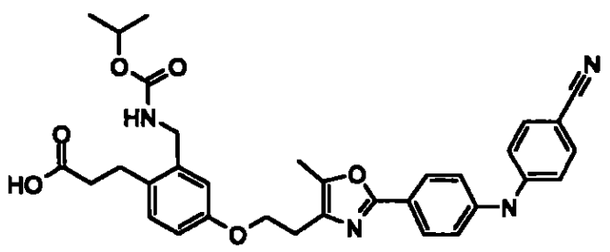


3-[4-{2-[2-(4-bromo-phenyl)-5-methoxy-oxazol-4-yl]-ethoxy}-2-(isopropoxy-carbonylamino-methyl)-propionic acid tert-butyl ester (0.10 g, 0.17 mmol) was dissolved in DME (5 mL) in a sealed tube apparatus. N_2 was bubbled through the solution, and 4-fluoroaniline (24 mg, 0.20 mmol), 2-(di-t-butylphosphino)-biphenyl (20 mg), $Pd_2(dba)_3$ (10 mg), and K_3PO_4 (50 mg, 0.24 mmol) were added. The tube was sealed and heated at 100 °C for 16 h. The reaction mixture was cooled, diluted with EtOAc, and washed with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified using silica gel chromatography (hexanes/EtOAc 2/1 to 1/1). Using the Standard hydrolysis procedure C, this material was converted into the title compound as an oil (25 mg): MS (ESI) m/z 594 $(M+H)^+$.

The following Examples 384 to 387 are prepared by following a substantially similar procedure as described in Example 383.

Example 384

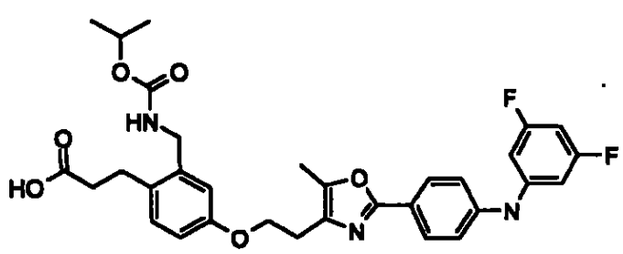
3-[4-(2-{2-[4-(4-Cyano-phenylamino)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 583 (M+1).

Example 385

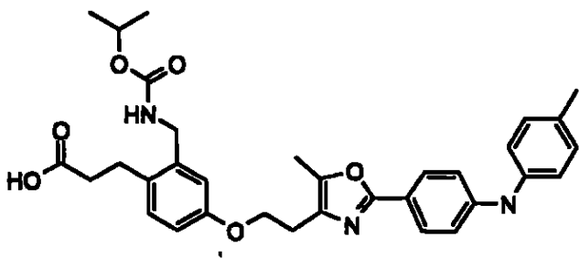
3-[4-(2-{2-[4-(3,5-Difluoro-phenylamino)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 594 (M+1).

Example 386

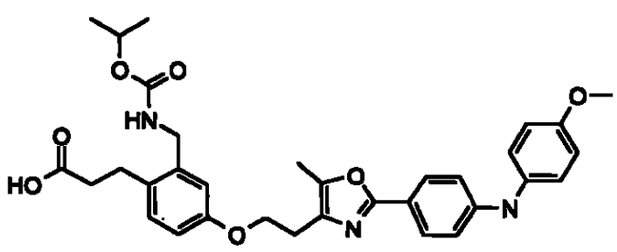
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-p-tolylamino-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ES) m/z 572 (M+1).

Example 387

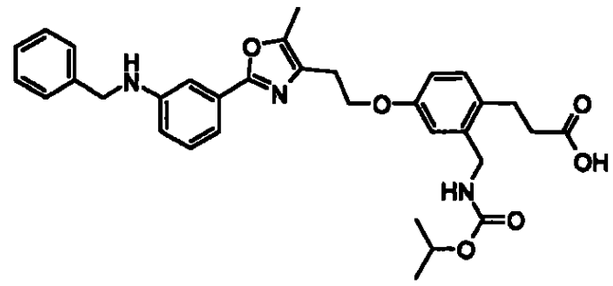
3-[2-(Isopropoxycarbonylamino-methyl)-4-(2-{2-[4-(4-methoxy-phenylamino)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid



MS (ES) m/z 588 (M+1).

Example 390

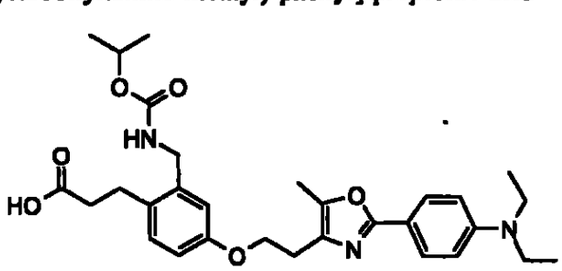
3[4-(2-{2-[3-Benzylamino-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



3-[4-{2-[2-(3-bromo-phenyl)-5-methoxy-oxazol-4-yl]-ethoxy}-2-(isopropoxy-carbonylamino-methyl)-propionic acid tert-butyl ester (0.10 g, 0.17 mmol) was dissolved in toluene (5 mL) in a sealed tube apparatus. N_2 was bubbled through the solution, and benzylamine (46 µL, 0.42 mmol), 2-(dicyclohexylphosphino)-biphenyl (12 mg), $Pd_2(dba)_3$ (16 mg) and t-BuONa (23 mg, 0.24 mmol) were added. The tube was sealed and heated at 100 °C for 16 h. The reaction mixture was cooled, diluted with EtOAc, and washed with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified using silica gel chromatography (hexanes/EtOAc 2/1 to 1/1). Using the Standard hydrolysis procedure C, this material was converted into the corresponding carboxylic acid; the title compound was isolated as the HCl salt by treatment with 1M HCl in ether (15 mg). MS (ES) m/z 572 $(M+H)^+$.

Example 391

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

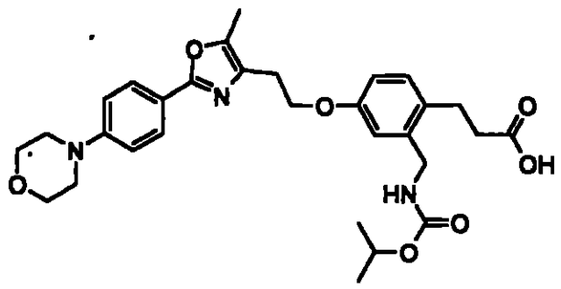


The above compound is prepared by following a substantially similar procedure as described in Example 390 except that the reaction is carried out in DME at 80°C.

MS (ES) m/z 538.2 $(M+H)^+$.

Example 392

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

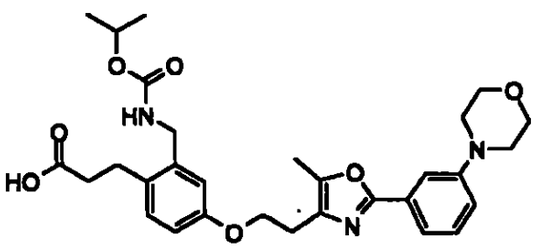


A solution of 3-[4-{2-[2-(4-bromo-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (60 mg, 0.100 mmol) in toluene (3.0 mL) in a sealed tube apparatus under a flow of N_2 was treated with $Pd(OAc)_2$ (5 mg) , 2-(di-t-butylphosphino)biphenyl (10 mg), morpholine (17 mg, 0.20 mmol), and sodium t-butoxide (19 mg, 0.200 mmol). The tube was sealed and heated at 105 °C for 14 h. The mixture was cooled and purified directly using silica gel chromatography (30-50% EtOAc/hexanes) to yield the intermediate ester. A solution of ester in TFA (1.0 ml)/CH_2Cl_2 (1.5 ml)/H_2O (0.1 mL) and stirred 14 h and concentrated. The residue was and purified using silica gel chromatography (hexanes/EtOAc/HOAc, 5/5/0.02) to afford the title compound (36 mg, 65%): MS (ESI) m/z 552.3 $(M+H)^+$.

The following Examples 393 to 395 are prepared by following a substantially similar procedure as described in Example 392.

Example 393

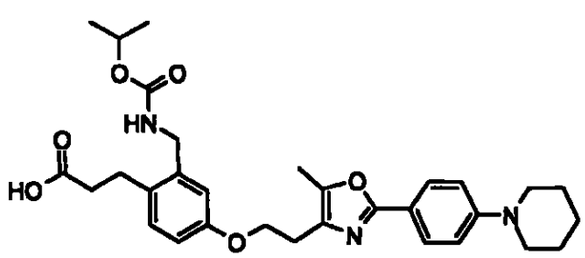
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(3-morpholin-4-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ESI) m/z 552.2 $(M+H)^+$.

Example 394

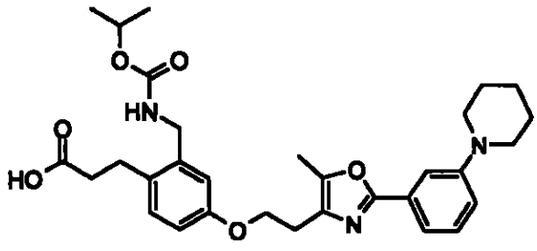
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-piperidin-1-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ESI) m/z 550.3 $(M+H)^+$.

Example 395

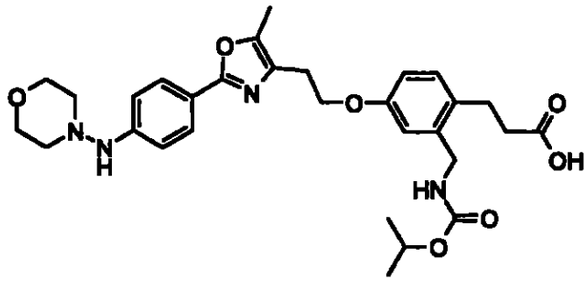
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(3-piperidin-1-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ESI) m/z 550.3 $(M+H)^+$.

Example 396

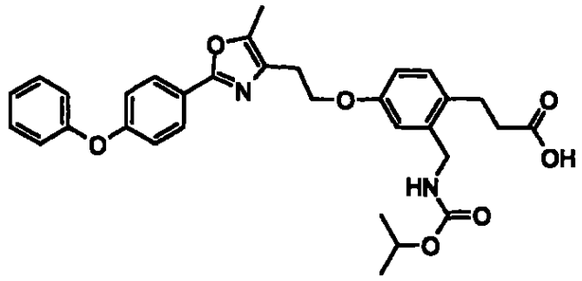
3-[2-(Isopropoxycarbonylamino-methyl)-4-(2-{5-methyl-2-[4-(morpholin-4-ylamino)-phenyl]-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid



A solution of 3-[4-{2-[2-(4-bromo-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (120 mg, 0.200 mmol) in toluene (2.0 mL) in a sealed tube under a flow of N_2 was treated $Pd_2(dba)_3$ (10 mg), 2-(di-t-butylphosphino)biphenyl (10 mg), N-aminomorpholine (29 mg, 0.28 mmol), and sodium t-butoxide (38 mg, 0.40 mmol). The tube was sealed and heated at 100 °C for 60 min. The mixture was cooled and purified using silica gel chromatography (5-10% MeOH/EtOAc) to yield the title compound directly (22 mg, 21%): MS (ESI) m/z 567.3 $(M+H)^+$.

Example 397

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



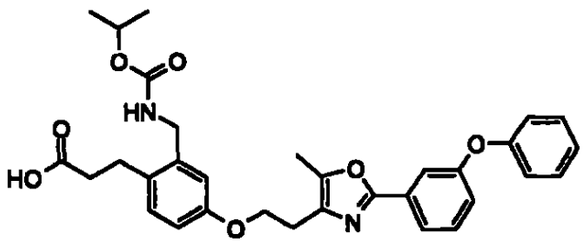
A mixture of 3-[4-{2-[2-(4-bromo-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl] -propionic acid tert-butyl ester (0.44 mmol, 0.24 g), phenol (0.53 mmol, 0.050 g), K_3PO_4 (0.88 mmol, 0.19g), 2-(di-t-butylphosphino)biphenyl (0.066 mmol, 0.020g), and $Pd(OAc)_2$ (0.044 mmol, 0.010g) in toluene (7 mL) was degassed under vacuum and backfilled with nitrogen (3x) and heated at 110 °C for 18 h. Additional $Pd(OAc)_2$ (10 mg) and 2-(di-t-butylphosphino)biphenyl (20 mg) were added to ensure complete reaction, and the mixture was heated 5 h. Upon cooling, the mixture was placed directly onto a silica gel column and eluted with 30%-50% EtOAc/hexanes to give 3-(2-(isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-phenoxy-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid tert-butyl ester (0.11 g).

The tert-butyl ester (0.18 mmol, 0.11g) was dissolved in CH_2Cl_2 (3 mL), and 90% TFA/water (5 mL) was added. The mixture was stirred for 3 h and concentrated. The residue was purified by silica gel chromatography (50% ethyl acetate/hexanes) to give an oil. Trituration with Et_2O gave the title compound as a white solid (90 mg, 90%): ^1H NMR (250 MHz, $CDCl_3$) δ 8.11 (d, 2H, J=8.8 Hz), 7.56 (t, 2H, J=7.9 Hz), 7.37-7.20 (m, 6H), 7.0-6.93 (m, 2H), 5.11 (heptet, 1H, J=6.3 Hz), 4.53 (d, 2H, J=5.1Hz), 4.38 (t, 2H, J=6.7 Hz), 3.12 (q, 4H, J=7.3 Hz), 2.80 (t, 2H, J=7.6 Hz), 2.54 (s, 3H), 1.41 (d, 6H, J=6.3 Hz).

The following Examples 398 to 405 are prepared by following a substantially similar procedure as described in Examples 396 and 397.

Example 398

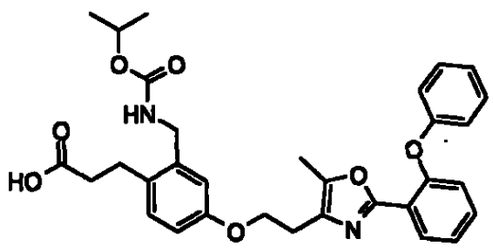
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(3-phenoxy-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ESI) m/z 559.2 $(M+H)^+$.

Example 399

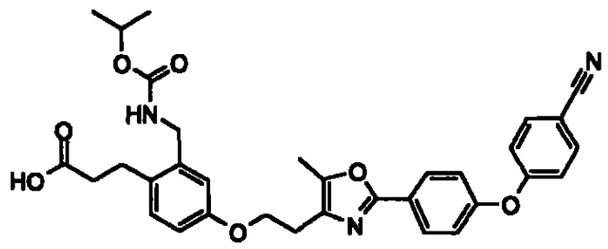
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(2-phenoxy-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ESI) 559 $(M+H)^+$. Anal Calculated for $C_{32}H_{34}N_2O_7$: C, 68.8; H, 6.1; N, 5.0. Found: C, 67.9; H, 6.2; N, 5.3.

Example 400

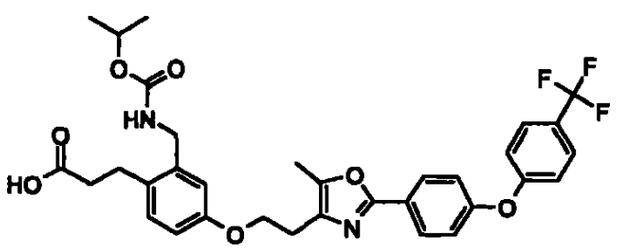
3-[4-(2-{2-[4-(4-Cyano-phenoxy)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 584.

Example 401

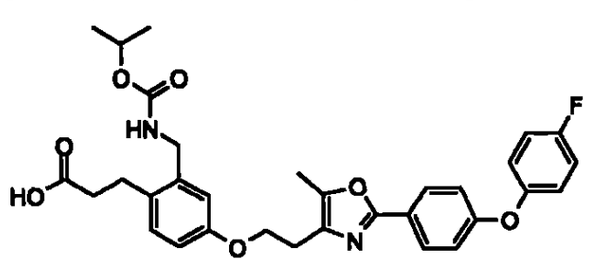
3-[2-(Isopropoxycarbonylamino-methyl)-4-(2-{5-methyl-2-[4-(4-trifluoromethyl-phenoxy)-phenyl]-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid



MS (ES) m/z 627 (M+1).

Example 402

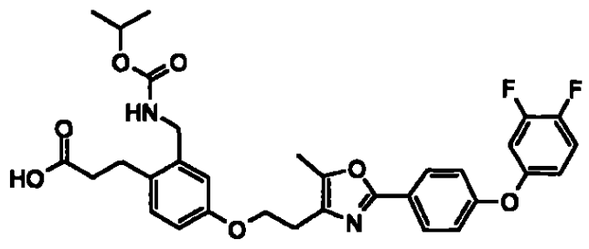
3-[4-(2-{2-[4-(4-Fluoro-phenoxy)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 577 (M+1).

Example 403

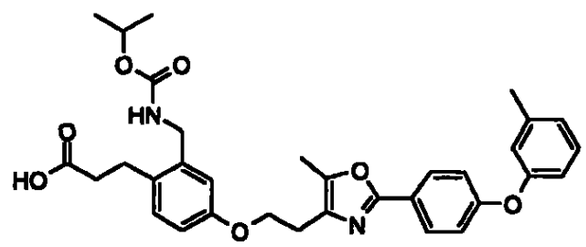
3-[4-(2-{2-[4-(3,4-Difluoro-phenoxy)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 595 (M+1).

Example 404

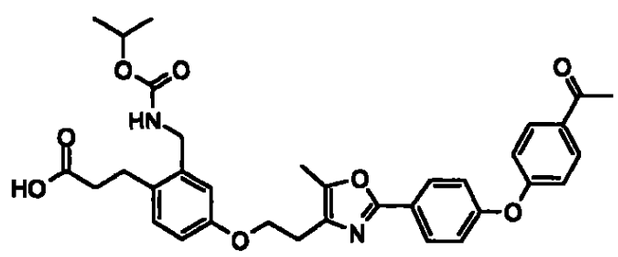
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-m-tolyloxy-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ES) m/z 573 (M+1).

Example 405

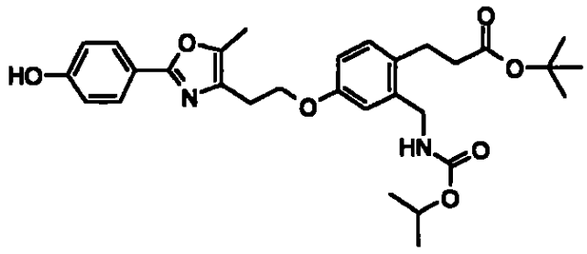
3-[4-(2-{2-[4-(4-Acetyl-phenoxy)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 601 (M+1).

Example 406

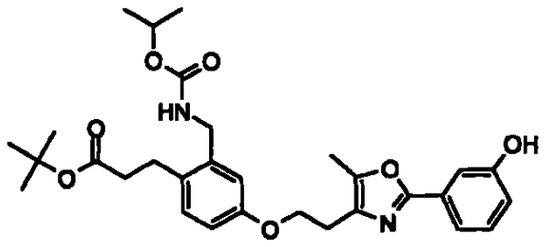
3-[4-{2-[2-(4-Hydroxy-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester



According to the procedure in *Organic Synthesis*, vol. V, p. 918, a solution of 3-[2-(isopropoxycarbonylamino-methyl)-4-(2-{5-methyl-2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid tert-butyl ester (1.4g, 2.16mmol, Example 368, Step A) in THF (8mL) was treated with glacial acetic acid (194mg, 3.24mmol) at 0°C. A solution of 30% H_2O_2 in water (4.75mL) was diluted with H_2O (1 mL) and added to the reaction mixture. The mixture was warmed to room temperature and treated with 1M aqueous $Na_2S_2O_3$ solution (50mL). The THF was removed under vacuum and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with 1M $Na_2S_2O_3$ (2 x 50mL), dried ($MgSO_4$), filtered, and concentrated to an oil containing (1.21 g). Purification using silica gel chromatography (1:1 ηεξανεσ:ετηψλ acetate) yielded the title compound as a white solid (1.10 g, 95%). ^{1}H NMR (300MHz $CDCl_3$) δ 1.15 (d, 6H), 1.19 (s, 9H), 2.26 (s, 3H), 2.39 (t, 2H), 2.75 (t, 2H), 2.85 (t, 2H), 4.10 (t, 2H), 4.28 (d, 2H), 4.85 (m, 1H), 5.01 (br d, 1H), 6.63 (dd, 1H), 6.74 (m, 3H), 6.96 (d, 1h), 7.70 (d, 2H); MS [EI+] m/z 539 (M+H).

Example 407

3-[4-{2-[2-(3-Hydroxy-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester:

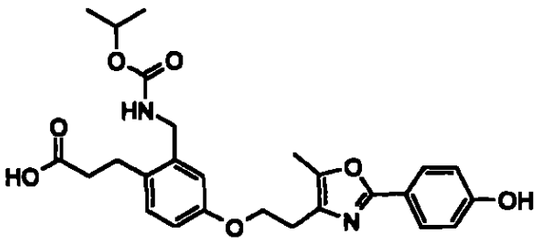


The above compound is prepared by following a substantially similar procedure as described in Example 406. MS [EI+] m/z 539 (M+H).

The following Examples 408 to 409 are prepared by following a substantially similar procedure as described in Example 406 and the corresponding carboxylic acids are obtained from Standard hydrolysis procedure C:

Example 408

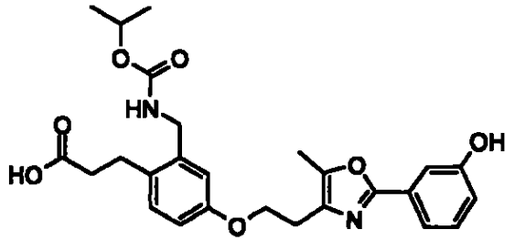
3-[4-{2-[2-(4-Hydroxyphenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 483 (M+1).

Example 409

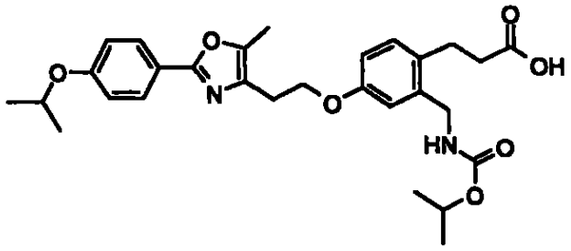
3-[4-{2-[2-(3-Hydroxyphenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid:



MS (ES) m/z 483 (M+1).

Example 410

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



A solution of 3-[4-{2-[2-(4-hydroxy-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (300mg, 0.557mmol, Example 406) in ethanol (20mL) was treated with 2-iodopropane (473mg, 2.78mmol) and K_2CO_3 (231mg, 1.67mmol) and was heated at reflux overnight. The reaction mixture was cooled and concentrated. The residue was diluted with H_2O and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield an oil. Purification using silica gel chromatography (3:1 hexane:ethyl acetate) yielded 3-(2-(isopropoxycarbonylamino-methyl)-4-{2-[2-(4-isopropoxy-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid tert-butyl ester as a yellow oil (210mg). ^1H NMR (300MHz $CDCl_3$) δ 1.28 (d, 6H), 1.40 (d, 6H), 1.45 (s, 9H), 2.38 (s, 3H), 2.53 (t, 2H), 2.91 (t, 2H), 2.99 (t, 2H), 4.25 (t, 2H), 4.39 (d,

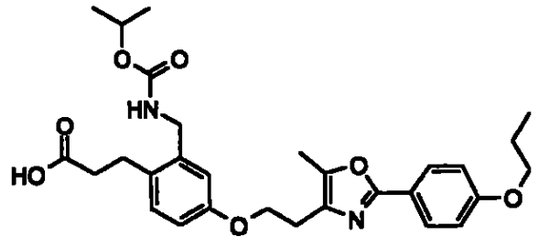
2H), 4.66 (m, 1H), 5.00 (br m, 2H), 6.80 (dd, 1H), 6.87 (d, 1H), 6.95 (d, 2H), 7.13 (d, 1H), 7.95 (d, 2H) MS [ES] 581 (M+H).

This ester was converted to the title compound according to Standard Procedure C; a white solid (134 mg). ^{1}H NMR (300MHz $CDCl_3$) δ 1.15 (d, 6H), 1.29 (d, 6H), 2.31 (s, 3H), 2.53 (t, 2H), 2.82 (t, 2H), 2.97 (t, 2H), 4.15 (t, 2H), 4.26 (d, 2H), 4.55 (m, 1H), 4.84 (m, 1H), 4.99 (br s, 1H), 6.68 (dd, 1H), 6.73 (d, 1H), 6.87 (d, 2H), 7.00 (d, 1H), 7.90 (d, 2H) MS [ES] m/z 525 (M+H).

The following Examples 411 to 422 are prepared by following a substantially similar procedure as described in Example 410.

Example 411

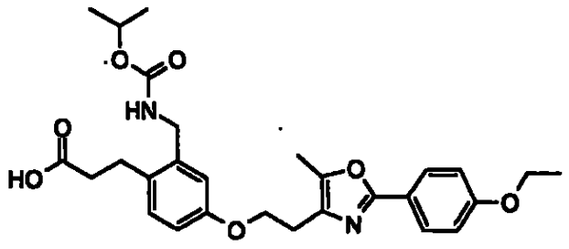
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(4-propoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 525 (M+1).

Example 412

3-[4-{2-[2-(4-Ethoxyphenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 511 (M+1).

Example 413

3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[2-(4-methoxyphenyl)-5-methyoxazol-4-yl]ethoxy}phenyl) propionic acid

MS (ES) m/z 497 (M+1).

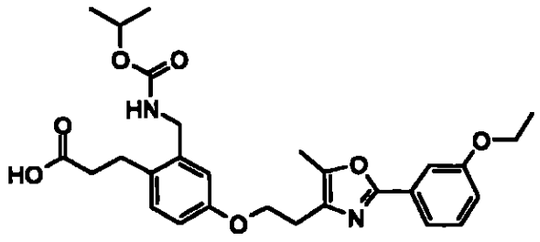
Example 414

3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[2-(3-methoxyphenyl)-5-methyoxazol-4-yl]ethoxy}phenyl) propionic acid

MS (ES) m/z 497 (M+1)

Example 415

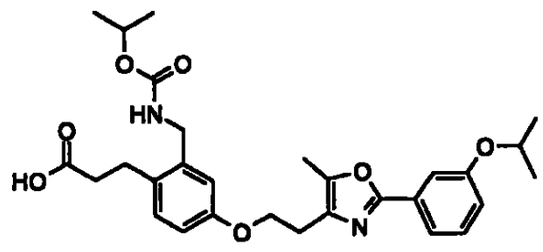
3-[4-{2-[2-(3-Ethoxyphenyl)-5-methyloxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 511 (M+1).

Example 416

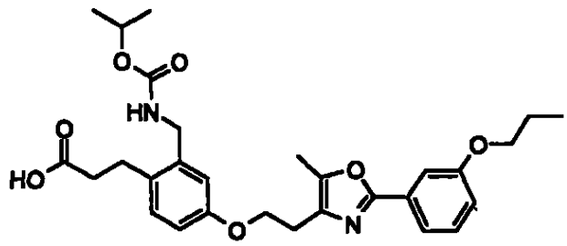
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[2-(3-isopropoxyphenyl)-5-methyloxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 525 (M+1).

Example 417

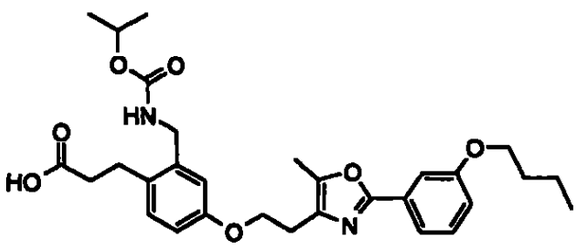
3-(2-(Isopropoxycarbonylaminomethyl)-4-{2-[5-methyl-2-(3-propoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 525 (M+1).

Example 418

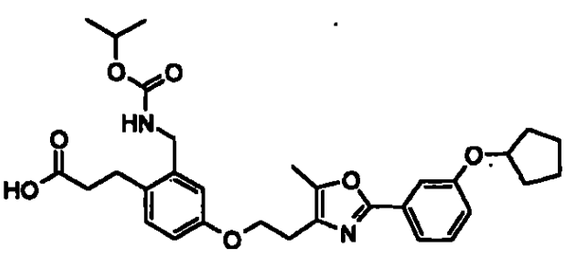
3-[4-{2-[2-(3-Butoxyphenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 539 (M+1).

Example 419

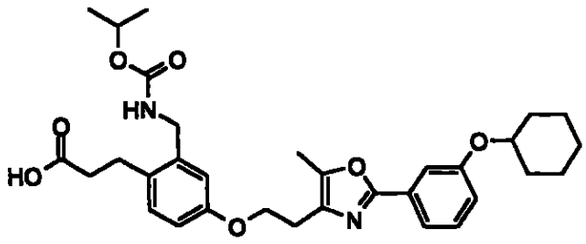
3-[4-{2-[2-(3-Cyclopentyloxyphenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 551 (M+1).

Example 420

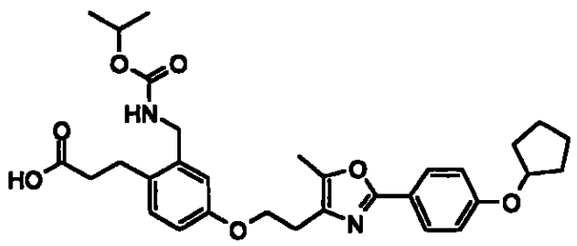
3-[4-{2-[2-(3-Cyclohexyloxyphenyl)-5-methyloxazol-4-yl] ethoxy}-2-(isopropoxycarbonylaminomethyl)-phenyl] propionic acid



MS (ES) m/z 565 (M+1).

Example 421

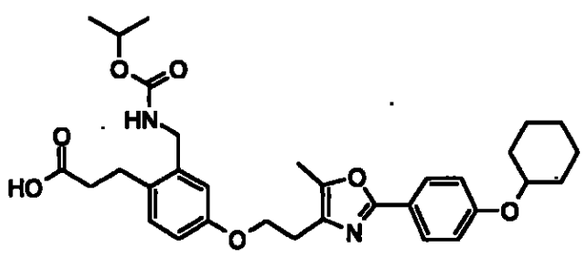
3-[4-{2-[2-(4-Cyclopentyloxyphenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 551 (M+1).

Example 422

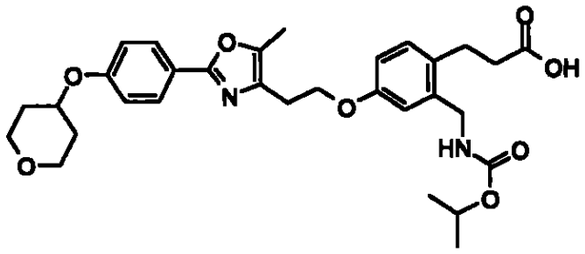
3-[4-{2-[2-(4-Cyclohexyloxyphenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 565 (M+1).

Example 423

3-[2-(Isopropoxycarbonylamino-methyl)-4-(2-{5-methyl-2-[4-(tetrahydro-pyran-4-yloxy)-phenyl]-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid

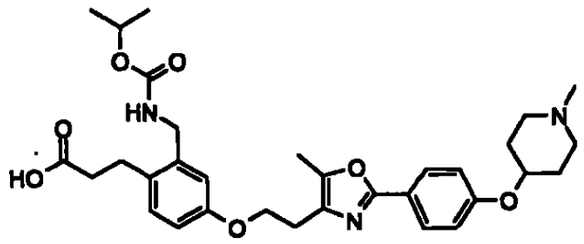


A mixture of 3-[4-{2-[2-(4-hydroxy-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (120 mg, 0.223 mmol, Example 406), tetrahydro-pyran-4-ol (22.7 mg, 0.223 mmol), triphenylphosphine (58.4 mg, 0.223 mmol) and toluene (10 mL) was treated dropwise with DIAD (45 mg, 0.223 mmol). The mixture was stirred under N_2 at ambient temperature for 16 h and concentrated. The crude product was purified by radial chromatography (10-70% EtOAc/hexanes) to give 3-[2-(isopropoxycarbonylamino-methyl)-4-(2-{5-methyl-2-[4-(tetrahydro-pyran-4-yloxy)-phenyl]-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid tert-butyl ester. The ester product was dissolved 4M HCl/dioxane (5 mL), stirred for 16 h and concentrated to give the title compound: MS [ES] m/z 525 (M+H).

The following Examples 424 to 431 are prepared by following a substantially similar procedure as described in Example 423.

Example 424

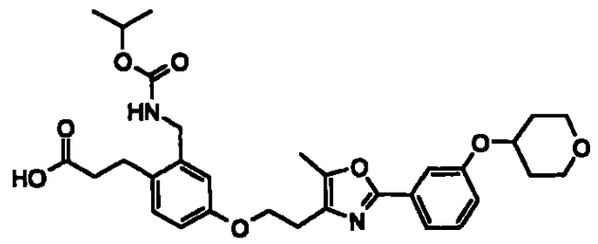
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(1-methylpiperidin-4-yloxy)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 580 (M+1).

Example 425

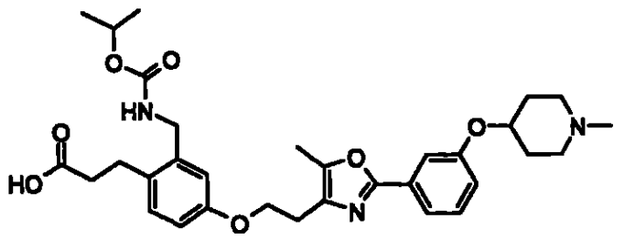
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[3-(tetrahydropyran-4-yloxy)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 567 (M+1).

Example 426

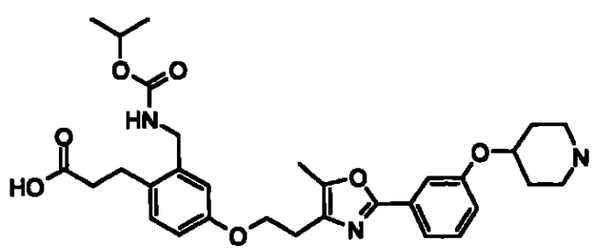
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[3-(1-methylpiperidin-4-yloxy)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 580 (M+1).

Example 427

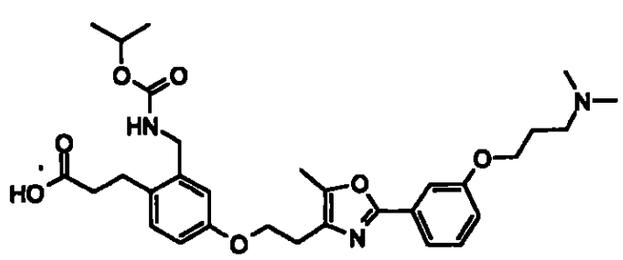
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[3-(piperidin-4-yloxy)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 566 (M+1).

Example 428

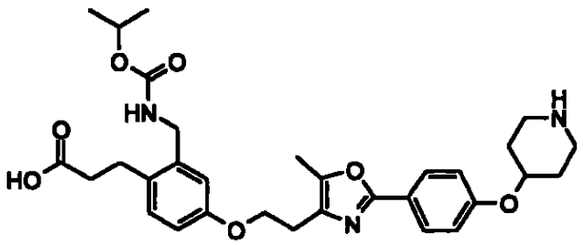
3-[4-(2-{2-[3-(3-Dimethylaminopropoxy)phenyl]-5-methyloxazol-4-yl}ethoxy)-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 568 (M+1).

Example 429

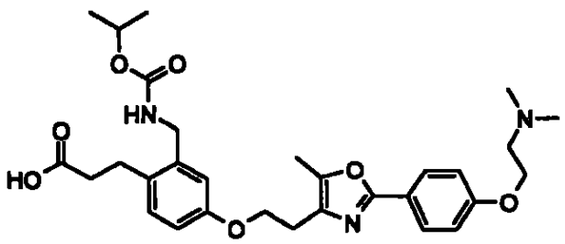
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(piperidin-4-yloxy)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 566 (M+1).

Example 430

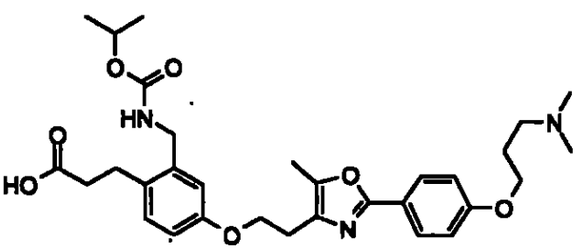
3-[4-(2-{2-[4-(2-Dimethylaminoethoxy)phenyl]-5-methyloxazol-4-yl}ethoxy)-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 554 (M+1).

Example 431

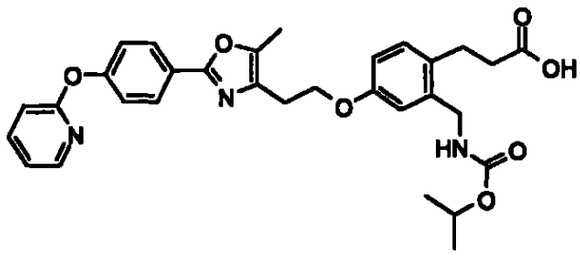
3-[4-(2-{2-[4-(3-Dimethylaminopropoxy)phenyl]-5-methyloxazol-4-yl}ethoxy)-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid



MS (ES) m/z 568 (M+1).

Example 432

3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(pyridin-2-yloxy)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid

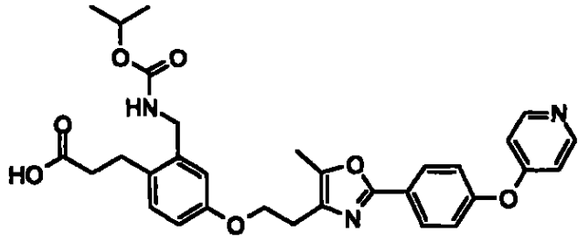


3-[4-{2-[2-(4-hydroxy-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxy-carbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (Example 406) was reacted with 2-bromopyridine by the procedure in Example 397 to give the title compound. MS (ES) m/z 560 (M+1).

The following Examples 433 to 435 are prepared by following a substantially similar procedure as described in Example 432.

Example 433

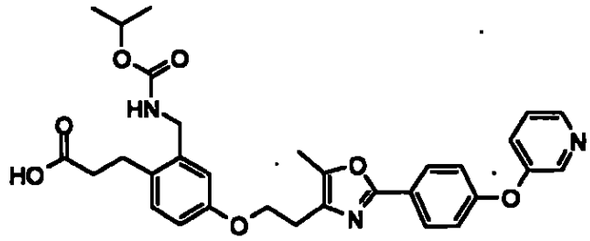
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(pyridin-4-yloxy)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 560 (M+1).

Example 434

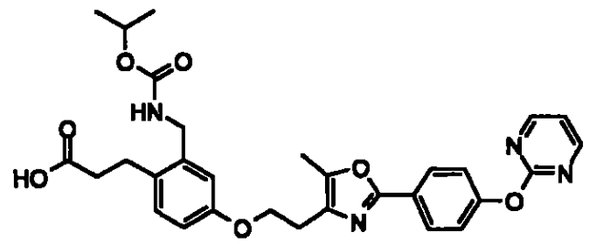
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(pyridin-3-yloxy)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



MS (ES) m/z 560 (M+1).

Example 435

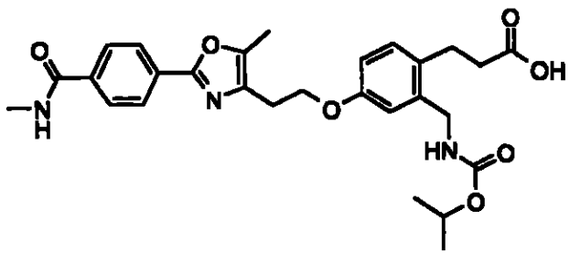
3-[2-(Isopropoxycarbonylaminomethyl)-4-(2-{5-methyl-2-[4-(pyrimidin-2-yloxy)phenyl]oxazol-4-yl}ethoxy)phenyl] propionic acid



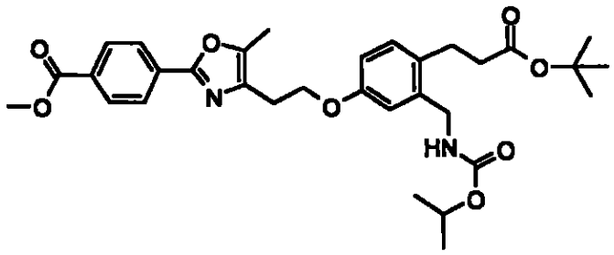
MS (ES) m/z 561 (M+1).

Example 436

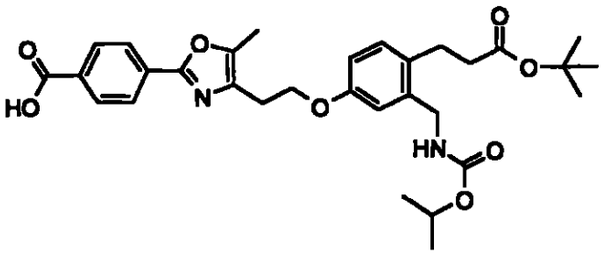
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-carbamoyl-phenyl)-oxazol-4yl]-ethoxy}-phenyl)-propionic acid



Step A: 4-(4-{2-[4-(2-tert-Butoxycarbonyl-ethyl)-3-(isopropoxycarbonylamino-methyl)-phenoxy]-ethyl}-5-methyl-oxazol-2-yl)-benzoic acid methyl ester



A mixture of 3-[4-{2-[2-(4-bromo-phenyl)-5-methoxy-oxazol-4-yl]-ethoxy}-2-(isopropoxy-carbonylamino-methyl-phenyl)-propionic acid tert-butyl ester (0.25 g, 0.42 mmol), 1,1'-bis(diphenylphosphino)-ferrocene palladium (II) chloride (50 mg), MeOH (0.1 mL) and triethylamine (0.12 mL, 0.66 mmol) in acetonitrile (2 mL) was stirred and heated at 70°C under CO gas (balloon) for 16 h. The reaction mixture was cooled and concentrated. The residue was purified by silica gel chromatography (hexanes/EtOAc, 5/1 to 1/1) to afford a the title compound as a white solid (0.12 g, 50%): MS (ESI) m/z 581 $(M+H)^+$.



A solution of 4-(4-{2-[4-(2-tert-Butoxycarbonyl-ethyl)-3-(isopropoxycarbonyl-amino-methyl)-phenoxy]-ethyl}-5-methyl-oxazol-2-yl)-benzoic acid

methyl ester (100 mg, 0.17 mmol) in methanol (2 mL) was treated with 1.5 N aqueous LiOH (1.0 mL) and stirred at ambient temperature for 3 h. The reaction mixture was acidified with 1N HCl and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), concentrated, and purified by silica gel chromatography (hexanes/EtOAc, 1/1 to 0/1) to afford the title compound (55 mg, 57%). MS (ESI) m/z 567 $(M+H)^+$.

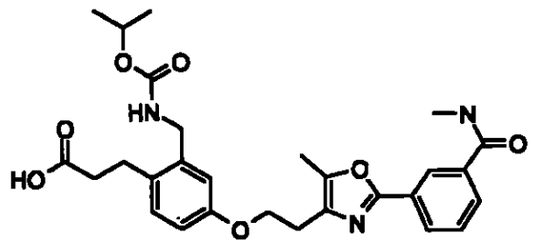
Step C: 3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-carbamoyl-phenyl)-oxazol-4yl]-ethoxy}-phenyl)-propionic acid

A solution of 4-(4-{2-[4-(2-tert-Butoxycarbonyl-ethyl)-3-(isopropoxycarbonyl-amino-methyl)-phenoxy]-ethyl}-5-methyl-oxazol-2-yl)-benzoic acid (40 mg, 0.07 mmol) in CH_2Cl_2 (2 mL) was treated with oxalyl chloride (1.0 µL, 0.12 mmol) and one drop of DMF. The reaction mixture was stirred at ambient temperature for 30 min, concentrated, and co-evaporated with toluene. The residue was dissolved in CH_2Cl_2 (2 mL) and was added to a flask charged with 2.0 M methylamine in THF (2M, 0.04 mL) and triethylamine (20 µL, 0.12 mmol). The mixture was stirred at ambient temperature for 16 h, diluted with CH_2Cl_2 (10 mL), and washed with H_2O. The organic layer was dried ($MgSO_4$), concentrated, and purified by silica gel chromatography (hexanes/EtOAc, 3:1 to 0:1) to afford the intermediate *tert*-butyl ester. The ester was converted to the acid by Standard procedure C; purification by mass directed HPLC yielded the title compound. MS (ESI) m/z 524 $(M+H)^+$.

The following Examples 437 to 448 are prepared by following a substantially similar procedure as described in Example 436.

Example 437

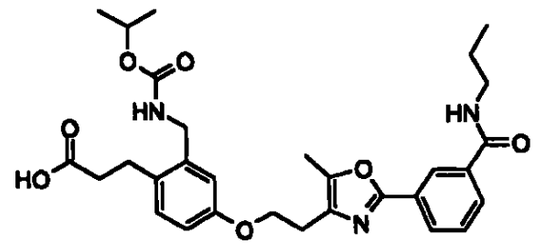
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(3-methylcarbamoyl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ES) m/z 524 (M+1).

Example 438

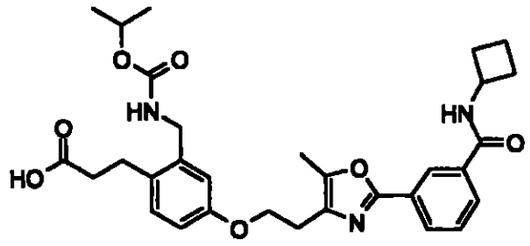
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(3-propylcarbamoyl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ES) m/z 552 (M+1).

Example 439

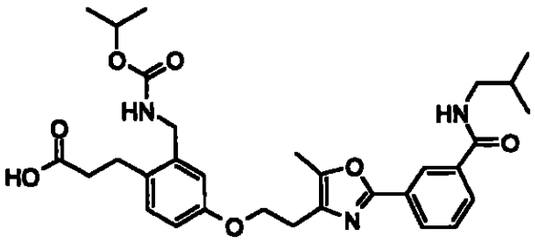
3-[4-{2-[2-(3-Cyclobutylcarbamoyl-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 564 (M+1).

Example 440

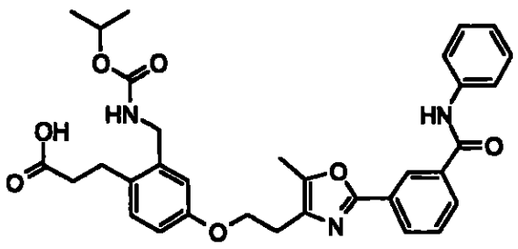
3-[4-{2-[2-(3-Isobutylcarbamoyl-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 566 (M+1).

Example 441

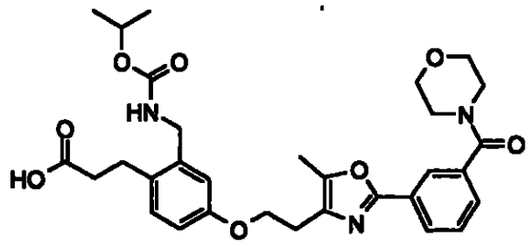
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(3-phenylcarbamoyl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ES) m/z 586 (M+1).

Example 442

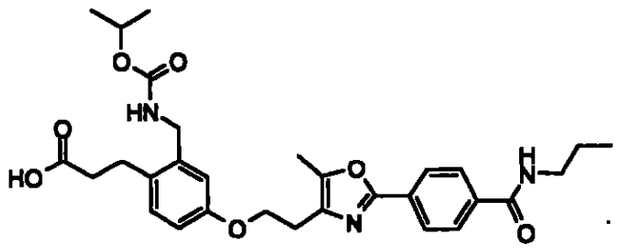
3-[2-(Isopropoxycarbonylamino-methyl)-4-(2-{5-methyl-2-[3-(morpholine-4-carbonyl)-phenyl]-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid



MS (ES) m/z 580 (M+1).

Example 443

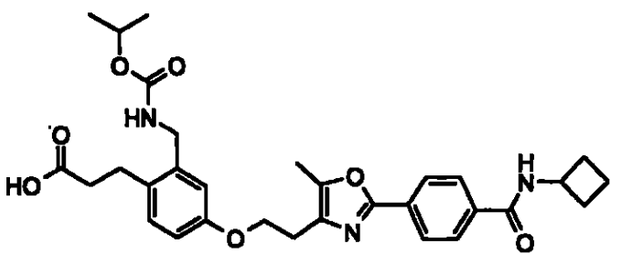
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-propylcarbamoyl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ES) m/z 552 (M+1).

Example 444

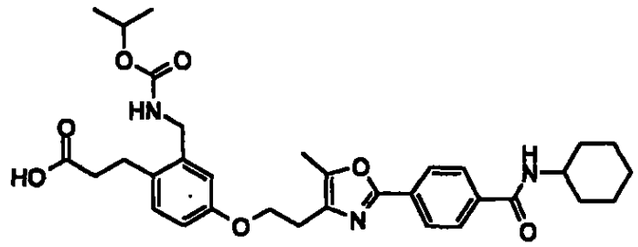
3-[4-{2-[2-(4-Cyclobutylcarbamoyl-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 564 (M+1).

Example 445

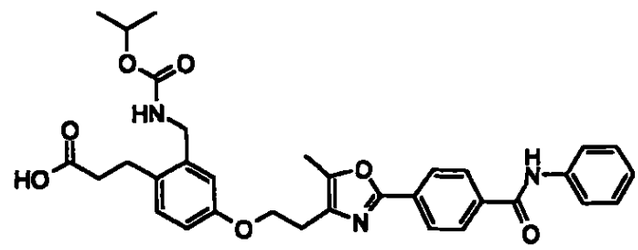
3-[4-{2-[2-(4-Cyclohexylcarbamoyl-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 592 (M+1).

Example 446

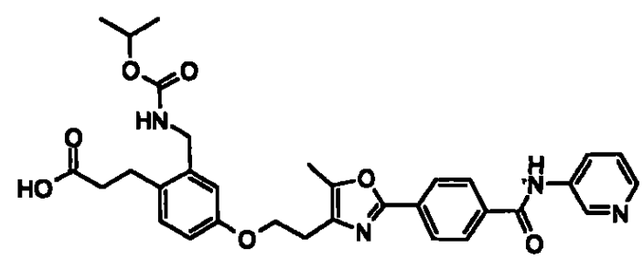
3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-phenylcarbamoyl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ES) m/z 586 (M+1).

Example 447

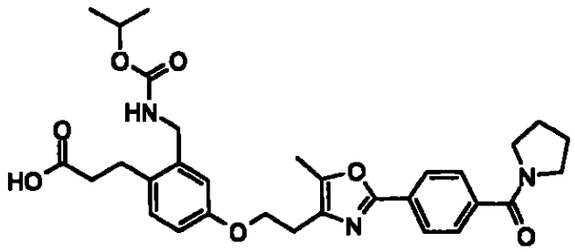
3-[2-(Isopropoxycarbonylamino-methyl)-4-(2-{5-methyl-2-[4-(pyridin-3-ylcarbamoyl)-phenyl]-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid



MS (ES) m/z 587 (M+1).

Example 448

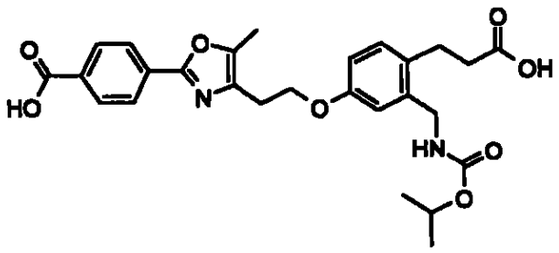
3-[2-(Isopropoxycarbonylamino-methyl)-4-(2-{5-methyl-2-[4-(pyrrolidine-1-carbonyl)-phenyl]-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid



MS (ES) m/z 564 (M+1).

Example 449

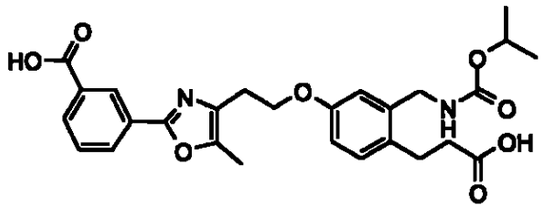
4-(4-{2-[4-(2-Carboxy-ethyl)-3-(isopropoxycarbonylamino-methyl)-phenoxy]-ethyl}-5-methyl-oxazol-2-yl)-benzoic acid



4-(4-{2-[4-(2-tert-Butoxycarbonyl-ethyl)-3-(isopropoxycarbonylamino-methyl)-phenoxy]-ethyl}-5-methyl-oxazol-2-yl)-benzoic acid (50 mg, 0.09 mmol, Example 436, Step B) was converted to the title compound using Standard Procedure C (40 mg, 95%): MS (ESI) m/z 525 $(M+H)^+$.

Example 450

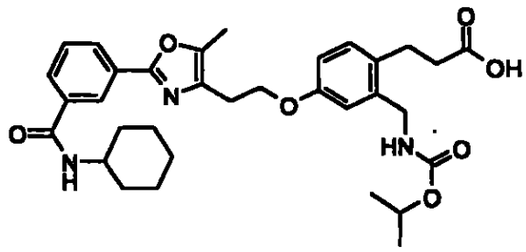
3-(4-{2-[4-(2-Carboxy-ethyl)-3-(isopropoxycarbonylamino-methyl)-phenoxy]-ethyl}-5-methyl-oxazol-2-yl)-benzoic acid:



The above compound is prepared by following a substantially similar procedure as described in Example 449. MS (ESI) m/z 525 $(M+H)^+$.

Example 451

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

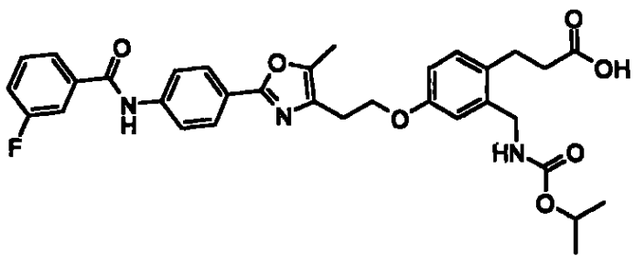


A solution of 3-[4-{2-[2-(4-bromo-phenyl)-5-methoxy-oxazol-4-yl]-ethoxy}-2-(isopropoxy-carbonylamino-methyl)-propionic acid tert-butyl ester (230 mg, 0.38 mmol) in acetonitrile (20 ml) in a dry 3-neck flask was treated with 2-hydroxypyridine (44 mg, 0.46 mmol) and 1,1'-bis(diphenylphosphino)-ferrocene palladium (II) chloride (47 mg, 0.057 mmol). The mixture was stirred for about 5 minutes under N_2, and triethylamine (58 mg, 0.57 mmol) was added dropwise. CO gas was bubbled through the mixture, and the reaction was heated at 70°C for 4 h. The CO bubbling was replaced by a balloon filled with CO, and the reaction was stirred an additional 16 h. The mixture was cooled and partitioned equally into 2 flasks. One portion was treated with cyclohexylamine (46 mg, 0.46 mmol) and triethylamine (58 mg, 0.57 mmol). The mixture was stirred at 70°C for 16 h, cooled, filtered through Celite,

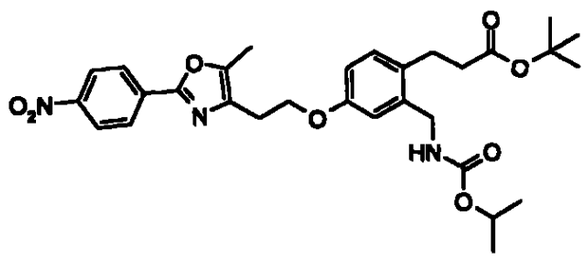
and concentrated to a brown solid (196 mg). The solid was purified by radial chromatography (10-70% EtOAc/hexanes) to give the penultimate *tert*-butyl ester (78 mg; MS (ESI) m/z 648.6 $(M+H)^+$). The ester was converted to the title compound by Standard procedure D (72 mg, 64%). MS (ESI) m/z 592.0 $(M+H)^+$.

Example 452

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

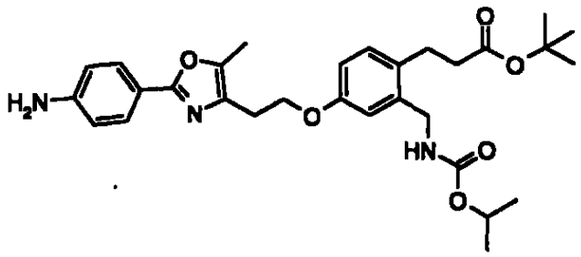


Step A: 3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-nitro-phenyl)-oxazol-4-yl]-ethoxy}-phenyl) -propionic acid *tert*-butyl ester



4-Methyl-3-nitro-benzenesulfonic acid 2-[5-methyl-2-(4-nitro-phenyl)-oxazol-4-yl]-ethyl ester (Preparation 7) and 3-[4-hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester were coupled by Standard procedure A to give the title compound.

Step B: 3-[4-{2-[2-(4-Amino-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl] -propionic acid *tert*-butyl ester



A mixture of 3-(2-(isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(4-nitro-phenyl)-oxazol-4-yl]-ethoxy}-phenyl) -propionic acid *tert*-butyl ester (207 mg, 0.365 mmol) and 10% Pd-C (27 mg) in EtOAc (20 mL) was stirred under H_2 (1 atm) for 18 h. The reaction mixture was filtered through Celite and concentrated (75°C) to give the title compound as a colorless oil (196 mg, 100%): MS (ESI) m/z 538 $(M+H)^+$.

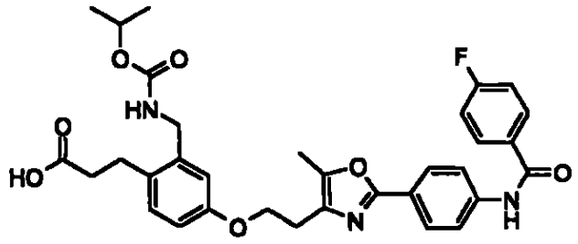
Step C: 3-[4-(2-{2-[4-(3-Fluoro-benzoylamino)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid

3-Fluorobenzoyl chloride (31 mg, 0.20 mmol, 1.8 equiv) was added to a solution of 3-[4-{2-[2-(4-amino-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonyl-amino-methyl)-phenyl] -propionic acid *tert*-butyl ester (58 mg, 0.11 mmol, 1 equiv) and triethylamine (30 µL, 22 mg, 0.22 mmol, 2.0 equiv) in CH_2Cl_2 (5 mL). After 16 h, the reaction solution was washed with 1 M aqueous HCl (5 mL) and saturated aq $NaHCO_3$ (5 mL). The organic layer was dried ($MgSO_4$) and concentrated (75 °C) to the intermediate ester as a light yellow oil. The oil was diluted with 4 M HCl in 1,4-dioxane (5 mL), stirred for 64 h, and concentrated to give the title compound (73 mg, 110%). HRMS Calculated for $C_{33}H_{35}FN_3O_7$: m/z 604.2459. Found: 604.2453.

The following Examples 453 to 475 are prepared by following a substantially similar procedure as described in Examples 451 and 452.

Example 453

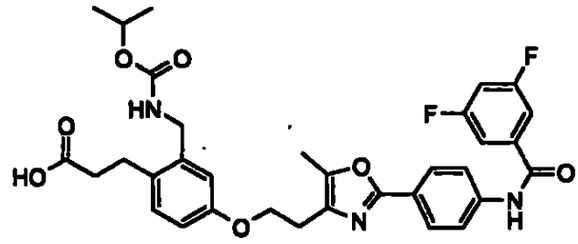
3-[4-(2-{2-[4-(4-Fluoro-benzoylamino)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



HRMS Calculated for $C_{33}H_{35}FN_3O_7$: m/z 604.2459. Found: 604.2454.

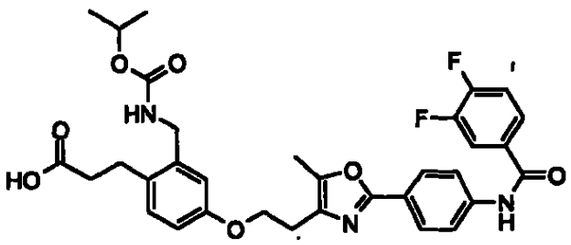
Example 454

3-[4-(2-{2-[4-(3,5-Difluoro-benzoylamino)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



Example 455

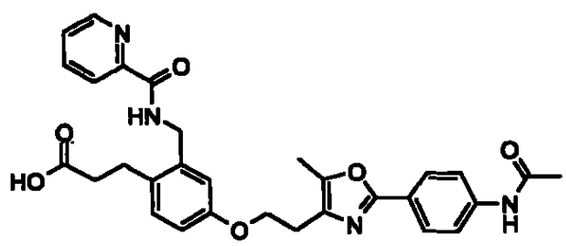
3-[4-(2-{2-[4-(3,4-Difluoro-benzoylamino)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



HRMS Calculated for $C_{33}H_{34}F_2N_3O_7$: m/z 622.2365. Found: 622.2382.

Example 456

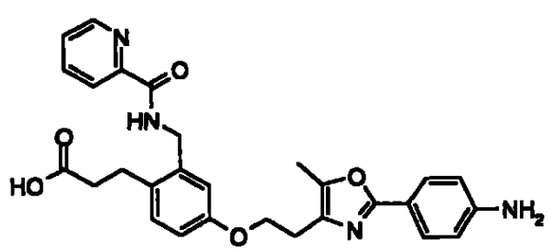
3-(4-{2-[2-(4-Acetylamino-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid



MS (ES) m/z 543 (M+1).

Example 457

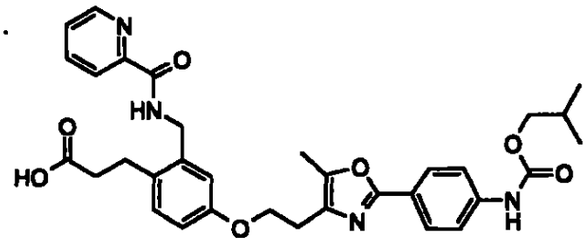
3-(4-{2-[2-(4-Amino-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid



MS (ES) m/z 501 (M+1).

Example 458

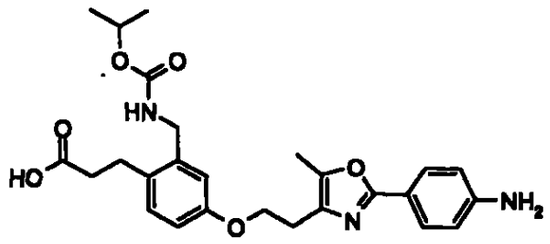
3-(4-{2-[2-(4-Isobutoxycarbonylamino-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid



MS (ES) m/z 601 (M+1).

Example 459

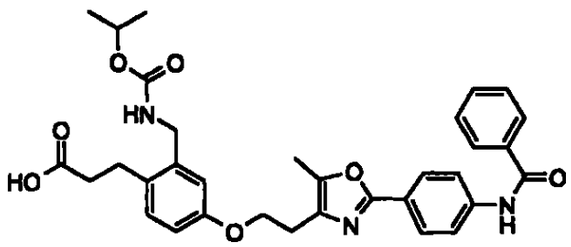
3-[4-{2-[2-(4-Amino-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl] -propionic acid



MS (ES) m/z 482 (M+1).

Example 460

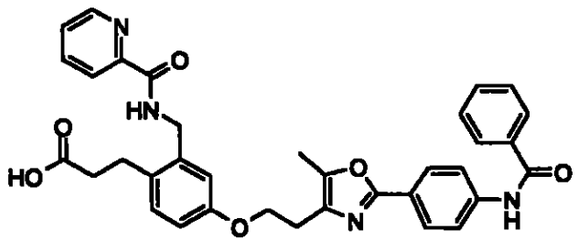
3-[4-{2-[2-(4-Benzoylamino-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 586 (M+1).

Example 461

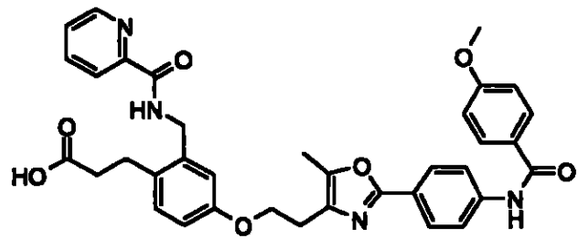
3-(4-{2-[2-(4-Benzoylamino-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid



MS (ES) m/z 661 (M+1).

Example 462

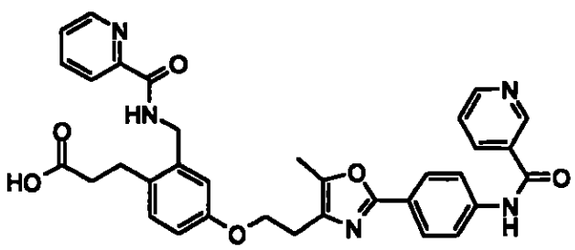
3-(4-(2-{2-[4-(4-Methoxy-benzoylamino)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid



MS (ES) m/z 635 (M+1).

Example 463

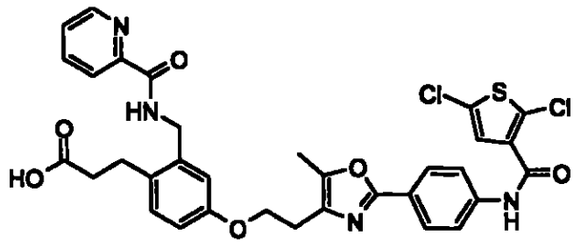
3-(4-[2-(5-Methyl-2-{4-[(pyridine-3-carbonyl)-amino]-phenyl}-oxazol-4-yl)-ethoxy]-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid



MS (ES) m/z 606 (M+1).

Example 464

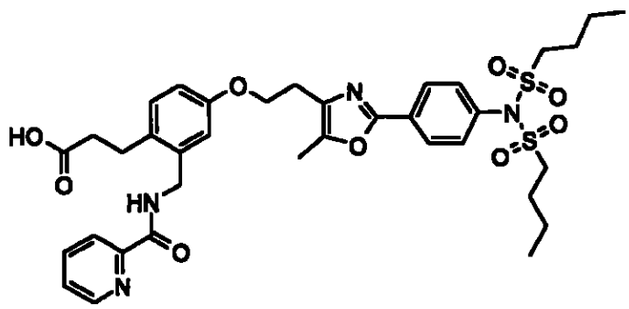
3-(4-[2-(2-{4-[(2,5-Dichloro-thiophene-3-carbonyl)-amino]-phenyl}-5-methyl-oxazol-4-yl)-ethoxy]-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid



MS (ES) m/z 680 (M+1).

Example 465

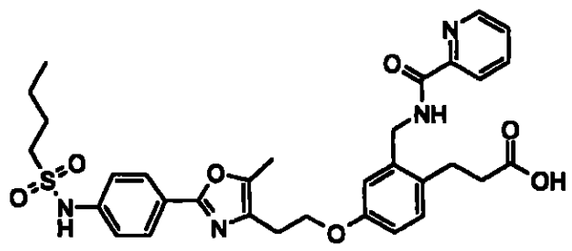
3-(4-(2-{2-[4-(*N*,*N*-Di-(butane-1-sulfonyl)amino)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid



MS (ES) m/z 741 (M+1).

Example 466

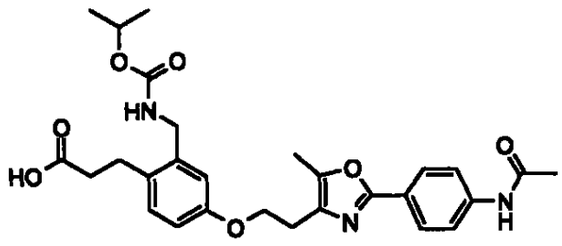
3-(4-(2-{2-[4-(Butane-1-sulfonylamino)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid



MS (ES) m/z 621 (M+1).

Example 467

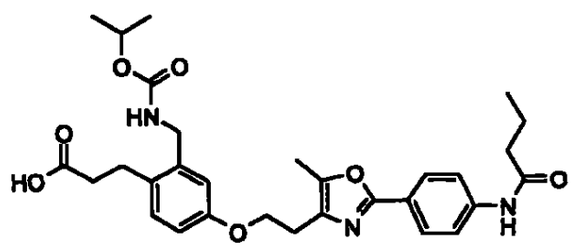
3-[4-{2-[2-(4-Acetylamino-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 524 (M+1).

Example 468

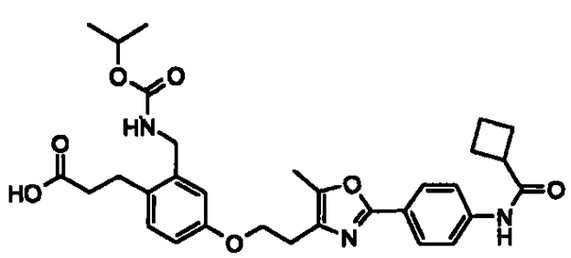
3-[4-{2-[2-(4-Butyrylamino-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 552 (M+1).

Example 469

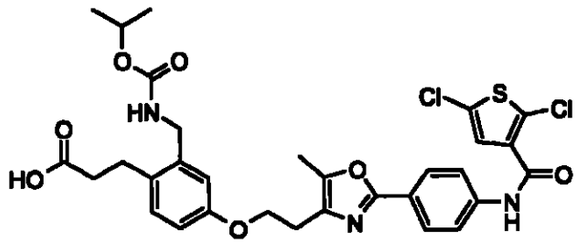
3-[4-(2-{2-[4-(Cyclobutanecarbonyl-amino)-phenyl]-5-methyl-oxazol-4-yl}-ethoxy)-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 564 (M+1).

Example 473

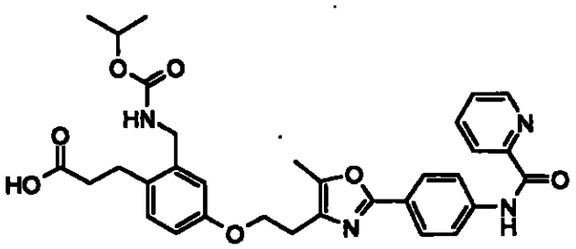
3-[4-[2-(2-{4-[(2,5-Dichloro-thiophene-3-carbonyl)-amino]-phenyl}-5-methyl-oxazol-4-yl)-ethoxy]-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 661 (M+1).

Example 474

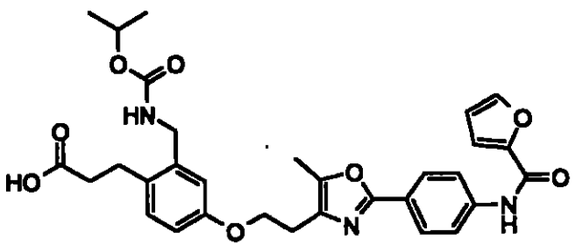
3-{2-(Isopropoxycarbonylamino-methyl)-4-[2-(5-methyl-2-{4-[(pyridine-2-carbonyl)-amino]-phenyl}-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS (ES) m/z 587 (M+1).

Example 475

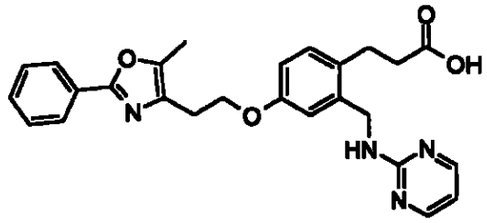
3-[4-[2-(2-{4-[(Furan-2-carbonyl)-amino]-phenyl}-5-methyl-oxazol-4-yl)-ethoxy]-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



MS (ES) m/z 576 (M+1).

Example 476

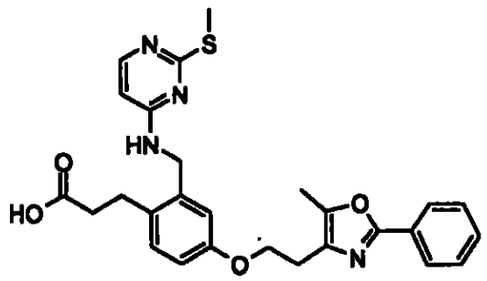
3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-(pyrimidin-2-ylaminomethyl)-phenyl]-propionic acid



A solution of 3-{2-Aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester: acetic acid salt (0.40 mmol, 0.20 g, Example 1 Step B) in DMF (2 mL) was treated with K_2CO_3 (1.0 mmol, 0.14 g) and 2-chloropyrimidine (1.2 mmol, 0.14 g). The mixture was heated at 60 °C for 18 h, cooled, diluted with water (50 mL, and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), concentrated and purified by silica gel chromatography to give the tert-butyl ester intermediate. This material was converted into the title compound (80 mg) using Standard procedure C. MS (ESI) m/z 459.2 $(M+H)^+$.

Example 477

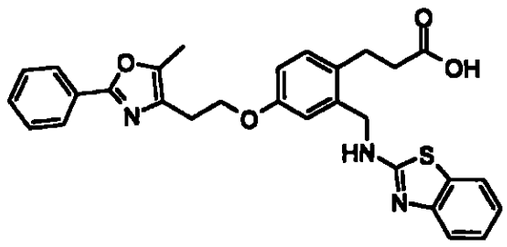
3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-phenyl}-propionic acid



The above compound is prepared by following a substantially similar procedure as described in Example 476. MS (ESI) m/z 505.1 $(M+H)^+$.

Example 478

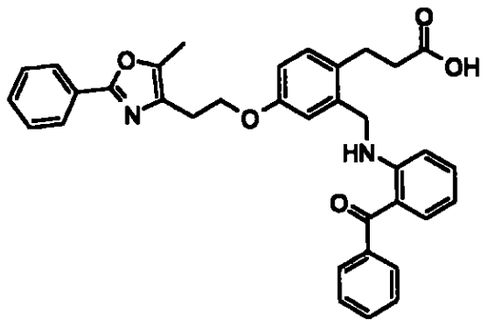
3-{2-(Benzothiazol-2-ylaminomethyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



A solution of 3-{2-aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester acetic acid salt (150 mg, 0.302 mmol; Example 1 Step B) and 2-chloro-benzothiazole (154 mg, 0.907 mmol) in toluene (5 mL) was treated with K_2CO_3 (42 mg). The suspension was heated at 110°C for 48 h and concentrated. The residue was purified by silica gel chromatography (25-50% EtOAc/hexanes) to afford the *tert*-butyl ester intermediate (15 mg). This material was converted into the title compound (80 mg) using Standard procedure C. The intermediate was treated with TFA (0.25 ml)/CH_2Cl_2 (1.0 ml)/H_2O (0.1 mL), stirred for 3 h, and concentrated. The residue was dissolved in CH_2Cl_2 (10 ml), washed with aqueous buffer (pH=7), dried (Na_2SO_4), and concentrated to afford the title compound (12 mg, 8%). MS (ESI) m/z 514.3 $(M+H)^+$.

Example 479

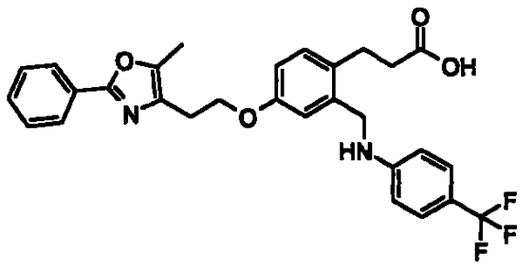
3-{2-[(2-Benzoyl-phenylamino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



A solution of 3-{2-aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester acetic acid salt (290 mg, 0.665 mmol, Example 1, Step B) and 2-benzoyl-cyclohexanone (161 mg, 0.797 mmol) in anisole (20 mL) was treated with a slurry of Pd/C (60 mg) in anisole (2 mL). The mixture was refluxed at 200°C with azeotropic removal of water for 2 h and cooled to room temperature. The catalyst was filtered and a fresh slurry of Pd/C (60 mg) in anisole was added. The mixture was heated at 110°C for 72 h and filtered through a pad of Celite. The filtrate was concentrated, purified by silica gel chromatography (25% EtOAc/hexanes) to afford a mixture of starting material and desired tert butyl ester intermediate. The mixture was treated with TFA (1.0 ml)/CH_2Cl_2(1.0 ml)/H_2O (0.1 mL), stirred for 3 h, and concentrated. The residue was and purified using silica gel chromatography (MeOH/EtOAc 1/9) to give the title compound (38 mg, 10%). MS (ESI) m/z 561.3 $(M+H)^+$.

Example 480

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

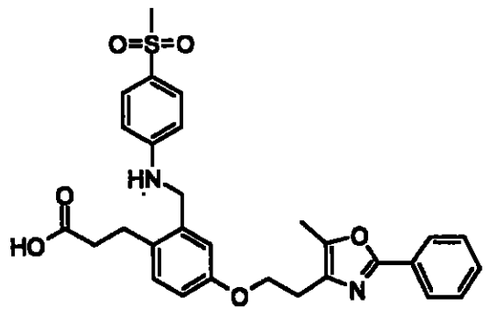


A solution of 3-{2-aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester (174 mg, 0.40 mmol, Example 1 and Procedure I) in toluene (5.0 mL) in a sealed tube apparatus under a flow of N_2 was added $Pd(OAc)_2$ (15 mg), 2-(di-t-butylphosphino)biphenyl (10 mg), sodium t-butoxide (54 mg, 0.56 mmol) and 4-trifluoromethylchlorobenzene (29 mg, 0.16 mmol). The tube was sealed and heated at 110 °C for 14 h. The reaction mixture was cooled, quenched with water (1.0 mL), and extracted with EtOAc (2 x 15 mL). The combined organics were concentrated and purified using silica gel chromatography column (10-50% EtOAc/hexanes) to yield the *tert*-butyl ester intermediate (80 mg). This material was converted into the title compound (40 mg, 48%) using Standard procedure C. MS (ESI) m/z 525.4 $(M+H)^+$.

The following Examples 481 to 484 are prepared by following a substantially similar procedure as described in Examples 478 to 480.

Example 481

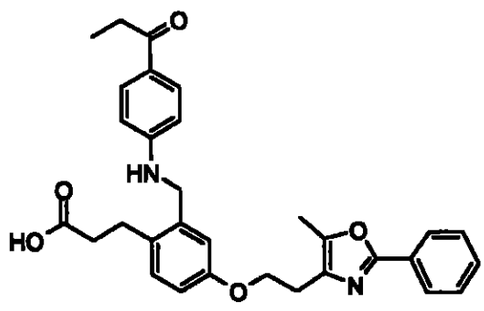
3-{2-[(4-Methanesulfonyl-phenylamino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS (ESI) m/z 535.1 $(M+H)^+$.

Example 482

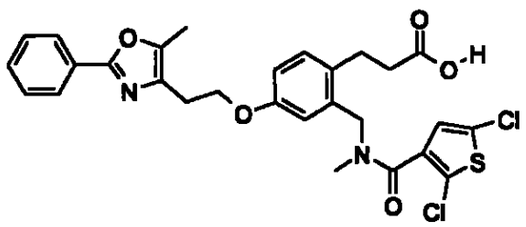
3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(4-propionyl-phenylamino)-methyl]-phenyl}-propionic acid



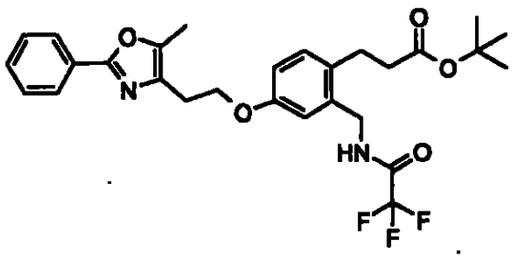
MS (ESI) m/z 513.2 $(M+H)^+$.

Example 485

3-{2-{[(2,5-Dichloro-thiophene-3-carbonyl)-methyl-amino]-methyl}-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

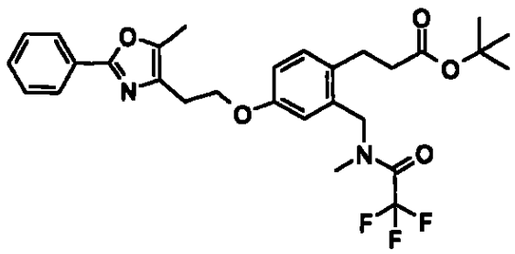


Step A: 3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(2,2,2-trifluoro-acetylamino)-methyl]-phenyl}-propionic acid tert-butyl ester



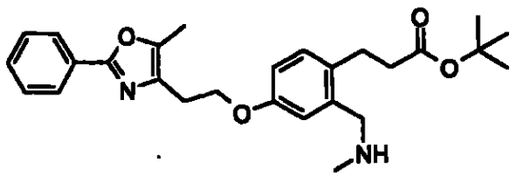
3-{2-Aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester: acetic acid salt (894 mg, 1.80 mmol) was dissolved in CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ solution (15 mL). The organic layer was dried ($NaSO_4$), filtered, and concentrated to a yellow oil (681 mg). The crude amine was dissolved in CH_2Cl_2 (25 mL) and treated with trifluoroacetic anhydride (0.66 mL, 4.7 mmol) then pyridine (0.37 mL, 4.6 mmol). The reaction mixture was stirred at ambient temperature for 4 h and concentrated. The residue was partitioned between EtOAc and 1N HCl, and the organic layer was washed with saturated $NaHCO_3$ solution then brine. The organic layer was dried (Na_2SO_4) and concentrated to give a pale yellow solid (839 mg, 88%).

Step B: 3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{[methyl-(2,2,2-trifluoro-acetyl)-amino]-methyl}-phenyl)-propionic acid tert-butyl ester



A solution of 3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(2,2,2-trifluoro-acetylamino)-methyl]-phenyl}-propionic acid tert-butyl ester (151 mg, 0.28 mmol) in dry DMF (10 mL) was cooled in an ice bath and treated with NaH (22 mg, 0.55 mmol, 60% oil dispersion). After the reaction mixture was stirred for 25 min, iodomethane (0.15 mL, 3.0 mmol) was added, and the reaction was allowed to warm to ambient temperature gradually. After 4 h, more iodomethane (0.10 mL, 2 mmol) was added. The mixture was stirred overnight and was partitioned between EtOAc and aqueous LiCl solution. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel radial chromatography (CH_2Cl_2/EtOAc 100/0 to 95/5) to give the title compound (111 mg, 73%).

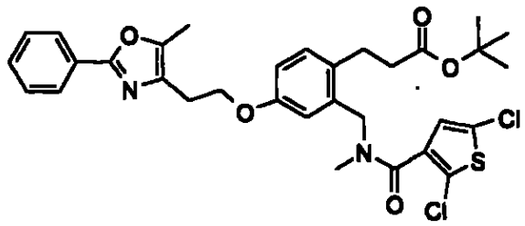
Step C: 3-{2-Methylaminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester



A solution of 3-(4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{[methyl-(2,2,2-trifluoro-acetyl)-amino]-methyl}-phenyl)-propionic acid tert-butyl ester (111 mg, 0.20 mmol) in methanol (5 mL) and THF (5 mL) was treated with 2N NaOH (1.0 mL, 2.0 mmol) and heated at 55°C for 1 h. The reaction mixture was cooled, concentrated, neutralized with 1N HCl and extracted into EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated.

The residue was purified by silica gel radial chromatography (CH_2Cl_2/methanol 95/5 to 90/10) to the title compound (37 mg, 42%). MS (ES) m/z 451.3 [M+1].

Step D: 3-{2-{[(2,5-Dichloro-thiophene-3-carbonyl)-methyl-amino]-methyl}-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert butyl ester



A solution of 3-{2-methylaminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert-butyl ester (37 mg, 0.083 mmol) in CH_2Cl_2 (5 mL) was treated with triethylamine (0.035 mL, 0.25 mmol) then 2,5-dichloro-thiophene-3-carbonyl chloride (0.054 mL, 0.25 mmol) and stirred at ambient temperature overnight. The mixture was diluted with EtOAc (25 mL) and washed with brine (3 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to the title compound (50 mg, 96%). MS (ES) m/z 629, 631 [M+1].

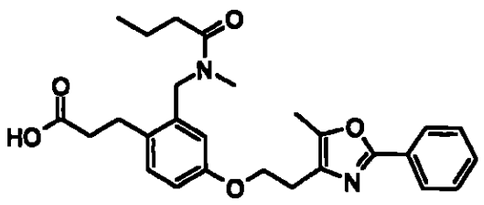
Step E: 3-{2-{[(2,5-Dichloro-thiophene-3-carbonyl)-methyl-amino]-methyl}-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

A solution of 3-{2-{[(2,5-dichloro-thiophene-3-carbonyl)-methyl-amino]-methyl}-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid tert butyl ester (50 mg, 0.079 mmol) in CH_2Cl_2 (2 mL) was treated with anisole (1.0 mL) then TFA (0.6 mL). The solution was stirred at ambient temperature 2 h, and more TFA (1.0 mL) was added. After 15 min, the reaction was concentrated and co-evaporated with CCl_4 (3 x). The residue was triturated with hexanes to yield a foam (43 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.48 (t, 0.6H, J = 7.8 Hz), 2.58 (t, 1.4H, J = 7.8 Hz), 2.72 (t, 0.6H, J = 7.8 Hz), 2.84 (s, 2H), 2.90 (t, 1.4H, J = 7.8 Hz), 2.93 (s, 1H), 2.98 (brs, 2H), 4.17 (t, 2H, J = 6.4 Hz), 4.47 (s, 0.6H), 4.71 (s, 1.4H), 6.61 (brs, 0.3H), 6.71-6.76 (m, 2H), 6.79 (s, 0.7H), 7.04 (d, 0.3H, J = 8.3 Hz), 7.08 (d, 0.7H, J = 8.3 Hz), 7.41-7.43 (m, 3H), 7.94 (brs, 2H).

The following Examples 486 to 488 are prepared by following a substantially similar procedure as described in Example 485.

Example 486

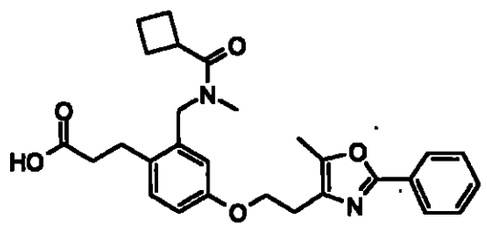
3-{2-[(Butyryl-methyl-amino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS (ES) m/z 465 (M+1).

Example 487

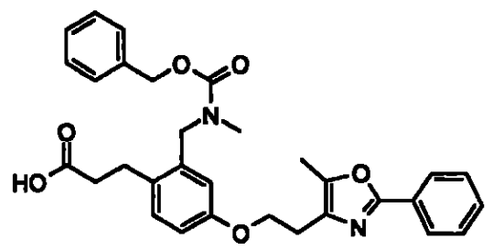
3-{2-[(Cyclobutanecarbonyl-methyl-amino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS (ES) m/z 477 (M+1).

Example 488

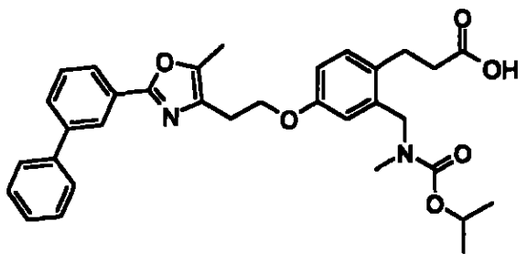
3-{2-[(Benzyloxycarbonyl-methyl-amino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS (ES) m/z 529 (M+1).

Example 489

3-{4-[2-(2-Biphenyl-3-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-[(isopropoxycarbonyl-methyl-amino)-methyl]-phenyl}-propionic acid

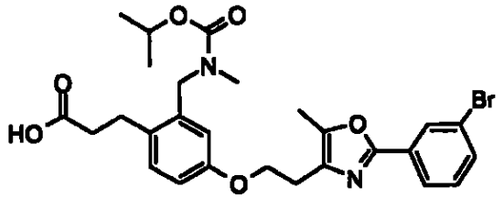


3-{4-Hydroxy-2-[(isopropoxycarbonyl-methyl-amino)-methyl]-phenyl}-propionic acid tert-butyl ester (500 mg, 1.4 mmol; Preparation 22) and toluene-4-sulfonic acid 2-(2-biphenyl-3-yl-5-methyl-oxazol-4-yl)ethyl ester (617 mg, 1.4 mmol; Preparation1/2) were coupled using Standard procedure A to give the penultimate *tert*-butyl ester. This ester was converted to the title compound using Standard procedure D (326 mg): MS (ESI) m/z 557 $(M+H)^+$.

The following Examples 490 to 501 are prepared by following a substantially similar procedure as described in Example 489.

Example 490

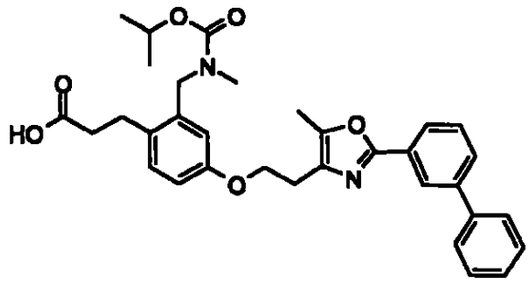
3-{4-{2-[2-(3-Bromophenyl)-5-methyloxazol-4-yl]ethoxy}-2-[(isopropoxy-carbonylmethylamino)methyl]phenyl} propionic acid



MS (ES) m/z 560 (M+1).

Example 491

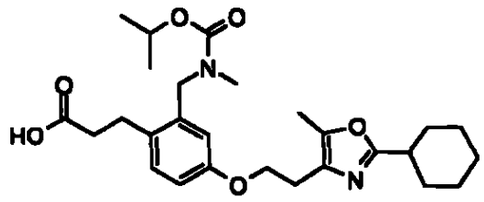
3-{4-[2-(2-Biphenyl-3-yl-5-methyloxazol-4-yl)ethoxy]-2-[(isopropoxy-carbonylmethylamino)methyl]phenyl} propionic acid



MS (ES) m/z 577 (M+1).

Example 492

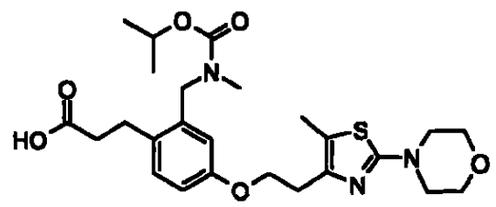
3-{4-[2-(2-Cyclohexyl-5-methyloxazol-4-yl)ethoxy]-2-[(isopropoxy-carbonylmethylamino)methyl]phenyl} propionic acid



MS (ES) m/z 487 (M+1).

Example 493

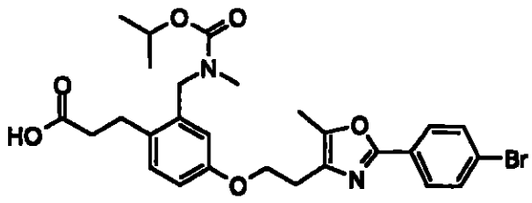
3-{2-[(Isopropoxycarbonylmethylamino)methyl]-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl)ethoxy]phenyl} propionic acid



MS (ES) m/z 506 (M+1).

Example 494

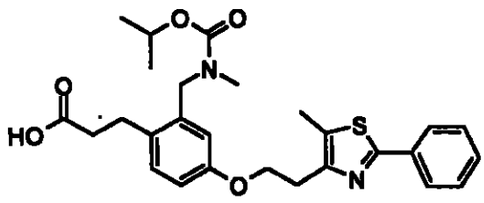
3-{4-{2-[2-(4-Bromophenyl)-5-methyloxazol-4-yl]ethoxy}-2-[(isopropoxy-carbonylmethylamino)methyl]phenyl} propionic acid



MS (ES) m/z 560 (M+1).

Example 495

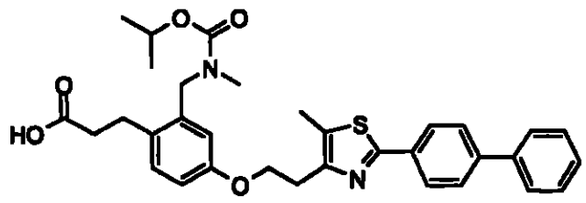
3-{2-[(Isopropoxycarbonylmethylamino)methyl]-4-[2-(5-methyl-2-phenylthiazol4-yl)ethoxy]phenyl} propionic acid



MS (ES) m/z 497 (M+1).

Example 496

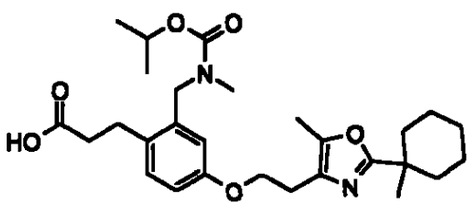
3-{4-[2-(2-Biphenyl-4-yl-5-methylthiazol-4-yl)ethoxy]-2-[(isopropoxy-carbonylmethylamino)methyl]phenyl} propionic acid



MS (ES) m/z 573 (M+1).

Example 497

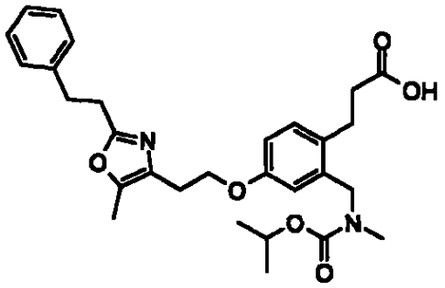
3-(2-[(Isopropoxycarbonylmethylamino)methyl]-4-{2-[5-methyl-2-(1-methyl-cyclohexyl)oxazol-4-yl]ethoxy}phenyl) propionic acid



MS (ES) m/z 501 (M+1).

Example 498

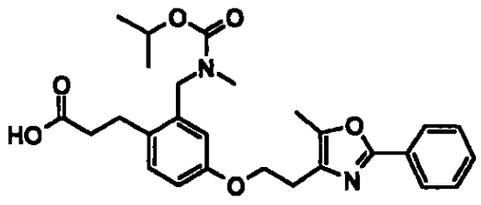
3-{2-[(Isopropoxycarbonylmethylamino)methyl]-4-[2-(5-methyl-2-phenethyl-oxazol-4-yl)ethoxy]phenyl} propionic acid



MS (ES) m/z 509 (M+1).

Example 499

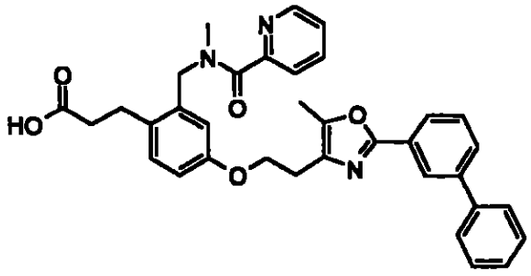
3-{2-[(Isopropoxycarbonylmethylamino)methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)ethoxy]phenyl} propionic acid



MS (ES) m/z 481 (M+1).

Example 500

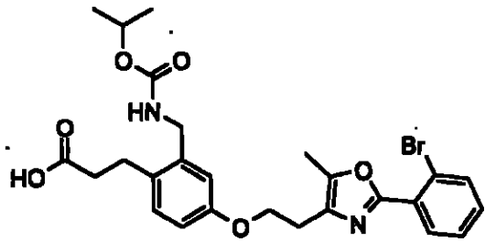
3-(4-[2-(2-Biphenyl-3-yl-5-methyloxazol-4-yl)ethoxy]-2-{[methyl(pyridine-2-carbonyl)amino]methyl}phenyl) propionic acid



MS (ES) m/z 576 (M+1).

Example 501

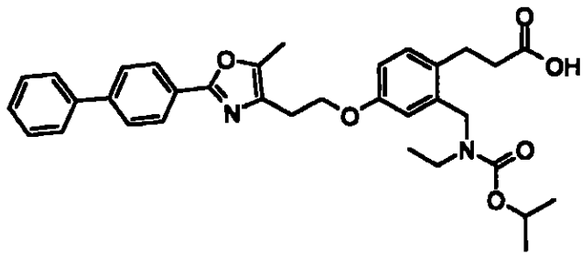
3-[4-{2-[2-(2-Bromophenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxy-carbonylaminomethyl)phenyl] propionic acid



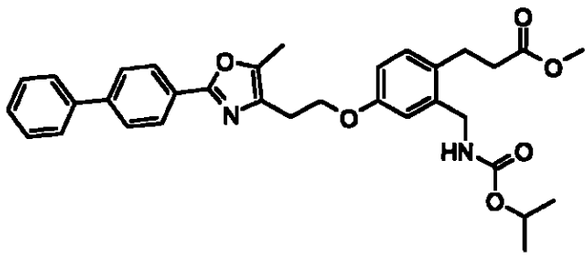
MS (ES) m/z 546 (M+1).

Example 502

3-{4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-[(ethyl-isopropoxycarbonyl-amino)-methyl]-phenyl}-propionic acid



Step A: 3-[4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid methyl ester



3-[4-Hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid methyl ester (Preparation 17) and toluene-4-sulfonic acid 2-(2-biphenyl-4-yl-5-methyl-oxazol-4-yl)ethyl ester (Preparation 1) were combined according to Standard procedure A to give the title compound.

Step B: 3-{4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-[(ethyl-isopropoxycarbonyl-amino)-methyl]-phenyl}-propionic acid

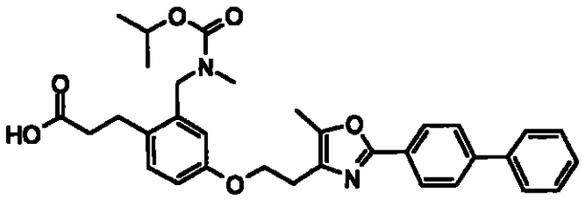
A solution of 3-[4-[2-(2-biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid methyl ester (200 mg, 0.36 mmol) in DMF (15 mL) was treated with sodium bis(trimethylsilyl)amide (132 mg, 0.719 mmol). Ethyl iodide (112 mg, 0.719 mmol) was added, and the reaction mixture was stirred overnight at room temperature under N_2. The mixture was diluted with EtOAc (100 mL) and washed with brine (100mL), then water (100 mL). The organic layer was dried ($MgSO_4$) and concentrated to the penultimate ester as white solid (179 mg). The material was dissolved in EtOH (20 mL), treated with 5N NaOH (20 mL), and stirred at

room temperature overnight. The mixture was acidified with 1N HCl(10mL) and extracted with EtOAc (50mL). The organics were dried ($MgSO_4$) and concentrated to give a white solid (201mg). MS [EI+] m/z 571 $(M+H)^+$. Anal. Calculated for $C_{34}H_{38}N_2O_6$: C, 71.6; H, 6.7; N, 4.9. Found: C, 70.8; H, 6.8; N, 5.0.

The following Examples 503 to 504 are prepared by following a substantially similar procedure as described in Example 502.

Example 503

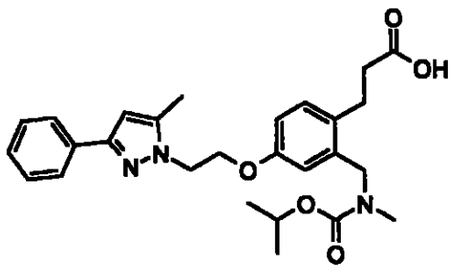
3-{4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-[(isopropoxycarbonyl-methyl-amino)-methyl]-phenyl}-propionic acid



MS [EI+] m/z 557 $(M+H)^+$. Anal. Calculated for $C_{33}H_{36}N_2O_6$: C, 71.2; H, 6.5; N, 5.0. Found: C, 70.6; H, 6.6; N, 5.1.

Example 504

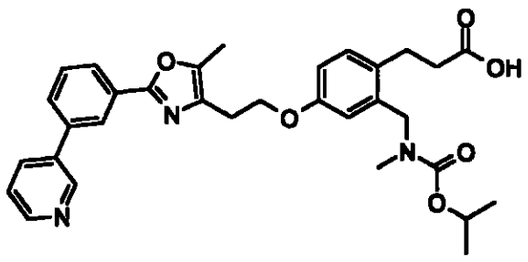
3-{2-[(Isopropoxycarbonyl-methyl-amino)-methyl]-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethoxy]-phenyl}-propionic acid



MS [EI+] m/z 480.1 $(M+H)^+$.

Example 505

3-(2-[(Isopropoxycarbonyl-methyl-amino)-methyl)-4-{2-[5-methyl-2-(3-pyridin-3-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid

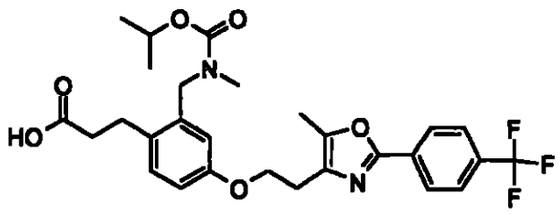


N-Methylation of carbamates: In a small screw cap vial was placed 3-(2(isopropoxycarbonylamino-methyl)-4-{2-[5-methyl-2-(3-pyridin-3-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid tert-butyl ester (0.5 mmol). A 1/1 mixture of $CHCl_3$/TFA (1.6 mL) was added followed by 37% HCHO (50 μL). The reaction mixture was shaken at ambient temperature for 0.5 h and triethylsilane (110 μL, 0.7 mmol) was added. The mixture was shaken for another 0.5 h and was concentrated. The product mixture was purified using mass guided reverse-phase HPLC to afford the title compound (85%). MS [EI+] m/z 571 $(M+H)^+$.

The following Examples 506 to 509 are prepared by following a substantially similar procedure as described in Example 505.

Example 506

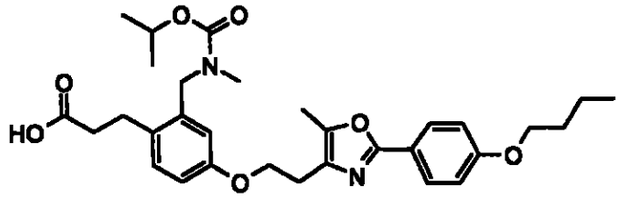
3-(2-[(Isopropoxycarbonyl-methyl-amino)-methyl]-4-{2-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ES) m/z 549 $(M+H)^+$.

Example 507

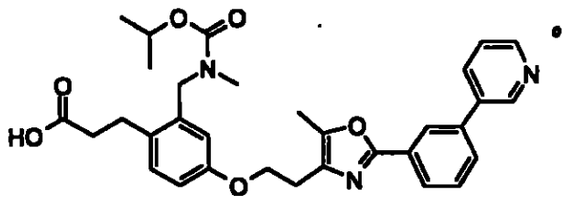
3-{4-{2-[2-(4-Butoxy-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-2-[(isopropoxycarbonyl-methyl-amino)-methyl]-phenyl}-propionic acid



MS (ES) m/z 553 $(M+H)^+$.

Example 508

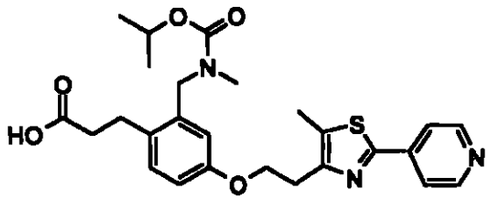
3-(2-[(Isopropoxycarbonyl-methyl-amino)-methyl]-4-{2-[5-methyl-2-(3-pyridin-3-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS (ES) m/z 558 $(M+H)^+$.

Example 509

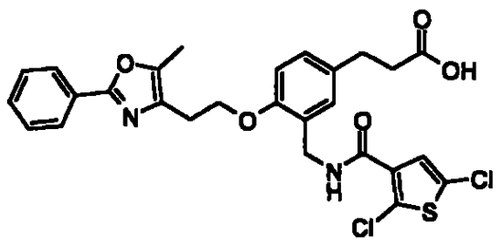
3-{2-[(Isopropoxycarbonyl-methyl-amino)-methyl]-4-[2-(5-methyl-2-pyridin-4-yl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid



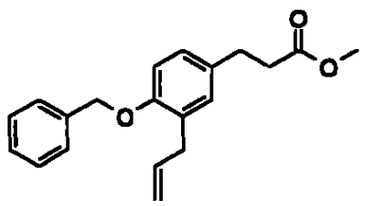
MS (ES) m/z 498 $(M+H)^+$.

Example 510

3-{3-{[(2,5-Dichloro-thiophene-3-carbonyl)-amino]-methyl}-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

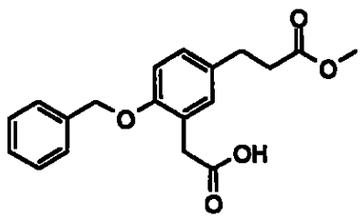


Step A: 3-(3-Allyl-4-benzyloxy-phenyl)-propionic acid methyl ester

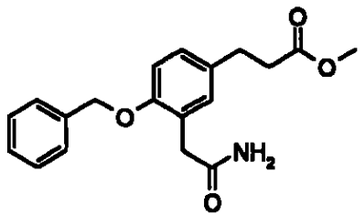


A solution of 3-(3-allyl-4-hydroxy-phenyl)-propionic acid methyl ester (20.5 g, 93.0 mmol; Brown GR, et al. *Bioorg. and Med. Chem. Lett.* 1997, 7, 597) in DMF (50 mL) was treated with Cs_2CO_3 (32.6 g, 100 mmol) then benzyl bromide (12.8 mL, 108 mmol) and heated at 55 °C for 16 h. Cs_2CO_3 (16.3 g, 50 mmol) and benzyl bromide (6.4 mL, 54 mmol) were added. The mixture was stirred at 55°C for 23 h, cooled, and partitioned between EtOAc (250 mL) and water (100 mL). The organic layer was washed with brine (75 mL). The combined aqueous layers were back-extracted with EtOAc (100 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/hexanes 1/1 to 100/0) to the title compound (27.0 g, 93%).

Step B: 3-(4-Benzyloxy-3-carboxymethyl-phenyl)-propionic acid methyl ester



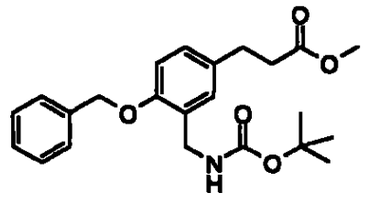
A solution of 3-(3-allyl-4-benzyloxy-phenyl)-propionic acid methyl ester (25.0 g, 80.5 mmol) in acetone (300 mL) and water (30 mL) was treated with 4-methyl-morpholine 4-oxide (12.96 g, 95.8 mmol) then osmium (IV) oxide (5 chips). The flask was covered with foil and stirred 20 h. The solution was diluted with EtOAc (1 L) and washed with 1N $Na_2S_2O_3$ (2 x 150 mL) and brine (125 mL). The organic layer was concentrated to a yellow oil (28.9 g). The oil was dissolved in THF (190 mL) and water (125 mL), and sodium periodate (49.0 g, 229 mmol) was added. THF (190 mL) and water (125 mL) were added. The thick white slurry was stirred for 2 h and filtered. The filtrate was extracted with EtOAc (1 L). The organic layer was washed successively with brine, 1N $Na_2S_2O_3$, and brine (150 mL each) and was concentrated to an orange oil (25.3 g). The oil was diluted with *tert*-butanol (400 mL) and 2-methyl-2-butene (100 mL) and was cooled in an ice bath. The mixture was treated with sodium chlorite (68 g, 0.76 mol), and a solution of NaH_2PO_4 (68 g, 0.49 mol) in water (250 mL) was added over 5 min. After 15 min, the ice bath was removed. The mixture was stirred for 2 h and was partitioned between EtOAc (1 L) and water (125 mL). The organic layer was washed with 1N $Na_2S_2O_3$ (125 mL) and brine (125 mL), dried (NaSO4), and concentrated to the title compound as a tan solid (31.4 g, 119%). This material was used in subsequent reactions without further purification.



3-(4-Benzyloxy-3-carboxymethyl-phenyl)-propionic acid methyl ester (80.5 mmol), ammonium chloride (7.75 g, 145 mmol), EDC (27.7 g, 144 mmol), and *N*-hydroxybenzotriazole hydrate (19.6 g, 145 mmol) were combined in a flask and diluted

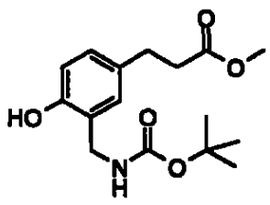
with DMF (320 mL). Ethyl-diisopropyl-amine (51 mL, 293 mmol) was added. The solution was stirred for 20 h and partitioned between EtOAc (1.2 L) and 1N HCl (250 mL). The organic layer was washed with saturated $NaHCO_3$ solution (200 mL) and brine (200 mL), dried (NaSO4), and concentrated. The crude product was slurred with ethyl ether and filtered to give the title compound (15.9 g, 60%).

Step C: 3-[4-Benzyloxy-3-(*tert*-butoxycarbonylamino-methyl)-phenyl]-propionic acid methyl ester



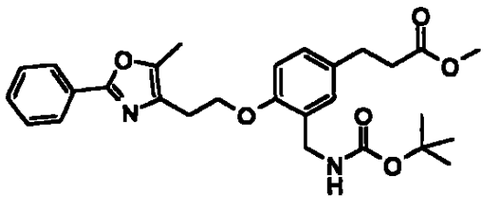
3-(4-benzyloxy-3-carbamoylmethyl-phenyl)-propionic acid methyl ester (15.9 g, 48.6 mmol) was dissolved in CH_3CN (850 mL) and DMF (8 mL) with warming. Water was added, the solution was cooled to ambient temperature, and [bis(trifluoroacetoxy)iodo]benzene (31.32 g, 72.8 mmol) was added. After 30 min, pyridine (8.2 mL) was added, and the solution was stirred for 17 h. Triethylamine (28 mL, 200 mmol) and di-tert-butyl dicarbonate (16.0 g, 73.3 mmol) were added. The mixture was stirred for 2.5 h and was concentrated. The residue was partitioned between EtOAc (1 L) and brine (150 mL). The organic layer was washed with ice-cold 1N HCl (150 mL), saturated $NaHCO_3$ solution (150 mL) and brine (100 mL); dried ($NaSO_4$); and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc 100/0 to 95/5) to a yellow oil (11.0 g, 57%).

Step D: 3-[3-(*tert*-Butoxycarbonylamino-methyl)-4-hydroxy-phenyl]-propionic acid methyl ester



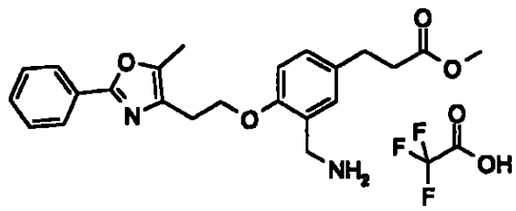
A solution of 3-[4-benzyloxy-3-(*tert*-butoxycarbonylamino-methyl)-phenyl]-propionic acid methyl ester (8.50 g, 21.3 mmol) in THF (100 mL) was treated with 5% Pd-on-carbon (1.1 g) and shaken under a hydrogen atmosphere (60 psi) at ambient temperature for 6 h. The mixture was filtered through Celite and concentrated to a pale yellow solid (5.63 g, 85%).

Step E: 3-{3-(*tert*-Butoxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester



3-[3-(*tert*-Butoxycarbonylamino-methyl)-4-hydroxy-phenyl]-propionic acid methyl ester (5.50 g, 17.8 mmol), toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl ester (7.93 g, 22.2 mmol) and Cs_2CO_3 (7.23 g, 22.2 mmol) were suspended in DMF (40 mL) and stirred at 55°C for 18 h. Additional toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl ester (3.00 g, 8.39 mmol) and Cs_2CO_3 (2.73 g, 8.39 mmol) were added and stirring was continued for 22 h. The reaction mixture was cooled and partitioned between EtOAc (125 mL) and water (50 mL). The organic layer was washed with brine (50 mL), dried ($NaSO_4$), and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc 97/3 to 80/20) to give pure product (3.33 g, 38%) and slightly impure product (7.08g).

Step F: 3-{3-Aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester: trifluoroacetic acid salt



A solution of 3-{3-(*tert*-butoxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (3.33 g, 6.73 mmol) in CH_2Cl_2 (24 mL) was treated at ambient temperature with TFA (10 mL) and stirred for 3 h. The solution was concentrated and co-evaporated with CCl_4 (3x) to yield the title compound as a foam (4.13 g, quantitative)

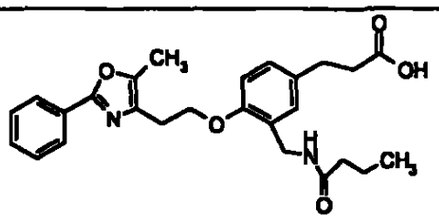
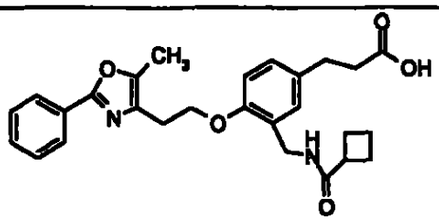
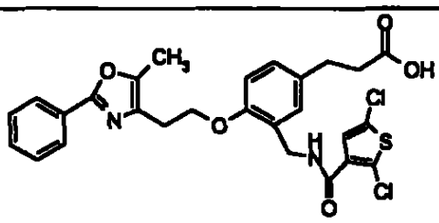
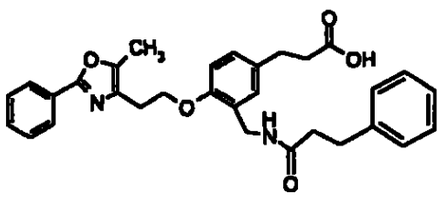
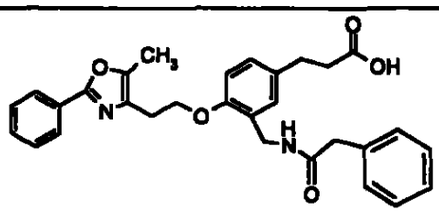
Step G: 3-{3-{[(2,5-Dichloro-thiophene-3-carbonyl)-amino]-methyl}-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

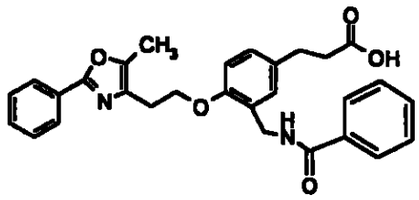
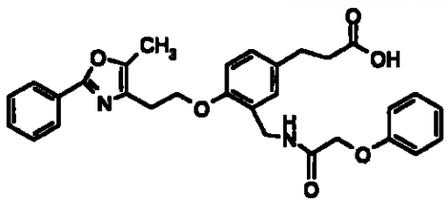
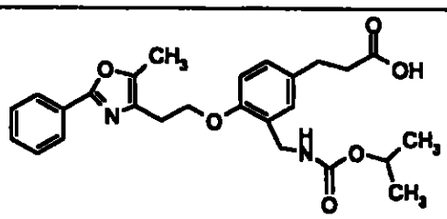
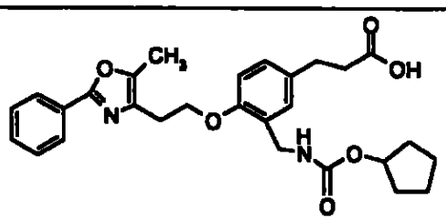
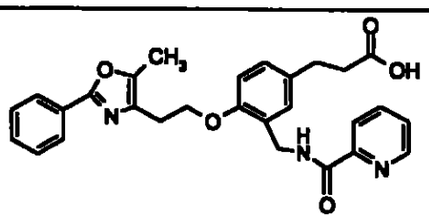
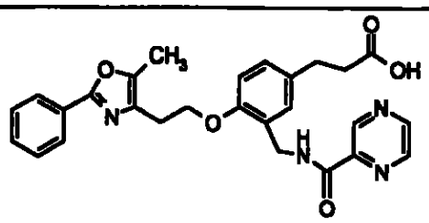
General Parallel Synthesis Procedure: 3-{3-Aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester: trifluoroacetic acid salt (565 mg, 1.1 mmol) was dissolved in CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ solution (15 mL). The organic layer was dried ($NaSO_4$), filtered, and concentrated to 3-{3-aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (368 mg, 0.93 mmol, 84%). A portion of this free base (26 mg, 0.071 mmol) in CH_2Cl_2 (0.5 mL) was treated with triethylamine (0.075 mL, 0.54 mmol) then 2,5-dichloro-thiophene-3-carbonyl chloride (0.049 mL, 0.22 mmol). The reaction mixture was shaken overnight and dimethylethylenediamine (0.15 mL, 1.4 mmol) was added. The reaction mixture was shaken for 2 h and passed through an SCX column (1g, equilibrated with 2 mL MeOH then 2 mL MeOH/CH_2Cl_2 1/1). The methyl ester-amide product was eluted with MeOH/CH_2Cl_2 (1:1, 10 mL) and concentrated. The residue was dissolved in THF (2 mL) and MeOH (2 mL) and treated with 5N NaOH (1 mL). The solution was heated at 55°C for 2.5 h, cooled, and acidified with 5N HCl (1.5 mL). The mixture was transferred to a ChemElute cartridge and eluted with CH_2Cl_2. The solvent was removed under a stream of N_2. The crude product was dried under vacuum

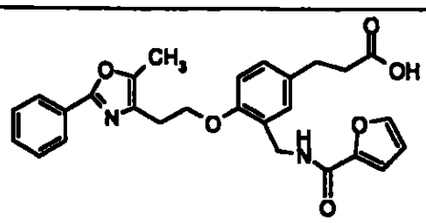
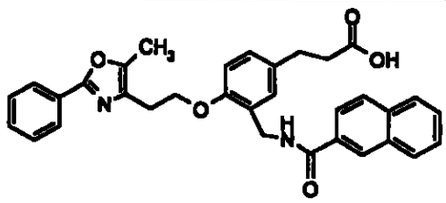
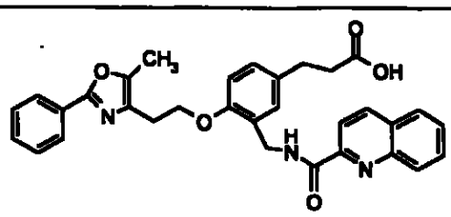
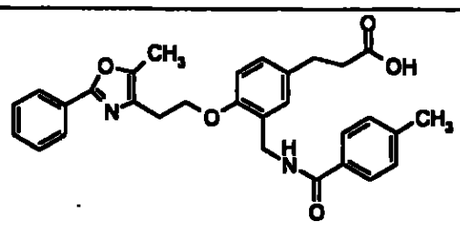
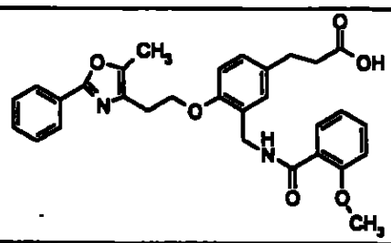
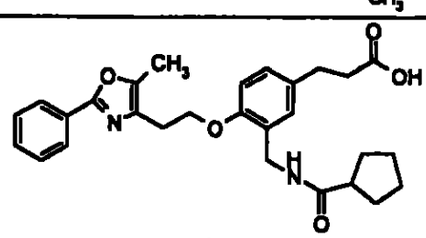
and purified by mass-directed HPLC to give the title compound as a foam (9.9mg, 26%). MS (ESI) m/z 559.1 $(M+H)^+$.

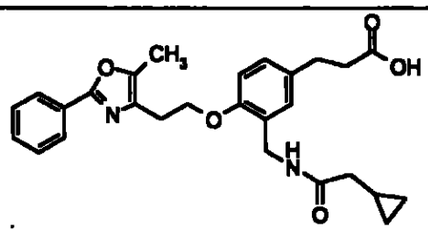
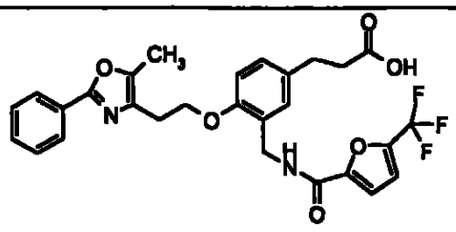
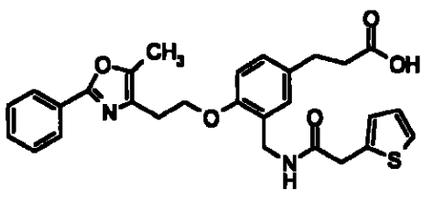
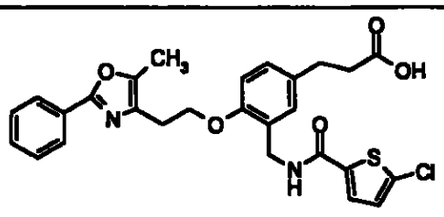
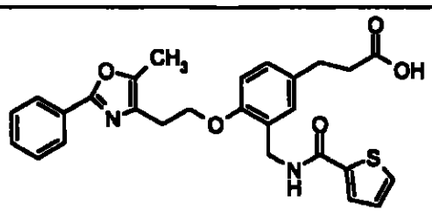
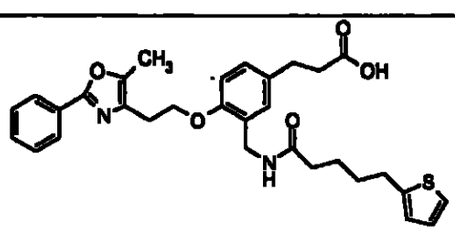
Examples 511-543

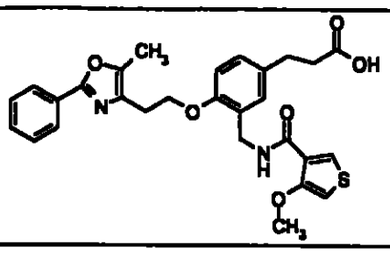
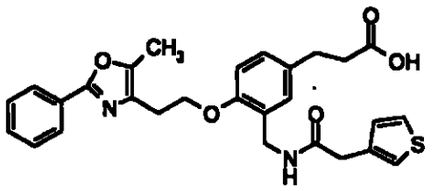
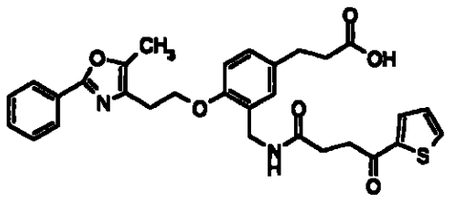
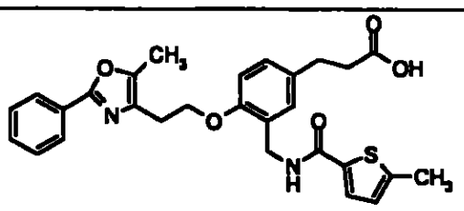
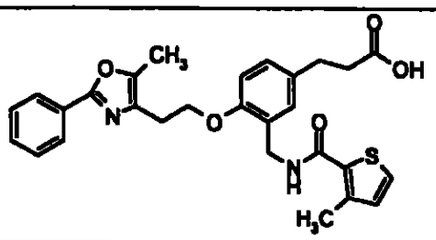
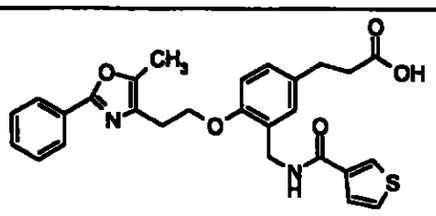
Examples 511 to 543 are prepared by following a substantially similar procedure as described in Example 510.

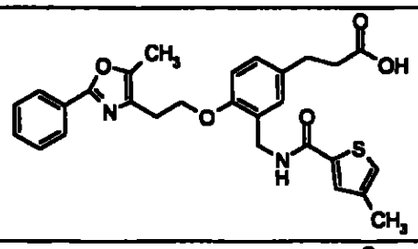
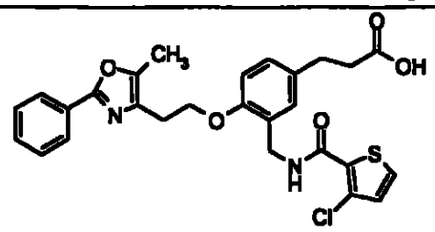
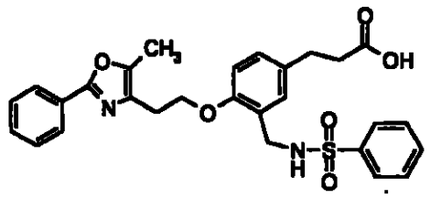
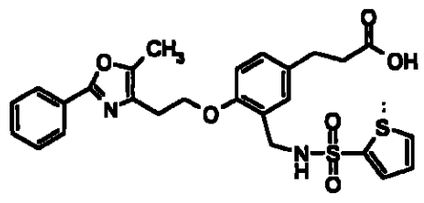
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512		463.3
513		559.1
514		513.3
515		499.3

No.	Compounds	MS (ES+)
516		485.3
517		515.3
518		481.3
519		493.3
520		486.2
521		487.2

No.	Compounds	MS (ES+)
522		475.2
523		535.2
524		536.2
525		499.2
526		515.2
527		477.3

No.	Compounds	MS (ES+)
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529		543.2
530		505.3
531		525.2
532		491.2
533		547.3

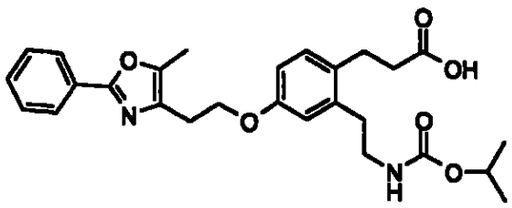
No.	Compounds	MS (ES+)
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535		505.3
536		547.3
537		505.3
538		505.3
539		491.3

No.	Compounds	MS (ES+)
540		505.3
541		525.2
542		521.2
543		527.1

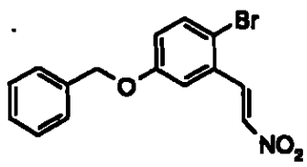
5

Example 544

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



Step A: 5-Benzyloxy-2-bromo-(2-nitrovinyl)benzene

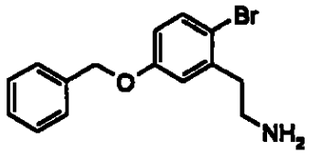


A solution of 2-bromo-5-hydroxy-benzaldehyde (5.99 g, 29.8 mmol, Preparation 13 Step A) in DMF (50 mL) was treated with benzyl bromide (7.65 g, 44.7 mmol) and Cs_2CO_3 (15.1 g, 44.7 mmol). The resulting mixture was heated at 80°C for 60 min and was quenched with water (200 mL). The mixture was extracted with EtOAc (2 x 100 mL), dried (Na_2SO_4), and concentrated to a residue, which was purified on silica gel chromatography (hexanes/EtOAc 9/1) to afford 5-benzyloxy-2-bromo-benzaldehyde as white solid in quantitative yield.

A solution of nitromethane (2.02 mL, 37.3 mmol) in ethanol (10 mL) was treated with 10N NaOH (3.0 mL) at ambient temperature. A white solid precipitated immediately, and a solution of 5-benzyloxy-2-bromo-benzaldehyde (8.67 g, 29.8 mmol) in CH_2Cl_2 (50 mL) was added. The reaction mixture was stirred for 18 h and quenched with water (100 mL). The mixture was extracted with CH_2Cl_2 (2 x 50 mL), dried (Na_2SO_4), and concentrated to a residue, which was then purified by silica gel chromatography (hexanes/EtOAc 8/2) to afford 1-(5-benzyloxy-2-bromo-phenyl)-2-nitro-ethanol as yellow oil.

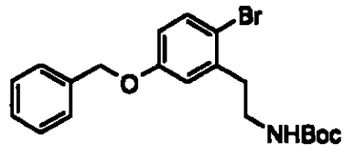
This intermediate was dissolved in CH_2Cl_2 (150 mL) and cooled to 0°C. Methanesulfonyl chloride (2.55 mL, 60.0 mmol) was added, and the mixture was stirred for 15 min. Triethylamine (8.41 mL) was added, and the mixture was stirred for 60 min. The reaction was quenched with water (200 mL) and extracted with CH_2Cl_2 (150 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (hexanes/EtOAc 8/2) to afford the title compound (8.60 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 (s, 2 H), 6.93 (dd, 1H, J = 2.7 Hz, 9.0 Hz), 7.11 (d, 1H, J=3.2 Hz), 7.34-7.37 (m, 5H), 7.48 (d, 1H, J=13.7 Hz), 7.51 (d, 1H, J=9.0 Hz), 8.28 (d, 1H, J = 13.7 Hz).

Step B: 2-(5-Benzyloxy-2-bromo-phenyl)-ethylamine



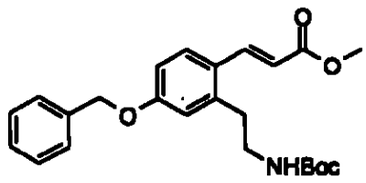
To a solution of 5-benzyloxy-2-bromo-(2-nitrovinyl)benzene (8.60 g, 25.6 mmol) in THF (100 mL) at -78°C was added LAH (4.1 g, 102 mmol) portion wise over 30 min. The reaction mixture was allowed to warm gradually to ambient temperature. After 18 h, the mixture was carefully quenched with water (4 mL), 2N NaOH (4 mL), and water (12 mL) successively. The slurry was filtered and the precipitate was washed with CH_2Cl_2 (3 x 150 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography (EtOAc, then CH_2Cl_2/MeOH/NH_4OH 10/1/0.01) to afford the title compound as an oil (3.36 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.84 (t, 2H, J = 6.7 Hz), 2.96 (t, 2H, J = 6.7 Hz), 5.03 (s, 2 H), 6.71 (dd, 1H, J = 2.7 Hz, 8.6 Hz), 6.86 (d, 1H, J=2.4 Hz), 7.33-7.43 (m, 6H).

Step C: 2-(5-Benzyloxy-2-bromo-phenyl)-ethyl]-carbamic acid tert-butyl ester



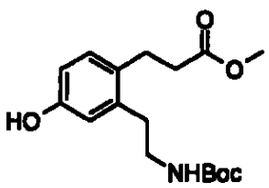
A solution of 2-(5-benzyloxy-2-bromo-phenyl)-ethylamine (3.36 g, 10.97 mmol) in CH_2Cl_2 (50mL) at 0°C was treated with Et_3N (3.08 mL, 21.9 mmol) and di-*tert*-butyl dicarbonate (2.87 g, 13.2 mmol). The mixture was stirred for 2 h while being allowed to warm gradually to ambient temperature and was concentrated. The residue was purified by silica gel chromatography (EtOAc/hexanes, 65:35) to afford the title compound as an oil (4.45 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.90 (t, 2H, J = 6.7 Hz), 3.39 (dt, 2H, J = 6.3 Hz, 6.7 Hz), 5.02 (s, 2 H), 6.72 (dd, 1H, J = 3.1 Hz, 8.6 Hz), 6.87 (br s, 1H), 7.33-7.43 (m, 6H).

Step D: 3-[4-Benzyloxy-2-(2-tert-butoxycarbonylamino-ethyl)-phenyl]-acrylic acid methyl ester



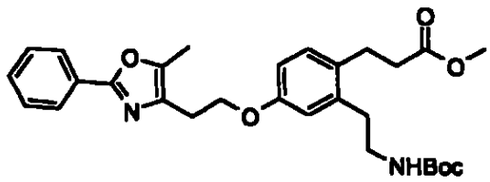
A solution of 2-(5-benzyloxy-2-bromo-phenyl)-ethyl]-carbamic acid tert-butyl ester (4.40 g, 10.8 mmol) in propionitrile (100 mL) was degassed (vacuum/ Ar purge, 3x). Tri-*ortho*-tolylphosphine (0.660 g, 2.17 mmol), methyl acrylate (2.93 mL, 32.5 mmol), and diisopropylethyl amine (3.76 mL, 21.6 mmol) were added. The mixture was de-gassed (vacuum/ Ar purge, 3x). $Pd(OAc)_2$ (242 mg, 1.08 mmol) was added, and the reaction mixture was degassed again. The mixture was stirred at 95 °C for 18 h and concentrated to a residue, which was purified by silica gel chromatography (EtOAc/hexanes, 7/3) to afford the title compound (4.15 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) (major isomer): δ 1.43 (s, 9H), 2.94 (t, 2H, J = 6.8 Hz), 3.33 (dt, 2H, J = 6.3 Hz, 6.8 Hz), 3.79 (s, 3 H), 5.08 (s, 2 H), 6.28 (d, 1H, J= 15.6 Hz), 6.84 (br s, 1 H), 6.86 (d, 1H, J= 8.3 Hz), 7.34-7.43 (m, 5 H), 7.55 (d, 1H, J= 8.3 Hz), 7.91 (d, 1H, J= 15.6 Hz).

Step E: 3-[2-(2-tert-Butoxycarbonylamino-ethyl)-4-hydroxy-phenyl]-propionic acid methyl ester



To a solution of 3-[4-benzyloxy-2-(2-tert-butoxycarbonylamino-ethyl)-phenyl]-acrylic acid methyl ester (4.15 g, 10.1 mmol) in THF (100 mL) and MeOH (10 mL) was added 5% Pd-C (200 mg) in THF (10 mL). The resulting suspension was treated with hydrogen under balloon pressure for 18 h. The mixture was filtered through a pad of Celite and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexanes, 6/4) to afford the title compound (1.20 g, 34%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.57 (t, 2H, J = 7.8 Hz), 2.77 (t, 2H, J = 7.3 Hz), 2.88 (t, 2H, J = 7.8 Hz), 3.33 (br s, 2H), 3.68 (s, 3 H), 6.65 (br s, 1 H), 6.67 (d, 1H, J= 8.3 Hz), 7.02 (d, 1H, J= 8.3 Hz). MS (ES^+) m/z 324.1 $[M+H]^+$.

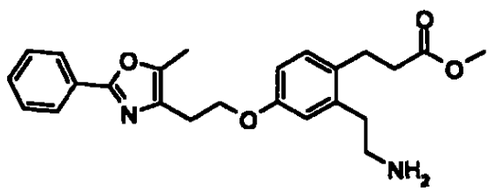
Step F: 3-{2-(2-tert-Butoxycarbonylamino-ethyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester



To a solution of 3-[2-(2-tert-butoxycarbonylamino-ethyl)-4-hydroxy-phenyl]-propionic acid methyl ester (0.807 g, 2.50 mmol) and toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl ester (1.34 g, 3.74 mmol) in DMF (5 mL) was added Cs_2CO_3 (1.22 g, 3.74 mmol). The suspension was stirred at 65°C for 48 h, quenched with H_2O (200 mL), and extracted with EtOAc (3 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated to a residue, which was purified on silica gel chromatography (hexanes/EtOAc 9/1 to 8/2 to 6/4) to afford the title compound as a colorless oil (0.90 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.37 (s, 3H), 2.54 (t, 2H, J = 7.8 Hz), 2.77 (t, 2H, J = 7.8 Hz), 2.88 (t, 2H, J = 6.8 Hz), 2.96 (t, 2H, J =

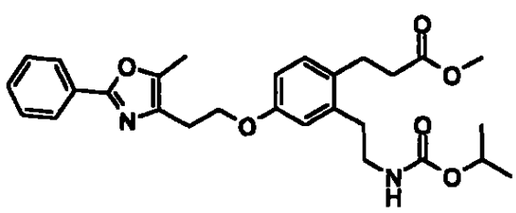
6.8 Hz), 3.33 (~dt, 2H, J = 6.8 Hz), 3.65 (s, 3 H), 4.20 (t, 2H, J = 6.8 Hz), 6.70 (br s, 1 H), 6.72 (d, 1H, J= 8.3 Hz), 7.05 (d, 1H, J= 8.3 Hz), 7.39-7.44 (m, 3H), 7.95-7.98 (m, 2H). MS (ES^+) m/z $[M+H]^+$.

Step G: 3-{2-(2-Amino-ethyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester



A solution of 3-{2-(2-tert-butoxycarbonylamino-ethyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (0.90 g, 1.77 mmol) in CH_2Cl_2 (10mL) at 0°C was treated with TFA (5.0 mL) and water (0.2 mL). The resulting solution was allowed to warm gradually to ambient temperature. After 18 h, the mixture was concentrated. The residue was partitioned between CH_2Cl_2 (30mL) and 5N NaOH (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 30mL). The combined organics were dried (K_2CO_3) and concentrated to a residue, which was purified by silica gel chromatography (CH_2Cl_2 /MeOH/NH_4OH, 8/2/0.05) to afford the title compound as a colorless oil (0.42 g, 58%). ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.52 (t, 2H, J = 7.8 Hz), 2.81 (t, 2H, J = 7.8 Hz), 2.91 (t, 4H, J = 6.4 Hz), 3.06 (t, 2H, J = 7.3 Hz), 3.60 (s, 3 H), 4.20 (t, 2H, J = 6.8 Hz), 6.68 (br s, 1 H), 6.71 (d, 1H, J= 8.3 Hz), 7.01 (d, 1H, J= 8.3 Hz), 7.37-7.39 (m, 3H), 7.89-7.92 (m, 2H).

Step H: 3-{2-(2-Isopropoxycarbonylamino-ethyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



A solution of 3-{2-(2-amino-ethyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid methyl ester (26 mg, 0.064 mmol) in CH_2Cl_2 (2 mL) at 0 °C was treated with TEA (0.2 mL) and isopropyl chloroformate (0.13 mL, 1.0 M in

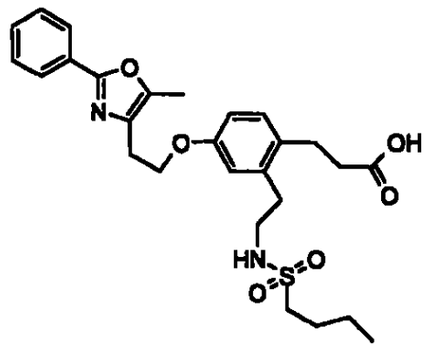
ether). The resulting mixture was allowed to warm gradually to ambient temperature. After 2 h, the mixture was concentrated to a residue, which was purified by silica gel chromatography (hexanes/EtOAc 7/3) to afford the isopropyl carbamate as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (d, 6H, J = 5.9 Hz), 2.42 (s, 3H), 2.54 (t, 2H, J = 7.8 Hz), 2.79 (t, 2H, J = 6.8 Hz), 2.89 (t, 2H, J = 7.8 Hz), 3.05 (br s, 2H), 3.38 (br s, 2H), 3.60 (s, 3 H), 4.26 (t, 2H, J = 6.8 Hz), 4.68 (br s, 1H), 4.89 (q, 1H, J = 6.4 Hz), 6.70 (br s, 1 H), 6.71 (d, 1H, J= 8.3 Hz), 7.05 (d, 1H, J= 8.3 Hz), 7.47 (m, 3H), 8.10 (m, 2H).

This compound was dissolved in THF (1.0 mL) and MeOH (0.5 mL). The solution was treated with 2N NaOH (0.32 mL) and heated at 60 °C for 60 min. The reaction mixture was concentrated, neutralized with 2N HCl (0.40 mL), and extracted with EtOAc (3 x 5 mL). The combined organics were dried (Na_2SO_4), and concentrated to a residue, which was purified by silica gel chromatography (hexanes/EtOAc 9/1, then EtOAc/MeOH 95/5) to afford the title compound as a white solid (12 mg, 32% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, 6H, J = 5.9 Hz), 2.36 (s, 3H), 2.52 (br s, 2H), 2.79 (t, 2H, J = 6.8 Hz), 2.89 (t, 2H, J = 7.8 Hz), 2.93 (t, 2H, J = 6.8 Hz), 3.31 (br s, 2H), 4.16 (t, 2H, J = 6.8 Hz), 4.68 (br s, 1H), 4.89 (q, 1H, J = 6.4 Hz), 6.67 (br s, 1 H), 6.71 (d, 1H, J= 8.3 Hz), 7.05 (d, 1H, J= 8.3 Hz), 7.47 (m, 3H), 8.10 (m, 2H). MS [ES] m/z 481.4 (M+1).

The following Examples 545 to 552 are prepared by following a substantially similar procedure as described in Example 544.

Example 545

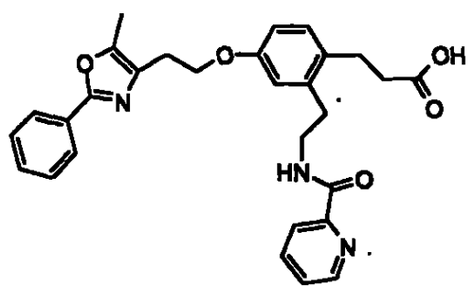
3-{2-[2-(Butane-1-sulfonylamino)-ethyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS [ES] m/z 515.3 (M+1).

Example 546

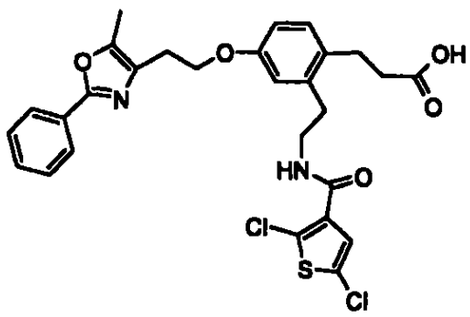
3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{2-[(pyridine-2-carbonyl)-amino]-ethyl}-phenyl)-propionic acid



MS [ES] m/z 500.3 (M+1).

Example 547

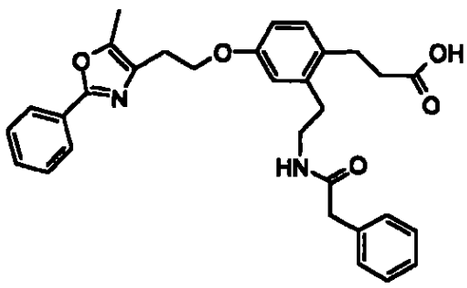
3-{2-{2-[(2,5-Dichloro-thiophene-3-carbonyl)-amino]-ethyl}-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS [ES-] m/z 573.0(M-1).

Example 548

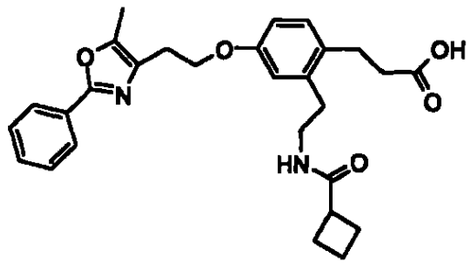
3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-(2-phenylacetylamino-ethyl)-phenyl]-propionic acid



MS [ES] m/z 513.2 (M+1).

Example 549

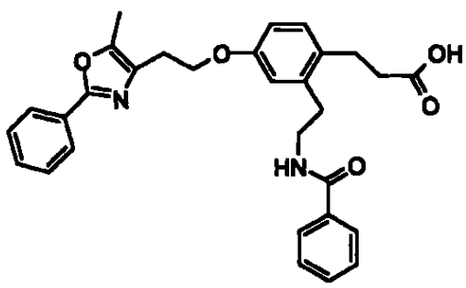
3-{2-[2-(Cyclobutanecarbonyl-amino)-ethyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS [ES] m/z 477.1 (M+1).

Example 550

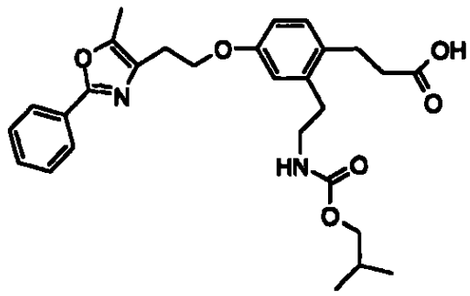
3-{2-(2-Benzoylamino-ethyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS [ES] m/z 499.3 (M+1).

Example 551

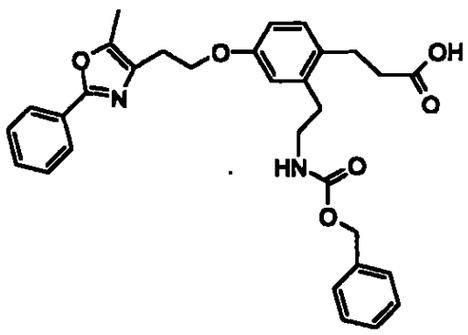
3-{2-(2-Isobutoxycarbonylamino-ethyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS [ES] m/z 495.3 (M+1).

Example 552

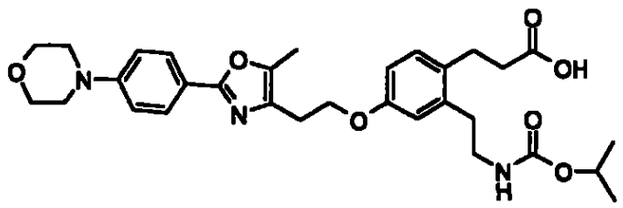
3-{2-(2-Benzyloxycarbonylamino-ethyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



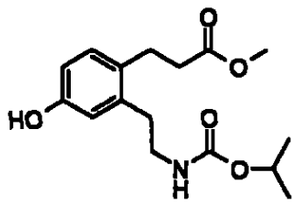
MS [ES] m/z 529.0 (M+1).

Example 553

3-(2-(2-Isopropoxycarbonylamino-ethyl)-4-{2-[5-methyl-2-(4-morpholin-4-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



Step A: 3-[4-Hydroxy-2-(2-isopropoxycarbonylamino-ethyl)-phenyl]-propionic acid methyl ester



A solution of 3-[2-(2-tert-butoxycarbonylamino-ethyl)-4-hydroxy-phenyl]-propionic acid methyl ester (282 mg, 0.876 mmol; Example 544, Step E) in CH_2Cl_2 (10 mL) at ambient temperature was treated with TFA (5.0 mL), stirred for 60 min, and concentrated. The residue in CH_2Cl_2 (10 mL) was treated with triethyl amine (2.0 mL) and iso-propyl chloroformate (0.97 mL, 1.0 M in toluene). The reaction mixture was stirred at ambient temperature for 16 h and concentrated. The crude material was purified using silica gel chromatography (50% EtOAc/hexanes) to yield the title compound (180 mg, 67%).

Step B: 3-(2-(2-Isopropoxycarbonylamino-ethyl)-4-{2-[5-methyl-2-(4-morpholin-4-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid

A solution of toluene-4-sulfonic acid 2-[5-methyl-2-(4-morpholin-4-yl-phenyl)-oxazol-4-yl]-ethyl ester (44 mg, 0.10 mmol; Preparation 5) and 3-[4-hydroxy-2-(2-isopropoxycarbonylamino-ethyl)-phenyl]-propionic acid methyl ester (31 mg, 0.10 mmol) in DMF (1.0 mL) was treated with K_2CO_3 (30 mg). The resulting suspension was stirred at 65 °C for 16 h and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated,

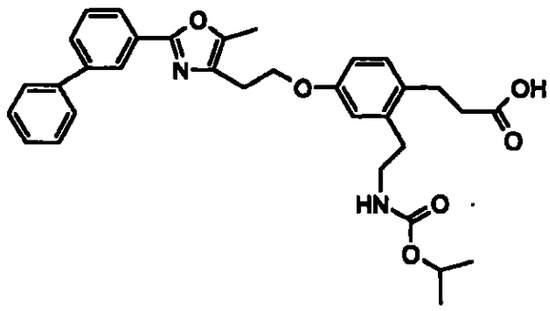
and purified using silica gel chromatography (50% EtOAc/hexanes to yield 3-(2-(2-isopropoxycarbonylamino-ethyl)-4-{2-[5-methyl-2-(4-morpholin-4-yl-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid methyl ester.

This ester intermediate was dissolved in THF (0.6 mL) and MeOH (0.4 mL) and treated with aqueous 2M LiOH (1.0 mL, 2.0 mmol). The mixture was stirred for 16 h at ambient temperature, neutralized with HCl (1.0 mL, 2.0 M), and concentrated. The residue was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified using silica gel chromatography column (hexanes/EtOAc/HOAc, 5/5/0.02) to afford the title compound (10 mg, 18%). MS (ES+) m/z 566.2 $(M+H)^+$.

The following Examples 554 to 560 are prepared by following a substantially similar procedure as described in Example 553.

Example 554

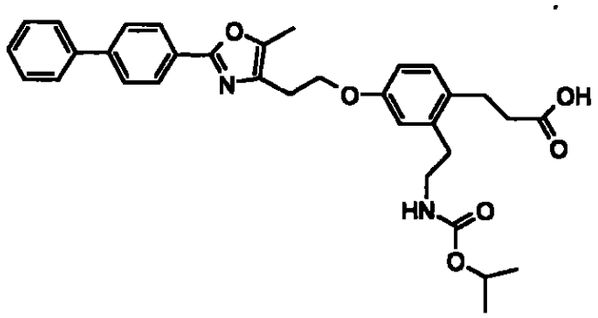
3-[4-[2-(2-Biphenyl-3-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-(2-isopropoxycarbonyl-amino-ethyl)-phenyl]-propionic acid



MS [ES] m/z 557.5 (M+1).

Example 555

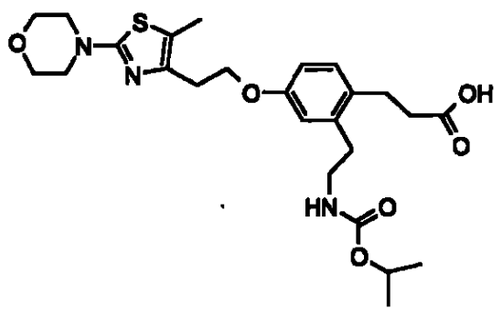
3-[4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-(2-isopropoxycarbonyl-amino-ethyl)-phenyl]-propionic acid



MS [ES] m/z 557.2 (M+1).

Example 556

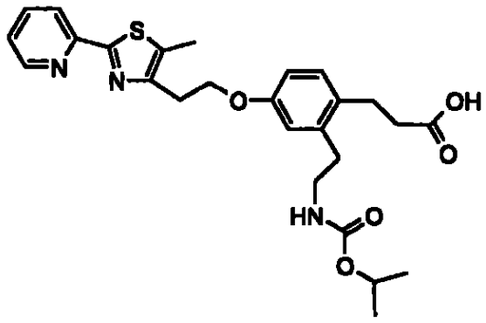
3-{2-(2-Isopropoxycarbonyl-amino-ethyl)-4-[2-(5-methyl-2-morpholin-4-yl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS [ES] m/z 506.2 (M+1).

Example 557

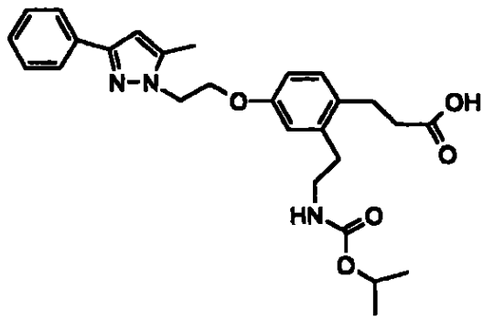
3-{2-(2-Isopropoxycarbonylamino-ethyl)-4-[2-(5-methyl-2-pyridin-2-yl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid



MS [ES] m/z 498.3 (M+1).

Example 558

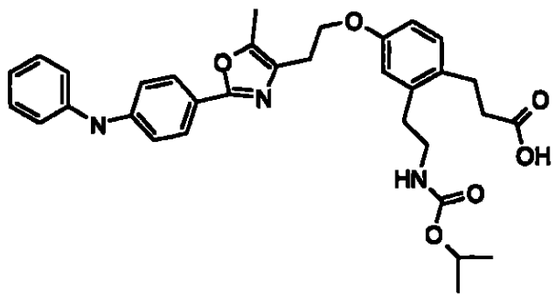
3-{2-(2-Isopropoxycarbonylamino-ethyl)-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethoxy]-phenyl}-propionic acid



MS [ES] m/z 480.3 (M+1).

Example 559

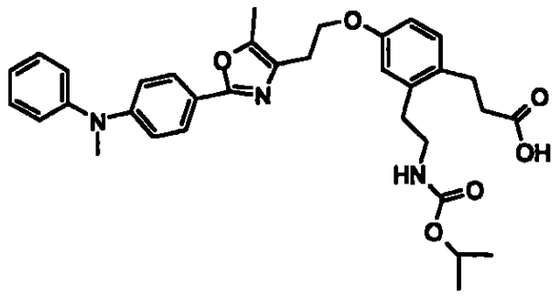
3-(2-(2-Isopropoxycarbonylamino-ethyl)-4-{2-[5-methyl-2-(4-phenylamino-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS [ES] m/z 572.2 (M+1).

Example 560

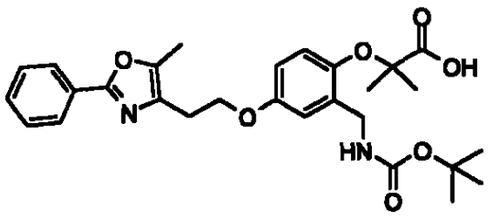
3-[2-(2-Isopropoxycarbonylamino-ethyl)-4-(2-{5-methyl-2-[4-(methyl-phenyl-amino)-phenyl]-oxazol-4-yl }-ethoxy)-phenyl]-propionic acid



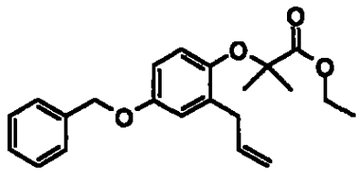
MS [ES] m/z 586.2 (M+1).

Example 561

2-{2-(tert-Butoxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid

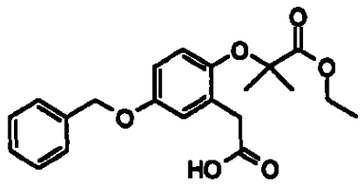


Step A: 2-(2-Allyl-4-benzyloxy-phenoxy)-2-methyl-propionic acid ethyl ester



2-Allyl-4-benzyloxy-phenol (WO 9728137 A1 19970807, Adams et al.) (6.04 g, 25.1 mmol) in dry DMF (75 mL) was cooled in an ice bath and treated with NaH (1.78 g, 44.5 mmol, 60 % oil dispersion). After 30 min, the red reaction mixture was treated over 5 min with ethyl bromoisobutyrate (7.4 mL, 50 mmol). The cold bath was removed after 5 min. The reaction was stirred 20 min and placed in an oil bath (T=85°C). After 18 h, the mixture was cooled and partitioned between brine (75 mL) and ether (200 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4), and concentrated to a brown oil (12g). The crude product was purified by flash chromatography using hexanes:ethyl acetate (100:0 to 5:1) to give the desired product (8.47 g, 95%).

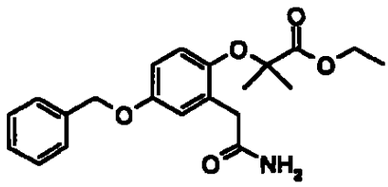
Step B: 2-(4-Benzyloxy-2-carboxymethyl-phenoxy)-2-methyl-propionic acid ethyl ester



A solution of 2-(2-allyl-4-benzyloxy-phenoxy)-2-methyl-propionic acid ethyl ester (8.07 g, 22.8 mmol) in acetone (85 mL) and water (8.5 mL) was treated with 4-methyl-morpholine 4-oxide (3.68 g, 27.2 mmol) then osmium (IV) oxide (2 chips). The flask was covered with foil and stirred 5 h. The solution was diluted with EtOAc (600

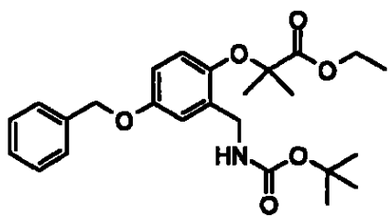
mL) and washed with 1N $Na_2S_2O_3$ (2 x 75 mL) and brine (75 mL). The organic layer was concentrated to a tan oil (8.74 g). The oil was dissolved in THF (54 mL) and water (36 mL), and sodium periodate (15.4 g, 72.0 mmol) was added. THF (54 mL) and water (36 mL) were added. The thick white slurry was stirred for 3 h and filtered. The filtrate was extracted with EtOAc (500 mL). The organic layer was washed successively with brine, 1N $Na_2S_2O_3$, and brine (75 mL each) and was concentrated to an orange oil (7.65 g). The oil was diluted with *tert*-butanol (180 mL) and 2-methyl-2-butene (60 mL) and was cooled in an ice bath. The mixture was treated with sodium chlorite (19 g, 0.21 mol), and a solution of NaH_2PO_4 (19 g, 0.14 mol) in water (120 mL) was added over 5 min. After 15 min, the ice bath was removed. The mixture was stirred for 2 h and was partitioned between EtOAc (500 mL) and water (50 mL). The organic layer was washed with 1N $Na_2S_2O_3$ (75 mL) and brine (75 mL), dried (NaSO4), and concentrated to the title compound as a pale yellow solid (6.52 g, 77%). This material was used in subsequent reactions without further purification.

Step C: 2-(4-Benzyloxy-2-carbamoylmethyl-phenoxy)-2-methyl-propionic acid ethyl ester



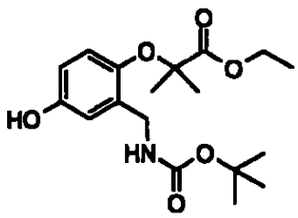
2-(4-Benzyloxy-2-carboxymethyl-phenoxy)-2-methyl-propionic acid ethyl ester (500 mg, 1.34 mmol), ammonium chloride (108 mg, 2.02 mmol), EDC (3.86 mg, 2.01 mmol), and *N*-hydroxybenzotriazole hydrate (272 mg, 2.01 mmol) were combined in a flask and diluted with DMF (5 mL). Ethyl diisopropyl amine (0.70 mL, 4.0 mmol) was added. The solution was stirred for 18 h and partitioned between EtOAc (25 mL) and 1N HCl (10 mL). The organic layer was washed with saturated $NaHCO_3$ solution (10 mL) then brine (10 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by radial chromatography (hexanes/EtOAc 1/2 to 1/4) to give the title compound (430 mg, 86%).

Step D: 2-[4-Benzyloxy-2-(tert-butoxycarbonylamino-methyl)-phenoxy]-2-methyl-propionic acid ethyl ester



2-(4-Benzyloxy-2-carbamoylmethyl-phenoxy)-2-methyl-propionic acid ethyl-ester (430 mg, 1.16 mmol) was dissolved in CH_3CN (4.5 mL) and water (4.5 mL), and [bis(trifluoroacetoxy)iodo]benzene (745 mg, 1.73 mmol) was added. After 10 min, pyridine (0.19 mL, 2.3 mmol) was added, and the solution was stirred for 17 h. Triethylamine (0.60 mL, 4.3 mmol) and di-tert-butyl dicarbonate (506 mg, 2.32 mmol) were added. The mixture was stirred for 1 h and was concentrated. The residue was partitioned between ether (50 mL) and brine (15 mL). The organic layer was washed with ice-cold 1N HCl, saturated $NaHCO_3$ solution, and brine (15 mL each); dried ($NaSO_4$); and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc 4/1 to 3/2) to a yellow oil (345 g, 67%).

Step E: 2-[2-(tert-Butoxycarbonylamino-methyl)-4-hydroxy-phenoxy]-2-methyl-propionic acid ethyl ester



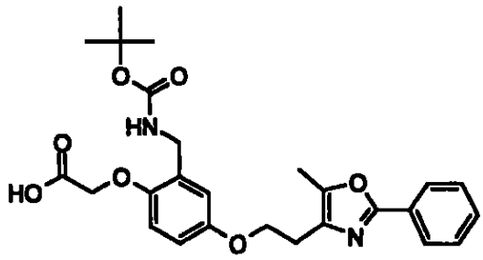
A solution of 2-[4-benzyloxy-2-(tert-butoxycarbonylamino-methyl)-phenoxy]-2-methyl-propionic acid ethyl ester (0.38 g, 0.86 mmol) in THF (15 mL) was treated with 5% Pd-on-carbon (47 mg) and shaken under a hydrogen atmosphere (60 psi) at ambient temperature for 18 h. The mixture was filtered through Celite and concentrated. The crude product was purified by radial chromatography (hexanes/EtOAc 2.5/1) to give the title compound (208 mg g, 69%).

Step F: 2-{2-(tert-Butoxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid

2-[2-(tert-Butoxycarbonylamino-methyl)-4-hydroxy-phenoxy]-2-methyl-propionic acid ethyl ester (200 mg, 0.566 mmol), toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl ester (245 mg, 686 mmol) and Cs_2CO_3 (185 mg, 0.567 mmol) were suspended in DMF (5 mL) and stirred at 55°C for 39 h. The reaction mixture was cooled and partitioned between Et_2O (50 mL) and water (10 mL). The organic layer was washed with brine (10 mL), dried ($NaSO_4$), and concentrated. The residue was purified by radial chromatography (hexanes/EtOAc 4/1) to give an oil (280 mg). A solution of the product in MeOH (6 mL) and THF (3 mL) was treated with 2.5N aqueous NaOH solution (2 mL) and heated at 55 °C for 2 h. The mixture was cooled and concentrated. Ice chips were added (~5) and the mixture was acidified using 5N aqueous HCL solution (2 mL). The reaction mixture was partitioned between EtOAc (30 mL) and brine (15 mL). The organic layer was washed with brine (2 x 10 mL), dried ($NaSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc/HOAc 3/2/0 to 3/2/0.05) to give the title compound as a white foam (156 mg, 54%). MS (ES^-) m/z 509.1 $[M-H]^-$. Anal. Calcd. For $C_{28}H_{34}N_2O_7$: C: 65.88; H: 6.71; N: 5.49. Found: C: 65.67; H: 6.79; N: 5.52.

Example 562

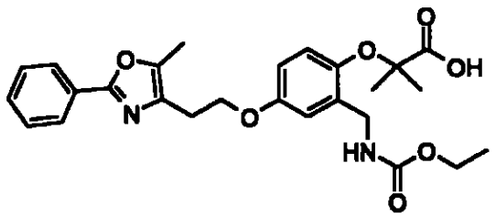
{2-(tert-Butoxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-acetic acid



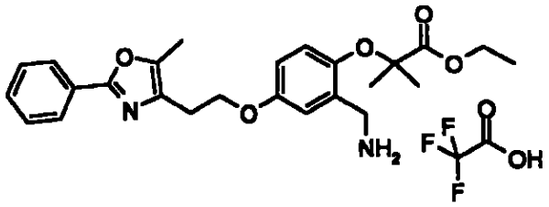
The above compound is prepared by following a substantially similar procedure as described in Example 561. MS [ES] m/z 483.2 (M+1).

Example 563

2-{2-(Ethoxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid



Step A: 2-{2-Aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid ethyl ester: trifluoroacetic acid salt



A solution of 2-{2-(tert-butoxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid ethyl ester (350 mg, 0.650 mmol) in CH_2Cl_2 (10 mL) was treated at ambient temperature with TFA (4 mL) and stirred for 2.5 h. The solution was concentrated and co-evaporated with CCl_4 (3x) to yield the title compound as a foam (381 mg, quantitative).

Step B: 2-{2-(Ethoxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid

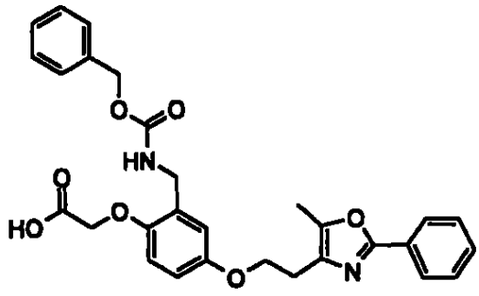
General Parallel Synthesis Procedure: 2-{2-Aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid ethyl ester: trifluoroacetic acid salt (381 mg, 0.650 mmol max.) was dissolved in CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ solution (15 mL). The organic layer was dried ($NaSO_4$), filtered, and concentrated to 2-{2-aminomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid ethyl ester (245 mg, 0.59 mmol, 86%). A portion of this free base (13 mg, 0.030 mmol) in CH_2Cl_2 (0.8 mL) was treated with triethylamine (0.050 mL, 0.36 mmol) then ethyl chloroformate (0.020 mL, 0.21 mmol). The reaction mixture was shaken overnight and dimethylethylenediamine (0.050 mL,

0.47 mmol) was added. The reaction mixture was shaken for 2 h, diluted with MeOH (0.5 mL), and passed through an SCX column (1g, equilibrated with 4 mL MeOH/CH_2Cl_2 1/1). The methyl ester-amide product was eluted with MeOH/CH_2Cl_2 (1:1, 8 mL) and concentrated. The residue was dissolved in THF (1 mL) and EtOH (1 mL) and treated with 2N NaOH (0.5 mL). The solution was heated at 45°C for 45 min, cooled, concentrated, and acidified with 1N HCl (2.5 mL). The mixture was diluted with diluted with CH_2Cl_2 (0.5 mL), transferred to a 3-mL ChemElute cartridge, and eluted with CH_2Cl_2 (8 mL). The solvent was removed under a stream of N_2. The crude product was dried under vacuum and purified by mass-directed HPLC to give a foam (2.7 mg, 19%). %). MS (ES+) m/z 483.5 $[M+H]^+$.

The following Examples 564 to 570 are prepared by following a substantially similar procedure as described in Example 563.

Example 564

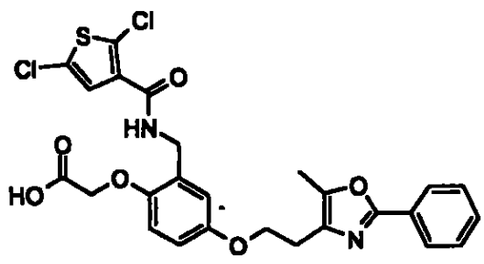
{2-(Benzyloxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-acetic acid



MS [ES] m/z 517.2 (M+1).

Example 565

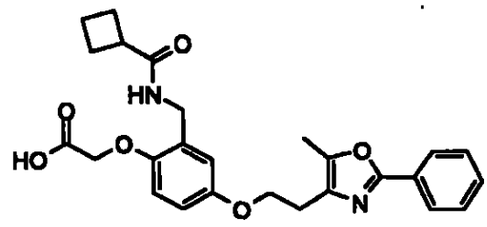
{2-{[(2,5-Dichloro-thiophene-3-carbonyl)-amino]-methyl}-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-acetic acid



MS [ES] m/z 561.1 (M+1).

Example 566

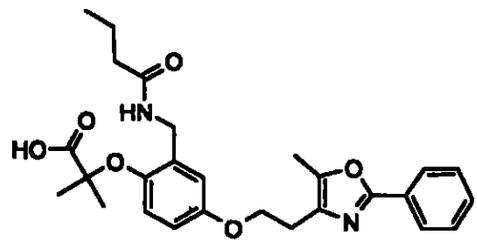
{2-[(Cyclobutanecarbonyl-amino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-acetic acid



MS [ES] m/z 465.2 (M+1).

Example 567

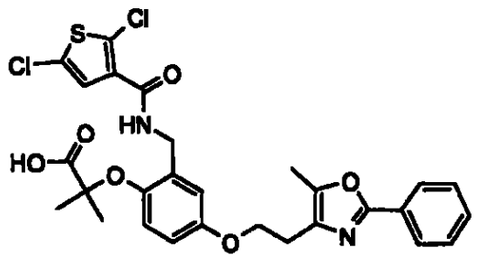
2-{2-(Butyrylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid



MS [ES] 481 m/z (M+1).

Example 568

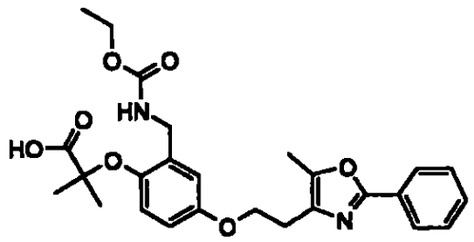
2-{2-{[(2,5-Dichloro-thiophene-3-carbonyl)-amino]-methyl}-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid



MS [ES] m/z 481 (M+1).

Example 569

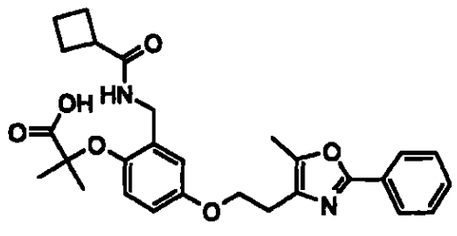
2-{2-(Ethoxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid



MS [ES] m/z 483 (M+1).

Example 570

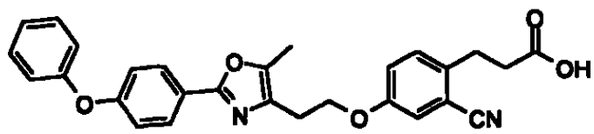
2-{2-[(Cyclobutanecarbonyl-amino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid



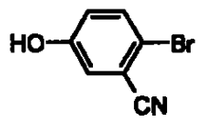
MS [ES] m/z 493 (M+1).

Example 571

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

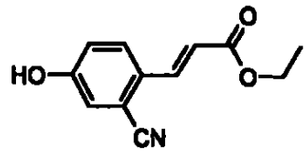


Step A: 2-Bromo-5-hydroxy-benzonitrile



To a stirred solution of 3-cyanophenol (2.00 g, 18.0 mmol) in anhydrous acetonitrile (20 mL) under N_2 at -30°C was added dropwise 54% $HBF_4.Et_2O$ (2.48 mL, 18.0 mmol). The temperature was maintained below -20° C during addition. To this stirred solution was added NBS (3.27 g, 18.0 mmol) portion wise keeping the temperature below -10°C. After the addition was complete, the solution was allowed to warm to 19°C. The reaction mixture was diluted with 38% $NaHSO_3$ (10 mL) and extracted with MTBE (2 x 25 mL). The organic layer was washed with H_2O (2 x 25 mL) and brine (25 mL), dried ($MgSO_4$), filtered, and concentrated to give a white solid (3.15 g). Purification of a portion of this product (1.0 g) by radial chromatography (30% EtOAc/hexane) gave 0.51g of the title compound as a white solid. mp 183-184°C. Anal. Calculated for C_7H_4BrNO: C, 42.46; H, 2.04; N, 7.07. Found: C, 42.44; H, 1.93; N, 6.90.

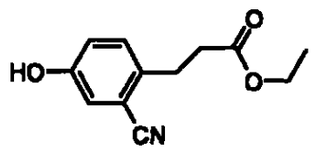
Step B: 2-(3-Ethoxy-buta-1,3-dienyl)-5-hydroxy-benzonitrile



To a stirred solution of 2-bromo-5-hydroxy-benzonitrile (1.4 g, 7.1 mmol), ethyl acrylate (2.12g, 21.2 mmol), palladium(II) acetate (0.159g, 7.0 mmol), diisopropylethylamine (0.82 g, 14.1 mmol), and tri-*ortho*-tolylphosphine (0.430g, 14.1 mmol) was added propionitrile (50 mL). The reaction was stirred overnight at 80°C under a stream of N_2. The mixture was cooled, filtered, and concentrated. The crude

material (3.0g) was purified by radial chromatography (10-70% EtOAc/hexanes) to give the title compound as a white solid (1.1 g). MS [EI] m/z 216 $(M+H)^+$.

Step C: 2-(3-Ethoxy-but-3-enyl)-5-hydroxy-benzonitrile



To a solution of 2-(3-ethoxy-buta-1,3-dienyl)-5-hydroxy-benzonitrile (600mg) in EtOAc (50mL) was added 5% Pd/C (0.3g). The reaction was exposed to hydrogen gas in a Parr apparatus at 60psi overnight at ambient temperature. The reaction mixture was filtered and concentrated to give the title compound (410 mg). MS [EI] m/z 218 $(M+H)^+$.

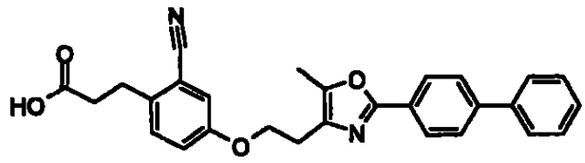
Step D: 3-(2-Cyano-4-{2-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid

A mixture of 2-(3-ethoxy-but-3-enyl)-5-hydroxy-benzonitrile (220 mg, 1.00 mmol), toluene-4-sulfonic acid 2-[5-methyl-2-(4-phenoxy-phenyl)-oxazol-4-yl]-ethyl ester (450 mg, 1.00 mmol; Preparation 6), and $CsCO_3$ (978 mg, 3.00 mmol) in DMF (10mL) was stirred overnight at 60°C under an N_2. The mixture was cooled, diluted with EtOAc (20 mL) and washed with brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. The product mixture was purified by radial chromatography (10-70% EtOAc/hexanes) to give 3-(2-cyano-4-{2-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid ethyl ester (201 mg). A solution of this ester in EtOH (10 mL) and 5N NaOH (10 mL) was heated at 70°C overnight, concentrated, acidified with 1N HCl, and extracted with EtOAc. The organic layer dried (Na_2SO_4) and concentrated to give the title compound (192 mg). MS [ES] m/z 469 (M+1).

The following Examples 572 to 573 and 575 to 581 are prepared by following a substantially similar procedure as described in Example 571.

Example 572

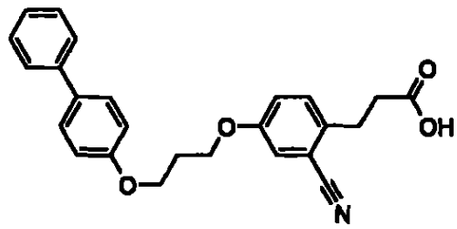
3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-cyanophenyl} propionic acid:



MS [ES] m/z 453 (M+1).

Example 573

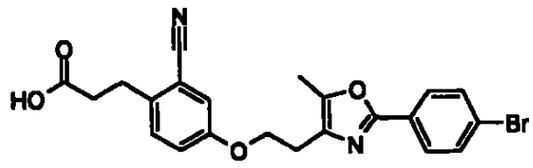
3-{4-[3-(Biphenyl-4-yloxy)propoxy]-2-cyanophenyl} propionic acid



MS [ES] m/z 402 (M+1).

Example 575

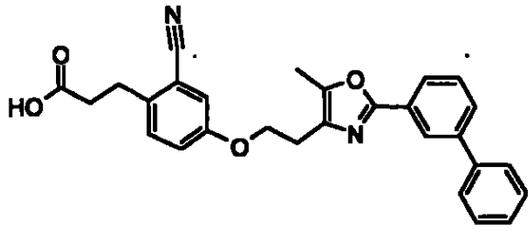
3-(4-{2-[2-(4-Bromo-phenyl)-5-methyloxazol-4-yl]ethoxy}-2-cyanophenyl) propionic acid



MS [ES] m/z 456 (M+1)..

Example 576

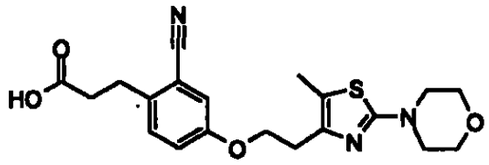
3-{4-[2-(2-Biphenyl-3-yl-5-methyloxazol-4-yl)ethoxy]-2-cyanophenyl} propionic acid



MS [ES] m/z 453 (M+1).

Example 577

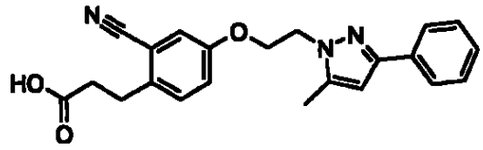
3-{2-Cyano-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl)ethoxy]phenyl} propionic acid



MS [ES] m/z 402 (M+1).

Example 578

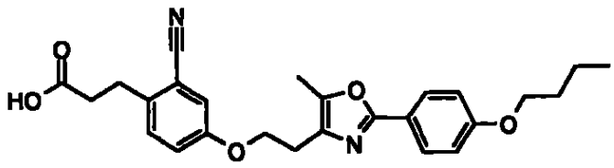
3-{2-Cyano-4-[2-(5-methyl-3-phenylpyrazol-1-yl)ethoxy]phenyl} propionic acid:



MS [ES] m/z 376 (M+1).

Example 579

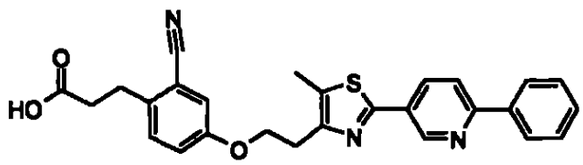
3-(4-{2-[2-(4-Butoxyphenyl)-5-methyloxazol-4-yl]ethoxy}-2-cyanophenyl) propionic acid



MS [ES] m/z 449 (M+1).

Example 580

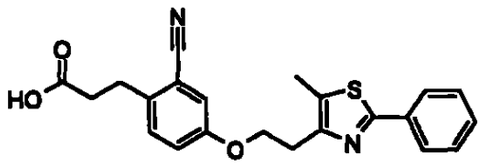
3-(2-Cyano-4-{2-[5-methyl-2-(6-phenylpyridin-3-yl)thiazol-4-yl]ethoxy}phenyl) propionic acid



MS [ES] m/z 470 (M+1).

Example 581

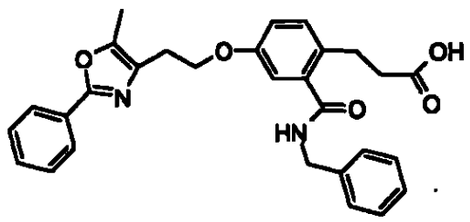
3-{2-Cyano-4-[2-(5-methyl-2-phenylthiazol-4-yl)ethoxy]phenyl} propionic acid



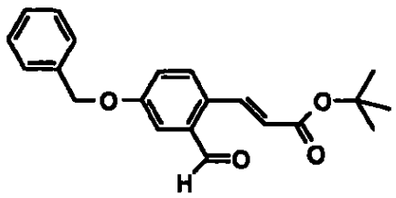
MS [ES] m/z 393 (M+1).

Example 582

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



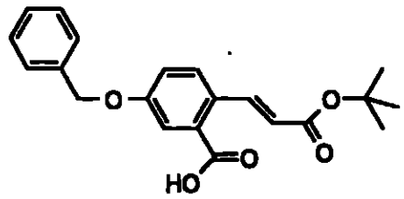
Step A: 3-(4-Benzyloxy-2-formyl-phenyl)-acrylic acid tert-butyl ester



To a solution of 3-(2-formyl-4-hydroxy-phenyl)-acrylic acid *tert*-butyl ester (4.97 g, 20.0 mmol) in DMF (40 mL) was added benzyl bromide (2.85 mL, 24.0

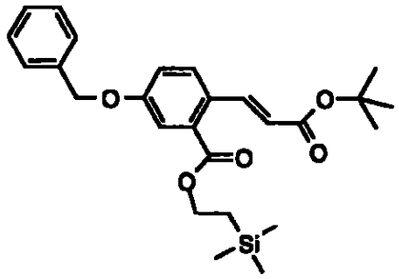
mmol) and Cs_2CO_3 (7.82 g, 24.0 mmol). The suspension was stirred at 80°C for 30 min, and TLC indicated the reaction was complete. The mixture was quenched with H_2O (500 mL) and extracted with EtOAc (2 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated to a residue, which was purified by silica gel chromatography (hexanes/EtOAc 9/1) to afford the title compound as yellow solid (6.70 g, 99%).

Step B: 5-Benzyloxy-2-(2-tert-butoxycarbonyl-vinyl)-benzoic acid



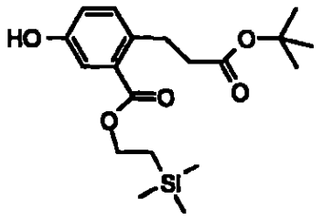
A solution of 3-(4-benzyloxy-2-formyl-phenyl)-acrylic acid tert-butyl ester (6.70 g, 19.8 mmol) in *tert*-butanol (150 mL) was treated with 2-methyl-2-butene (50 mL) and cooled to 0°C. A solution of $NaClO_2$ (17.0 g, 188 mmol) and NaH_2PO_4 (17.0 g, 142 mmol) in H_2O (200 mL) was added, and the mixture was stirred at 0°C for 15 min. The ice bath was removed, and the mixture was stirred at room temperature for 2 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified using silica gel chromatography (hexanes/EtOAc 9/1 to 0/10) to afford the title compound as white solid (6.78 g, 96%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.52 (s, 9 H), 5.12 (s, 2 H), 6.20 (d, 1H, J = 16.2 Hz), 7.13 (dd, 1H, J=3.6, 9.0 Hz), 7.34-7.45 (m, 5H), 7.58 (d, 1H, J=8.8 Hz), 7.64 (d, 1H, J=2.4 Hz), 8.41 (d, 1H, J = 16.2 Hz).

Step C: 5-Benzyloxy-2-(2-tert-butoxycarbonyl-vinyl)-benzoic acid 2-trimethylsilanyl-ethyl ester



To a solution of 5-benzyloxy-2-(2-tert-butoxycarbonyl-vinyl)-benzoic acid (5.50 g, 15.5 mmol) in CH_2Cl_2 (100 mL) was added 2-trimethylsilyl-ethanol (3.67 g, 31.0 mmol), EDC (5.36 g, 27.9 mmol), and DMAP (3.67 g, 31.0 mmol). The resulting mixture was stirred at room temperature for 12 h, washed with aqueous NH_4Cl (150 mL), and extracted with CH_2Cl_2 (100 mL). The combined organics were dried (Na_2SO_4) and concentrated. The residue was purified using silica gel chromatography (hexanes/EtOAc 9/1) to afford the title compound as an oil (5.90 g, 84%). ^1H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 9H), 1.14 (t, 2H, J = 8.8 Hz), 1.52 (s, 9 H), 4.41 (t, 2H, J = 8.8 Hz), 5.10 (s, 2 H), 6.20 (d, 1H, J = 15.6 Hz), 7.13 (dd, 1H, J=3.0, 8.3 Hz), 7.34-7.44 (m, 5H), 7.50 (d, 1H, J=3.0 Hz), 7.53 (d, 1H, J=8.8 Hz), 8.41 (d, 1H, J = 16.1 Hz).

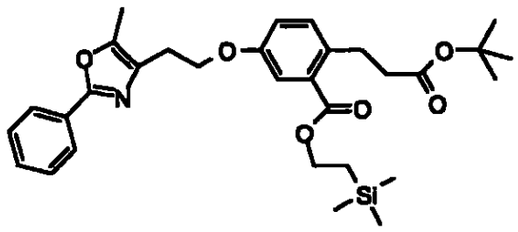
Step D: 2-(2-tert-Butoxycarbonyl-ethyl)-5-hydroxy-benzoic acid 2-trimethylsilanyl-ethyl ester



A solution of 5-benzyloxy-2-(2-tert-butoxycarbonyl-vinyl)-benzoic acid 2-trimethylsilanyl-ethyl ester (6.20 g, 13.6 mmol) in EtOH (95 mL) was treated with Pd/C (5%, 0.775 g). The resulting suspension was treated with hydrogen at 60 psi for 6 h at room temperature. The catalyst was filtered through a pad of Celite, and the filtrate was concentrated to an oil (4.30 g, 86%). ^1H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 9H), 0.96 (t,

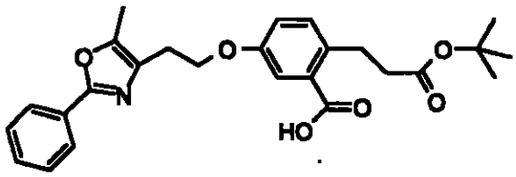
1H, J = 8.8 Hz), 1.12 (t, 1H, J = 8.8 Hz), 1.40 (s, 9 H), 2.52 (t, 1H, J = 7.8 Hz), 3.13 (t, 1H, J = 7.8 Hz), 3.73 (t, 1H, J = 8.5 Hz), 4.36 (t, 1H, J = 8.5 Hz), 5.00 (br s, 1 H), 6.88 (dd, 1H, J=2.4, 8.3 Hz), 7.14 (d, 1H, J=8.3 Hz), 7.35 (d, 1H, J=2.4 Hz).

Step E: 2-(2-tert-Butoxycarbonyl-ethyl)-5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzoic acid 2-trimethylsilanyl-ethyl ester



To a solution of 2-(2-tert-butoxycarbonyl-ethyl)-5-hydroxy-benzoic acid 2-trimethylsilanyl-ethyl ester (4.30 g, 11.7 mmol) and toluene-4-sulfonic acid 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl ester (4.61 g, 12.9 mmol) in DMF (30 mL) was added Cs_2CO_3 (4.59 g, 14.1 mmol). The suspension was stirred at 55°C for 12 h. The reaction mixture was quenched with H_2O (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated to a residue, which was purified using silica gel chromatography (hexanes/EtOAc 9/1 to 8/2) to afford the title compound as a colorless oil (5.04 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 9H), 1.11 (t, 2H, J = 8.8 Hz), 1.40 (s, 9 H), 2.36 (s, 3 H), 2.51 (t, 1H, J = 7.8 Hz), 2.97 (t, 2H, J = 6.8 Hz), 3.12 (t, 1H, J = 7.8 Hz), 4.24 (t, 2H, J = 6.8 Hz), 4.35 (t, 2H, J = 8.8 Hz), 6.88 (dd, 1H, J=3.0, 8.3 Hz), 7.15 (d, 1H, J=8.3 Hz), 7.37-7.44 (m, 4H), 7.97 (d, 2H, J=7.8 Hz).

Step F: 2-(2-tert-Butoxycarbonyl-ethyl)-5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzoic acid



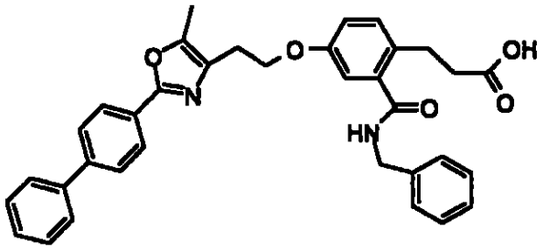
A solution of 2-(2-tert-butoxycarbonyl-ethyl)-5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzoic acid 2-trimethylsilanylethyl ester (5.04 g, 9.13 mmol) in THF (100 mL) was treated with TBAF (20 mL, 1.0 M) at room temperature for 1 h. The reaction mixture was concentrated and purified using silica gel chromatography (hexanes/EtOAc 1/1) to afford the title compound as a colorless oil (4.04 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 9 H), 2.37 (s, 3 H), 2.55 (t, 2H, J = 7.3 Hz), 2.98 (t, 2H, J = 6.5 Hz), 3.15 (t, 2H, J = 7.3 Hz), 4.26 (t, 2H, J = 6.5 Hz), 4.35 (t, 2H, J = 8.8 Hz), 6.99 (dd, 1H, J=2.9, 8.8 Hz), 7.18 (d, 1H, J=8.3 Hz), 7.38-7.43 (m, 3H), 7.49 (d, 1H, J=2.9 Hz), 7.97 (d, 2H, J=7.8 Hz). MS (ES) m/z 522.3 $[M+H]^+$.

Step G: 3-{2-Benzylcarbamoyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

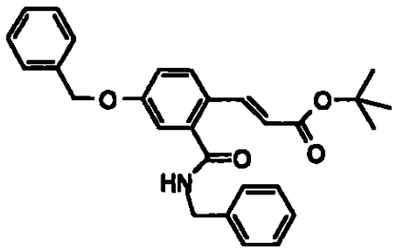
To a solution of 2-(2-tert-butoxycarbonyl-ethyl)-5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzoic acid (93 mg, 0.200 mmol) in CH_2Cl_2 (2 mL) was added benzylamine (52 mg g, 0.49 mmol), EDC (54 mg, 0.28 mmol), triethylamine (0.057 ml, 0.40 mmol), and DMAP (catalyst). The resulting mixture was stirred at room temperature for 12 h and washed with aqueous NH_4Cl (2 mL). The organic layer was purified using a silica gel column (Sep-Pak column, 10 g; hexanes/EtOAc 1/1) to afford the *tert*-butyl ester intermediate. The ester was treated a mixture of CH_2Cl_2 (1.0 mL), TFA (0.8 mL), and water (0.1 mL) at room temperature for 2 h. The reaction mixture was concentrated and dried under vacuum to afford the title product as a white solid (35 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3 H), 2.59 (t, 2H, J = 7.3 Hz), 2.88-2.98 (m, 4H, J = 6.5 Hz), 4.16 (t, 2H, J = 6.5 Hz), 4.52 (s, 2H), 6.83 (dd, 1H, J=2.6, 8.4 Hz), 6.87 (d, 1 H, J=2.4 Hz), 7.10 (d, 1H, J=8.3 Hz), 7.20-7.30 (m, 3H), 7.37-7.40 (m, 3 H), 7.88-7.91(m, 2H). MS (ES) m/z 485.2 $[M+H]^+$, m/z 483.4 $[M-H]^-$.

Example 583

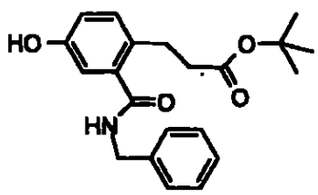
3-{2-Benzylcarbamoyl-4-[2-(2-biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid



Step A: 3-(2-Benzylaminocarbonyl-4-benzyloxy-phenyl)-acrylic acid *tert*-butyl ester



To a solution of 5-benzyloxy-2-(2-tert-butoxycarbonyl-vinyl)-benzoic acid (1.45 g, 4.09 mmol) in CH_2Cl_2 (40 mL) was added benzylamine (0.613 g, 5.73 mmol), EDC (1.254 g, 6.54 mmol), and DMAP (1.00 g, 8.18 mmol). The resulting mixture was stirred at room temperature for 12 h, washed with aqueous NH_4Cl (50 mL), and extracted with CH_2Cl_2 (2X50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was then purified using silica gel chromatography (hexanes/EtOAc 8/2) to afford the title compound as an oil (720 mg, 40%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.52 (s, 9 H), 4.63 (d, 2H, J = 5.5 Hz), 5.09 (s, 2 H), 5.97 (br s, 1 H), 6.22 (d, 1H, J = 15.6 Hz), 7.01 (dd, 1H, J=2.7, 8.6 Hz), 7.10 (d, 1H, J = 2.8 Hz), 7.28-7.42 (m, 10H), 7.55 (d, 1H, J=9.0 Hz), 7.88 (d, 1H, J = 16.0 Hz).



A solution of 3-(2-benzylaminocarbonyl-4-benzyloxy-phenyl)-acrylic acid *tert*-butyl ester (720 mg, 1.625 mmol) in EtOH (15 mL) and THF (5 mL) was treated with

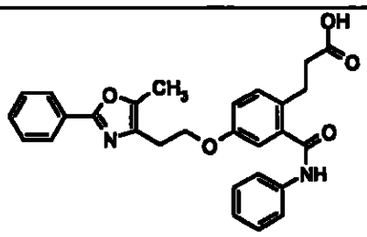
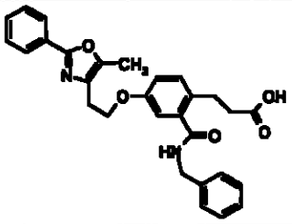
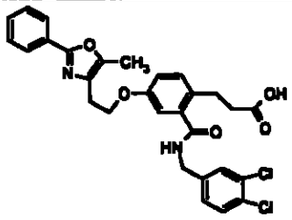
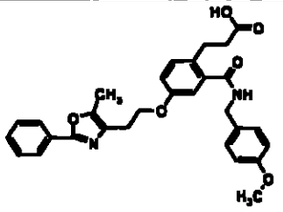
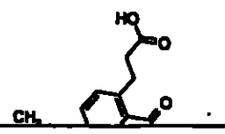
Pd/C (5%, 70 mg). The resulting suspension was treated with hydrogen using a balloon for 4 h at room temperature. The catalyst was filtered through a pad of celite and the filtrate was concentrated to an oil (450 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 9 H), 2.56 (t, 2H, J = 7.0 Hz), 2.90 (t, 2H, J = 7.0 Hz), 4.59 (d, 1H, J = 5.9 Hz), 6.74 (dd, 1H, J=2.7, 8.2 Hz), 6.89 (d, 1H, J = 2.7 Hz), 7.01(d, 1H, J = 8.2 Hz), 7.25-7.36 (m, 5H). MS (ES) m/z 356.2 $[M+H]^+$, m/z 354.0 $[M-H]^-$.

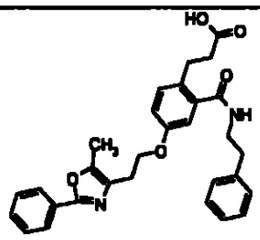
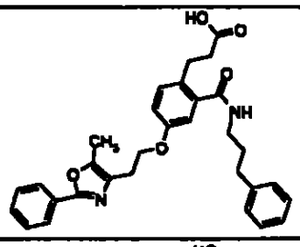
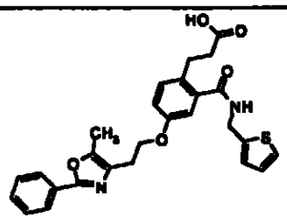
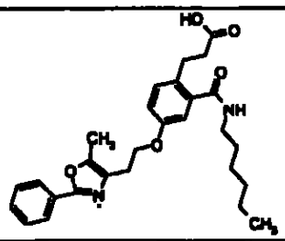
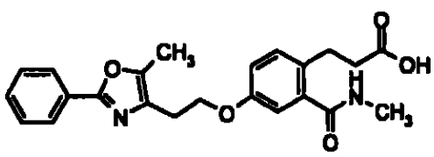
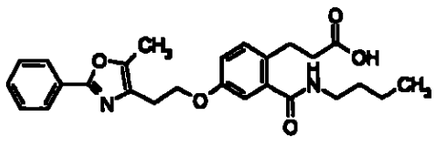
Step C: 3-{2-Benzylcarbamoyl-4-[2-(2-biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

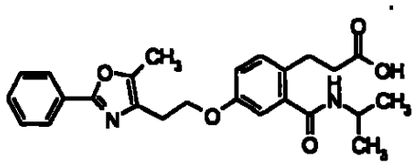
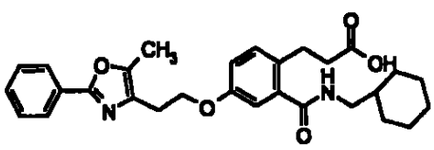
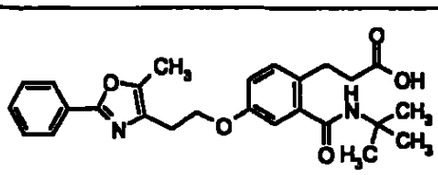
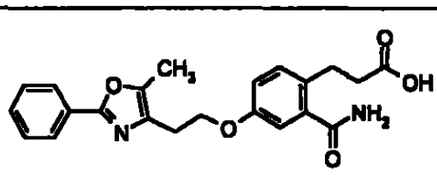
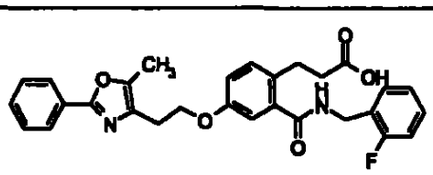
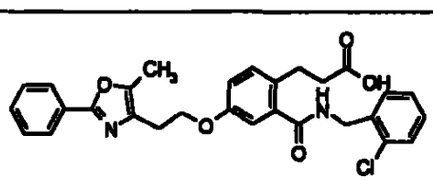
To a solution of 3-(2-benzylaminocarbonyl-4-hydroxy-phenyl)-propionic acid *tert*-butyl ester (50 mg, 0.140 mmol) and toluene-4-sulfonic acid 2-(5-methyl-2-(4-phenylphenyl)-oxazol-4-yl)-ethyl ester (73 mg, 0.168 mmol) in DMF (1.0 mL) was added K_2CO_3 (100 mg, 0.724 mmol). The suspension was stirred at 65°C for 12 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3x10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to a residue, which was purified using silica gel chromatography (hexanes/EtOAc 7/3) to afford the *tert*-butyl ester intermediate as an oil. The ester was treated a mixture of CH_2Cl_2 (1.0 mL), TFA (0.8 mL) and water (0.1 mL) at room temperature for 2 h. The reaction mixture was concentrated and dried under vacuum to afford the title product as a white solid (37 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3 H), 2.59 (t, 2H, J = 7.3 Hz), 2.94 (t, 4H, J = 7.2 Hz), 4.20 (t, 2H, J = 6.5 Hz), 4.55 (s, 2H), 6.85 (dd, 1H, J=2.9, 8.2 Hz), 6.90 (d, 1 H, J=2.4 Hz), 7.12 (d, 1H, J=8.6 Hz), 7.20-7.36 (m, 6H), 7.42 (t, 2H, J=7.4 Hz), 7.59 (d, 2H, J=8.6 Hz), 7.64 (d, 2H, J=8.2 Hz), 8.00 (d, 2H, J=8.6 Hz). MS (ES) m/z 561.3 $[M+H]^+$, m/z 559.5 $[M-H]^-$.

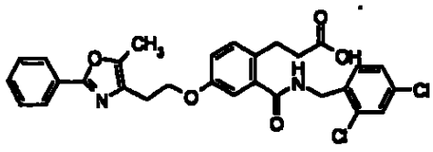
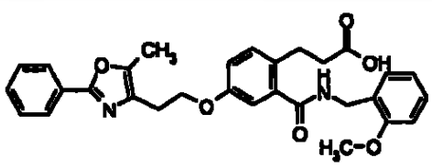
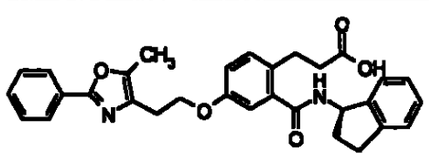
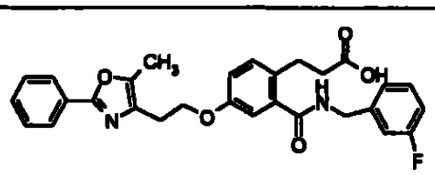
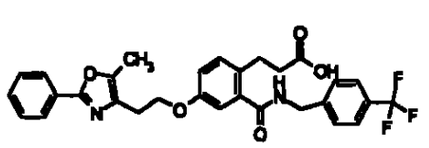
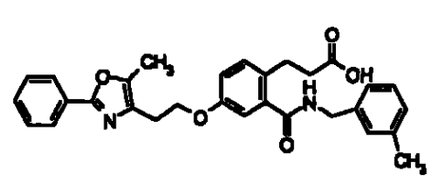
Examples 584-643

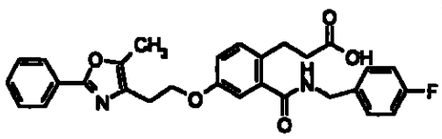
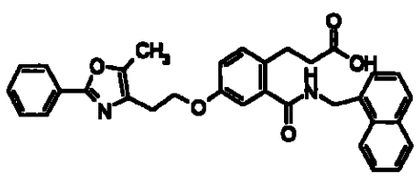
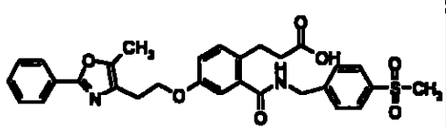
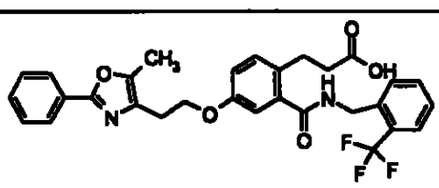
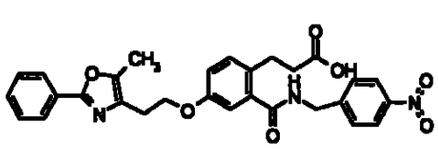
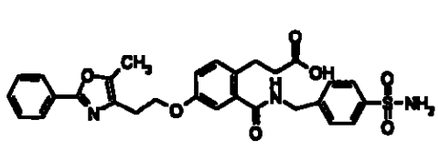
Examples 584 to 643 are prepared by following a substantially similar procedure as described in Examples 582 and 583. Examples 584 to 628 are prepared by following a substantially similar procedure as described in Example 582. Examples 629 to 643 are prepared by following a substantially similar procedure as described in Example 583.

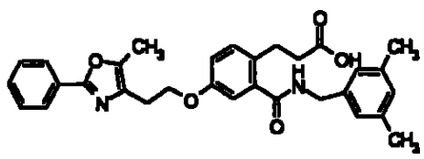
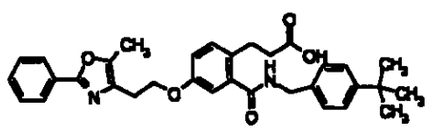
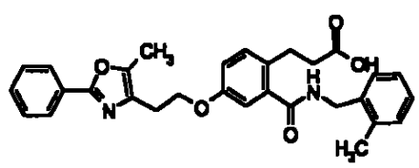
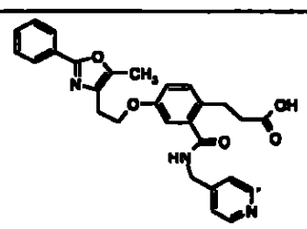
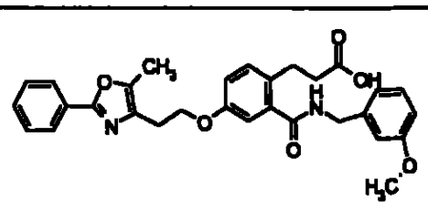
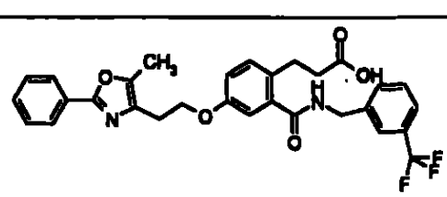
No.	Compounds	Name	MS (ES+)
584		3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-phenyl-carbamoyl-phenyl}-propionic acid	471.2
585		3-{2-Benzylcarbamoyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	485.2
586		3-{2-(3,4-Dichloro-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	553
587		3-{2-(4-Methoxy-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	515.2
588		3-{2-[(Biphenyl-3-yl methyl)-carbamoyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	561.2

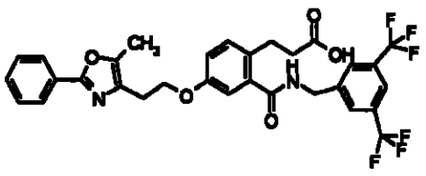
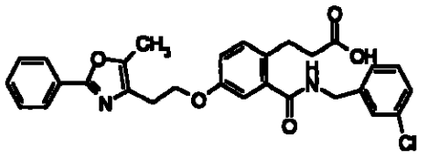
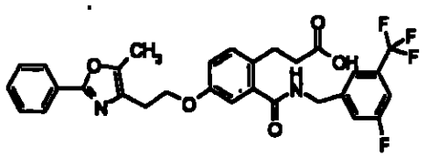
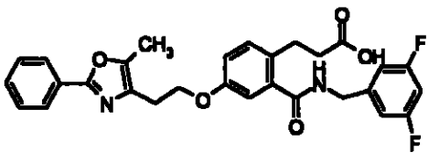
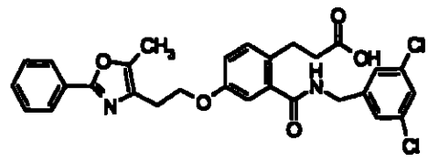
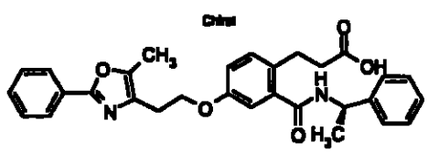
No.	Compounds	Name	MS (ES+)
589		3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-phenethyl-carbamoyl-phenyl}-propionic acid	499.3
590		3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-(3-phenyl-propylcarbamoyl)-phenyl]-propionic acid	513.3
591		3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(thiophen-2-ylmethyl)-carbamoyl]-phenyl}-propionic acid	491.2
592		3-{2-Hexylcarbamoyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	479.3
593		3-{2-Methylcarbamoyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	409.1
594		3-{2-Butylcarbamoyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	451.1

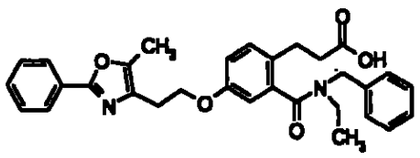
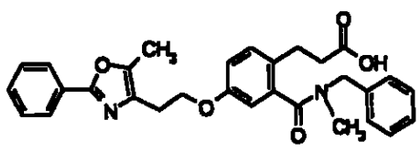
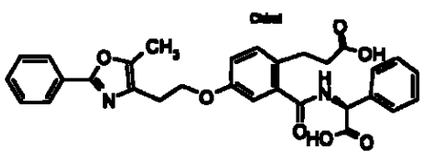
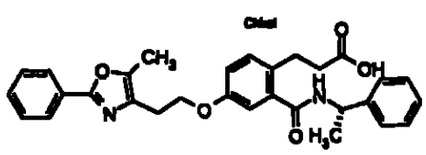
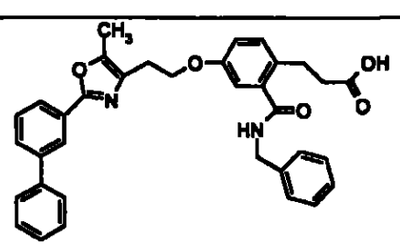
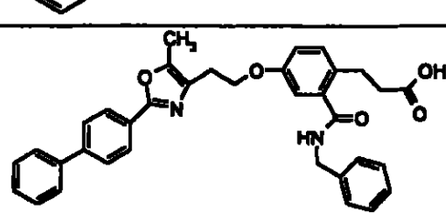
No.	Compounds	Name	MS (ES+)
595		3-{2-Isopropylcarbamoyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	437.2
596		3-{2-(Cyclohexylmethyl-carbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	491.2
597		3-{2-tert-Butylcarbamoyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	451.2
598		3-{2-Carbamoyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	395.1
599		3-{2-(2-Fluoro-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	503.1
600		3-{2-(2-Chloro-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	519.1

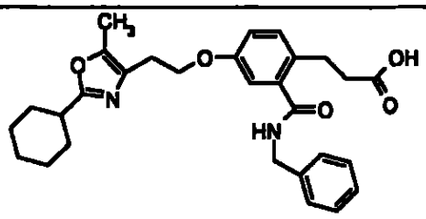
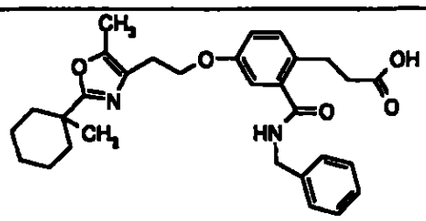
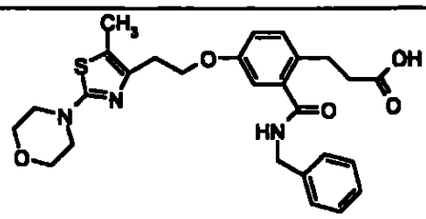
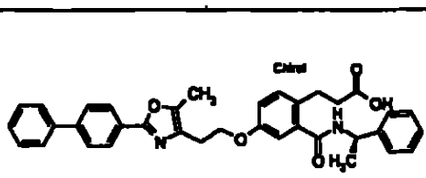
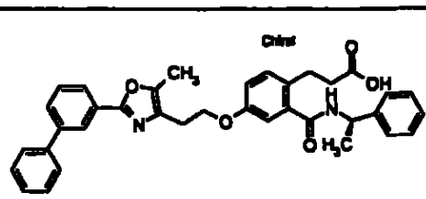
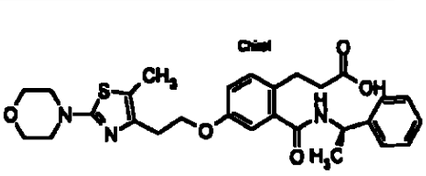
No.	Compounds	Name	MS (ES+)
601		3-{2-(2,4-Dichloro-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	553
602		3-{2-(2-Methoxy-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	515.1
603		3-{2-(Indan-1-ylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	511.1
604		3-{2-(3-Fluoro-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	503.1
605		3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-(4-trifluoro methyl-benzylcarbamoyl)-phenyl]-propionic acid	553
606		3-{2-(3-Methyl-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	499.1

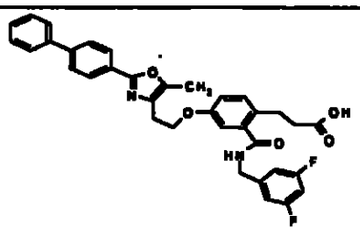
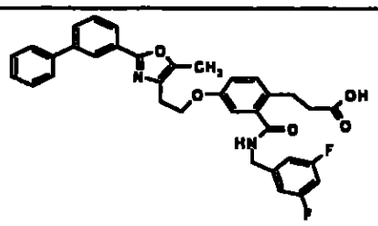
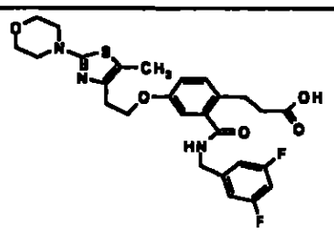
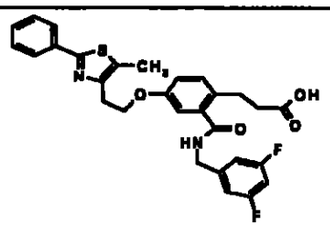
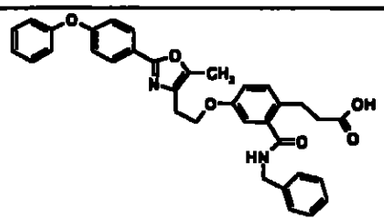
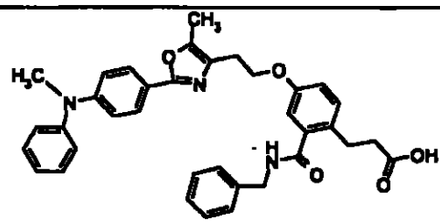
No.	Compounds	Name	MS (ES+)
607		3-{2-(4-Fluoro-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	503.1
608		3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(naphthalen-1-ylmethyl)-carbamoyl]-phenyl}-propionic acid	535.1
609		3-{2-(4-Methanesulfonyl-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	563.1
610		3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-(2-trifluoro methyl-benzylcarbamoyl)-phenyl]-propionic acid	553.1
611		3-{2-(4-Nitro-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	530.1
612		3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-(4-sulfamoyl-benzylcarbamoyl)-phenyl]-propionic acid	564.1

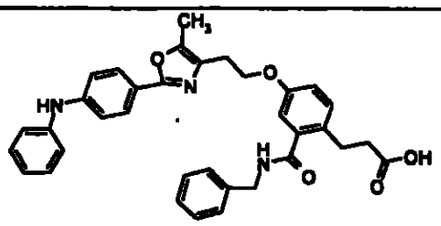
No.	Compounds	Name	MS (ES+)
613		3-{2-(3,5-Dimethyl-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	513.2
614		3-{2-(4-tert-Butyl-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	541.2
615		3-{2-(2-Methyl-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	499.2
616		3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(pyridin-4-ylmethyl)-carbamoyl]-phenyl}-propionic acid	486.2
617		3-{2-(3-Methoxy-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	515.2
618		3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-(3-trifluoro methyl-benzylcarbamoyl)-phenyl]-propionic acid	553.1

No.	Compounds	Name	MS (ES+)
619		3-{2-(3,5-Bis-trifluoro methyl-benzyl-carbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	621.1
620		3-{2-(3-Chloro-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	519.1
621		3-{2-(3-Fluoro-5-trifluoro methyl-benzyl carbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	571.1
621		3-{2-(3,5-Difluoro-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	521.1
623		3-{2-(3,5-Dichloro-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	553
624		(R)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-(1-phenyl-ethylcarbamoyl)-phenyl]-propionic acid	499.2

No.	Compounds	Name	MS (ES+)
625		3-{2-(Benzyl-ethyl-carbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	513.2
626		3-{2-(Benzyl-methyl-carbamoyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	499.2
627		(S)-3-{2-[(Carboxy-phenyl-methyl) carbamoyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	529.1
628		(S)-3-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-(1-phenyl-ethylcarbamoyl)-phenyl]-propionic acid	499.2
629		3-{2-Benzylcarbamoyl-4-[2-(2-biphenyl-3-yl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	561.3
630		3-{2-Benzylcarbamoyl-4-[2-(2-biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	561.3

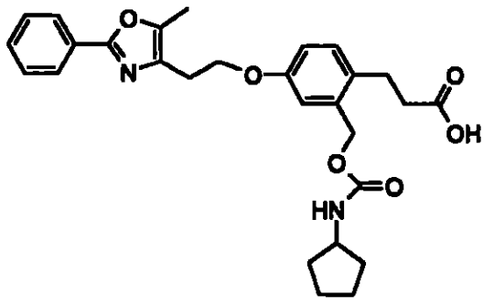
No.	Compounds	Name	MS (ES+)
631		3-{2-Benzylcarbamoyl-4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid	491.3
632		3-(2-Benzylcarbamoyl-4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid	505.4
633		3-{2-Benzylcarbamoyl-4-[2-(5-methyl-2-morpholin-4-yl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid	510.3
634		(R)-3-[4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-(1-phenyl-ethylcarbamoyl)- phenyl]-propionic acid	575.3
635		(R)-3-[4-[2-(2-Biphenyl-3-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-(1-phenyl-ethylcarbamoyl)-phenyl]-propionic acid	575.3
636		(R)-3-[4-[2-(5-Methyl-2-morpholin-4-yl-thiazol-4-yl)-ethoxy]-2-(1-phenyl ethylcarbamoyl)-phenyl]-propionic acid	524.2

No.	Compounds	Name	MS (ES+)
637		3-[4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-(3,5-difluoro-benzylcarbamoyl)-phenyl]-propionic acid	597.3
638		3-[4-[2-(2-Biphenyl-3-yl-5-methyl-oxazol-4-yl)-ethoxy]-2-(3,5-difluoro-benzylcarbamoyl)-phenyl]-propionic acid	597.3
639		3-{2-(3,5-Difluoro-benzylcarbamoyl)-4-[2-(5-methyl-2-morpholin-4-yl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid	546.1
640		3-{2-(3,5-Difluoro-benzylcarbamoyl)-4-[2-(5-methyl-2-phenyl-thiazol-4-yl)-ethoxy]-phenyl}-propionic acid	537.1
641		3-(2-Benzylcarbamoyl-4-{2-[5-methyl-2-(4-phenoxy-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid	577.3
642		3-[2-Benzylcarbamoyl-4-(2-{5-methyl-2-[4-(methyl-phenyl-amino)-phenyl]-oxazol-4-yl}-ethoxy)-phenyl]-propionic acid	590.2

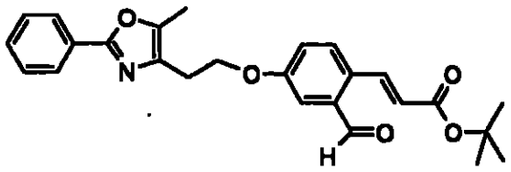
No.	Compounds	Name	MS (ES+)
643		3-(2-Benzylcarbamoyl-4-{2-[5-methyl-2-(4-phenylamino-phenyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid	576.2

Example 644

3-{2-Cyclopentylcarbamoyloxymethyl-4-[2-(2-phenyloxazol-4-yl)ethoxy]phenyl}-propionic acid



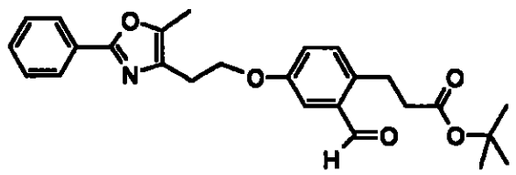
Step A: 3-{2-Formyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}acrylic acid *tert*-butyl ester



A flame-dried 100 mL round bottomed flask was charged with toluene-4-sulfonic acid 2-(5-methyl-2-phenyloxazol-4-yl) ethyl ester (3.74 g, 10.5 mmol), 3-(2-formyl-4-hydroxyphenyl)acrylic acid *tert*-butyl ester (2.0 g, 8.05 mmol), and anhydrous DMF (40 mL). Cesium carbonate (3.94 g, 12.1 mmol) was added, and the reaction was heated to 55° C under a nitrogen atmosphere for 18 h. The volatiles were removed *in vacuo*, and the crude residue was dissolved in EtOAc (250 mL). The organic layer was washed with brine (2x), dried (Na_2SO_4), and concentrated to a yellow oil (1.70 g, 49%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 2.38 (s, 3H), 3.01 (t, J= 6.6 Hz, 2H), 4.34 (t,

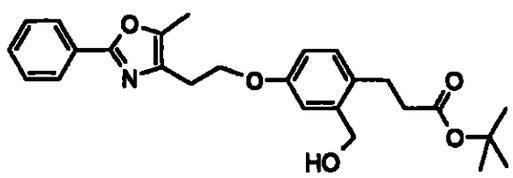
J= 6.6 Hz, 2H), 6.24 (d, J= 15.6 Hz, 1H), 7.12 (dd, J= 8.8, 2.9 Hz, 1H), 7.38 (d, J= 2.9 Hz, 1H), 7.40-7.45 (m, 3H), 7.58 (d, J= 8.8 Hz, 1H), 7.98 (dd, J= 6.4, 2.0 Hz, 2H), 8.33 (d, J= 15.6 Hz, 1H), 10.3 (s, 1H). MS (ES) *m/e* 434 (M+1).

Step B: 3-{2-Formyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}acrylic acid *tert*-butyl ester



A 100 mL round bottomed flask was charged with 3-{2-formyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)-ethoxy]phenyl}acrylic acid *tert*-butyl ester (1.69 g, 3.90 mmol), THF (40 mL), and then 10% Pd/C catalyst (0.17 g). The reaction was stirred vigorously under a hydrogen atmosphere at one atmosphere for 18 h. The mixture was filtered through Celite and concentrated to a yellow solid (1.70 g, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, J= 4.9 Hz, 9H), 2.37 (d, J= 2.9 Hz, 3H), 2.51 (t, J= 7.6 Hz, 2H), 2.99 (t, J= 6.6 Hz, 2H), 3.23 (t, J= 7.1 Hz, 2H), 4.29 (t, J= 6.6 Hz, 2H), 7.04-7.10 (m, 1H), 7.21 (d, J= 8.3 Hz, 1H), 7.34 (d, J= 2.4 Hz, 1H), 7.38-7.45 (m, 3H), 7.97 (dd, J= 7.3, 2.0 Hz, 2H), 10.2 (s, 1H). MS (ES) *m/e* 436 (M+1).

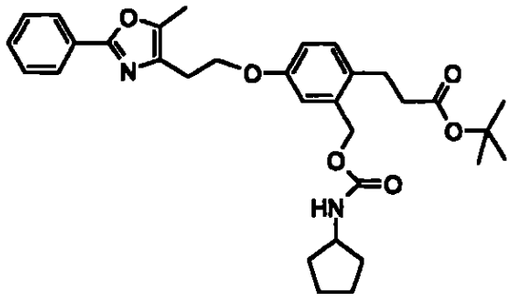
Step C: 3-{2-Hydroxymethyl-4-[2-(2-phenyl-oxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester



A 100 mL round bottomed flask was charged with 3-{2-formyl-4-[2-(2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester (1.82 g, 4.18 mmol) and absolute ethanol (20 mL). The stirring solution was cooled in an ice/ethanol bath and treated with sodium borohydride (0.31 g, 8.36 mmol). The cold bath was removed, and the mixture was stirred at ambient temperature under a nitrogen atmosphere for 2 h. The

reaction mixture was poured into EtOAc (100 mL) and ice water (100 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to a yellow oil (1.62 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.37 (s, 3H), 2.54 (t, J= 7.6 Hz, 2H), 2.88 (t, J= 7.6 Hz, 2H), 2.97 (t, J= 6.6 Hz, 2H), 4.23 (t, J= 6.6 Hz, 2H), 4.66 (s, 2H), 6.78 (dd, J= 8.3, 2.9 Hz, 1H), 6.94 (d, J= 2.4 Hz, 1H), 7.09 (d, J= 8.3 Hz, 1H), 7.38-7.45 (m, 3H), 7.97 (dd, J= 8.1, 1.7 Hz, 2H). MS (ES) *m/e* 438 (M+1).

Step D: 3-{2-Cyclopentylcarbamoyloxymethyl-4-[2-(2-phenyloxazol-4-yl)ethoxy]phenyl}-propionic acid *tert*-butyl ester



A 15 mL round bottomed flask was charged with 3-{2-hydroxymethyl-4-[2-(2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester (0.10 g, 0.23 mmol), cyclopentylisocyanate (0.15 mL, 1.38 mmol), and anhydrous CH_2Cl_2 (0.75 mL). A 1.0 M HCl solution in ether (0.115 mL, 0.115 mmol) was added, and the reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 24 h. The reaction mixture was diluted with CH_2Cl_2, (30 mL), washed with brine, dried (Na_2SO_4), and concentrated to an oil. The crude product was purified using radial chromatography (EtOAc:hexanes 10:90 to 35:65) to a colorless oil (0.105 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.56-1.65 (m, 4H), 1.94-2.04 (m, 2H), 2.37 (s, 3H), 2.46 (t, J= 7.6 Hz, 2H), 2.87 (t, J= 8.1 Hz, 2H), 2.96 (t, J= 6.6 Hz, 2H), 3.97 (br s, 1H), 4.22 (t, J= 6.6 Hz, 2H), 4.76 (br s, 1H), 5.07 (s, 2H), 6.90 (dd, J= 8.3, 2.4 Hz, 1H), 6.89 (s, 1H), 7.10 (d, J= 8.8 Hz, 1H), 7.40-7.45 (m, 3H), 7.96-7.98 (m, 2H). MS (ES) *m/e* 549 (M+1).

Step E: 3-{2-Cyclopentylcarbamoyloxymethyl-4-[2-(2-phenyloxazol-4-yl)ethoxy]phenyl}-propionic acid

A 15 mL round bottom flask was charged with 3-{2-cyclopentylcarbamoyloxymethyl-4-[2-(2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester (0.097 g, 0.18 mmol), CH_2Cl_2 (1.2 mL), and then trifluoroacetic acid (1.2 mL). The solution was stirred at ambient temperature under a nitrogen atmosphere for 4 h and was concentrated. The residue was purified using radial chromatography (MeOH:CH_2Cl_2 2:98 to 10:90) to give a white solid (0.085 g, 93%) . ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (br s, 2H), 1.63 (br s, 4H), 1.93-2.05 (m, 2H), 2.39 (s, 3H), 2.64 (br s, 2H), 2.91-3.18 (m, 4H), 3.99 (br s, 1H), 4.21 (s, 2H), 4.87 (br s, 1H), 5.10 (br s, 2H), 6.80 (s, 1H), 6.89 (s, 1H), 7.00-7.25 (br s, 1H), 7.36-7.52 (m, 3H), 7.95 (s, 2H). MS (ES) *m/e* 493 (M+1).

The following Examples 645 to 651 are prepared by following a substantially similar procedure as described in Example 644.

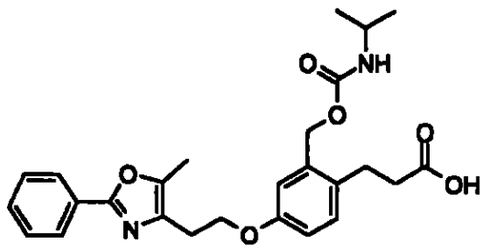
Example 645

3-{2-Isopropylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester

MS (ES) *m/e* 523 (M+1).

Example 646

3-{2-Isopropylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J= 5.4 Hz, 6H), 2.37 (s, 3H), 2.61 (t, J= 7.8 Hz, 2H), 2.92-2.98 (m, 4H), 3.80 (br s, 1H), 4.21 (t, J= 6.6 Hz, 2H), 4.66 (br s, 1H), 5.08 (s,

2H), 6.81 (dd, J= 8.6, 2.7 Hz, 1H), 6.90 (s, 1H), 7.11 (d, J= 8.3 Hz, 1H), 7.41-7.44 (m, 3H), 7.97 (dd, J= 4.4, 2.9 Hz, 2H). MS (ES) *m/e* 467 (M+1).

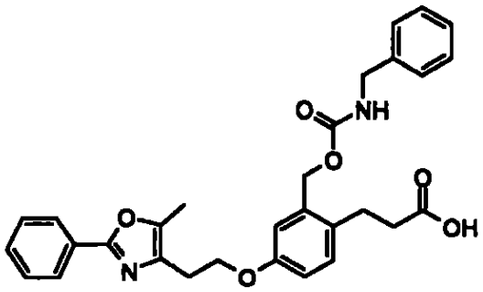
Example 647

3-{2-Benzylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester

MS (ES) *m/e* 571 (M+1).

Example 648

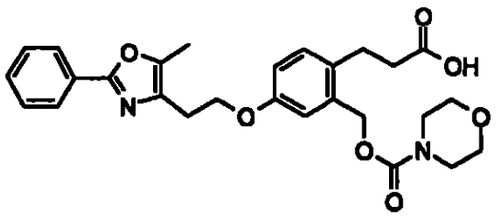
3-{2-Benzylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.60 (t, J= 7 Hz, 2H), 2.92-2.97 (m, 4H), 4.20 (t, J= 7 Hz, 2H), 4.36 (d, J= 5.9 Hz, 2H), 5.13 (s, 2H), 5.18 (br s, 1H), 6.80 (d, J= 8.3 Hz, 1H), 6.91 (s, 1H), 7.10 (d, J= 8.3 Hz, 1H), 7.24-7.30 (m, 5H), 7.42 (s, 3H), 7.97 (s, 2H). MS (ES) *m/e* 515 (M+1).

Example 649

Morpholine-4-carboxylic acid 2-(2-carboxyethyl)-5-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzyl ester



MS (ES) *m/e* 495 (M+1).

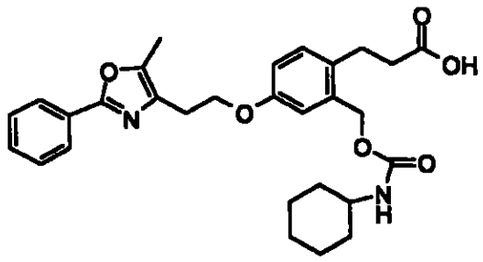
Example 650

3-{2-Cyclohexylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester

MS (ES) *m/e* 563 (M+1)

Example 651

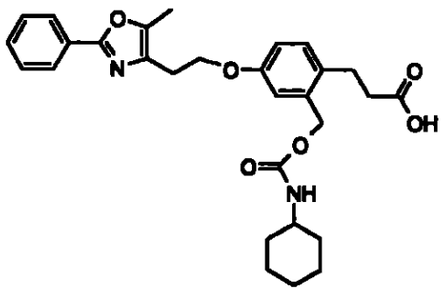
3-{2-Cyclohexylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



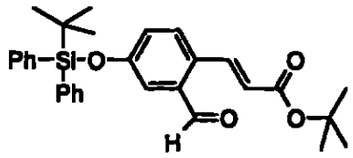
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08-1.18 (m 3H), 1.21-1.42 (m, 2H), 1.57 (br s, 1H), 1.66-1.70 (m, 2H), 1.90 (br s, 2H), 2.40 (s, 3H), 2.61 (t, J= 7.7 Hz, 2H), 2.94 (t, J= 7.8 Hz, 2H), 3.01 (t, J= 6.4 Hz, 2H), 3.48 (br s, 1H), 4.22 (t, J= 6.4 Hz, 2H), 4.74 (br s, 1H), 5.07 (s, 2H), 6.79-6.89 (m, 1H), 6.90 (s, 1H), 7.11 (d, J= 8.3 Hz, 1H), 7.44-7.46 (m, 3H), 7.98 (dd, J= 6.7, 2.8 Hz, 2H). MS (ES) *m/e* 507 (M+1).

Example 652

3-{2-Cyclohexylcarbamoyloxymethyl-4-[2-(2-phenyloxazol-4-yl)ethoxy]phenyl}-propionic acid

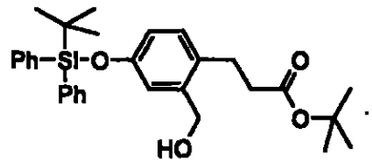


Step A: 3-[4-(tert-Butyldiphenylsilanyloxy)-2-formylphenyl]acrylic acid *tert*-butyl ester



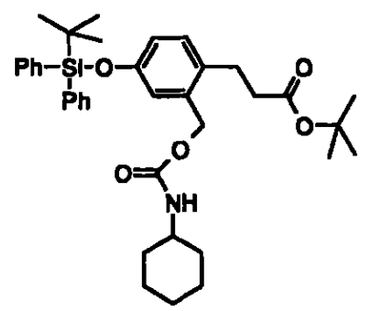
A flame-dried 200 mL round bottomed flask was charged with 3-(2-formyl-4-hydroxyphenyl)acrylic acid *tert*-butyl ester (10.0 g, 40.3 mmol), *tert*-butylchlorodiphenylsilane (12.6 mL, 48.3 mmol), and dry CH_2Cl_2 (150 mL). Triethylamine (11.2 mL, 80 mmol) and N,N-dimethylaminopyridine (1.0 g, 1.0 mmol) were added, and the mixture was stirred at ambient temperature under a nitrogen atmosphere for 16 h. The reaction mixture was diluted with additional CH_2Cl_2, washed with brine (2x), dried (Na_2SO_4), and concentrated to an oil. The crude product was purified using the Biotage medium pressure chromatography system (EtOAc:hexanes 5:95) to give a pale yellow oil (18.3 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 1.51 (d, J= 15.1 Hz, 9H), 6.15 (d, J= 5.1 Hz, 1H), 6.87 (dd, J= 8.6, 2.7 Hz, 1H), 7.34-7.47 (m, 7H), 7.68-7.73 (m, 5H), 8.28 (d, J= 15.6 Hz, 1H), 10.1 (s, 1H). MS (ES) *m/e* 487 (M+1).

Step B: 3-[4-(*tert*-Butyldiphenylsilanyloxy)-2-hydroxymethylphenyl]propionic acid *tert*-butyl ester



A 500 mL Parr hydrogenation bottle was charged with 3-[4-(*tert*-butyldiphenylsilanyloxy)-2-formylphenyl]acrylic acid *tert*-butyl ester (18.3 g, 37.6 mmol), THF (60 mL), and methanol (120 mL). Triethylamine (2 mL) and then 5% Pd/C (5.9 g) were added. The mixture was shaken with hydrogen at 60 psi pressure for 48 h. The mixture was filtered through Celite and concentrated to an oil. This oil was purified using the Biotage medium pressure chromatography (EtOAc:hexanes 15:85) to a pale yellow oil (12.8 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.35 (s, 9H), 2.49 (t, J= 7.6 Hz, 2H), 2.83 (t, J= 7.6 Hz, 2H), 4.55 (s, 2H), 6.56 (dd, J= 8.3, 2.4 Hz, 1H), 6.83 (d, J= 2.9 Hz, 1H), 6.87 (d, J= 8.3 Hz, 1H), 7.33-7.44 (m, 6H), 7.70 (dd, J= 7.8, 1.5 Hz, 4H). MS (ES) *m/e* 508 ($M+NH_4$).

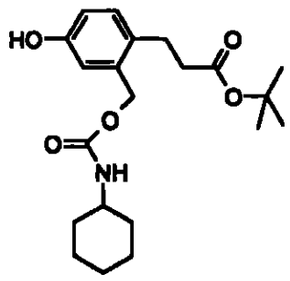
Step C: 3-[4-(*tert*-Butyldiphenylsilanyloxy)-2-cyclohexylcarbamoyl-oxymethylphenyl]propionic acid *tert*-butyl ester



A 100 mL round bottomed flask under N_2 were charged with 3-[4-(*tert*-butyldiphenylsilanyloxy)-2-hydroxymethylphenyl]propionic acid *tert*-butyl ester (3.0 g, 6.11 mmol), cyclohexylisocyanate (4.7 mL, 36.7 mmol), and anhydrous CH_2Cl_2 (25 mL). A 1.0 M HCl solution in ether (3.06 mL, 3.06 mmol) was added, and the reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 16 h. The mixture was diluted with CH_2Cl_2 (100 mL), washed with brine, dried (Na_2SO_4), and concentrated

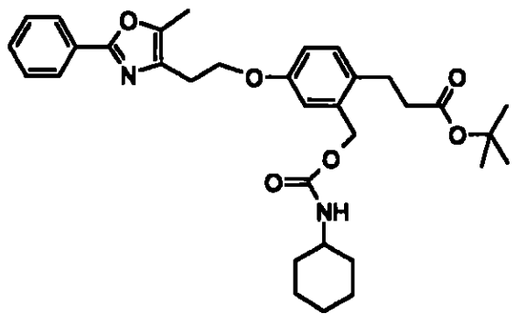
to a brown oil. This crude oil was purified using the Biotage medium pressure chromatography system (EtOAc:hexanes 5:95) to a colorless oil (3.1 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08-1.24 (m, 1H), 1.26-1.40 (m, 11H), 1.56-1.62 (m, 2H), 1.68-1.72 (m, 2H), 2.41 (t, J= 8.3 Hz, 2H), 2.80 (t, J= 7.8 Hz, 2H), 3.47 (br s, 1H), 4.56 (br s, 1H), 4.95 (s, 2H), 6.57 (dd, J= 8.3, 2.7 Hz, 1H), 6.80 (s, 1H), 6.87 (d, J= 8.6 Hz, 1H), 7.33-7.44 (m, 6H), 7.69-7.72 (m, 4H). MS (ES) *m/e* 616 (M+1).

Step D: 3-(2-Cyclohexylcarbamoyloxymethyl-4-hydroxyphenyl)propionic acid *tert*-butyl ester



A 500 mL round bottomed flask was charged with 3-[4-(*tert*-butyl-diphenylsilanyloxy)-2-cyclohexylcarbamoyloxymethylphenyl]propionic acid *tert*-butyl ester (3.1 g, 5.03 mmol) and anhydrous THF (180 mL). Tetrabutylammonium fluoride (15.1 mL, 15.1 mmol, 1.0M in THF) was added, and the reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 4 h. The mixture was concentrated, and the residue was diluted with EtOAc (100 mL), washed with brine, dried over (Na_2SO_4), and concentrated to give an oil. This crude oil was purified using the Biotage medium pressure chromatography system (EtOAc:hexanes 10:90 to 50:50) to a colorless oil (1.67 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04-1.19 (m, 3H), 1.24-1.38 (m, 2H), 1.42 (s, 9H), 1.57-1.62 (m, 1H), 1.66-1.71 (m, 2H), 1.91-2.05 (m, 2H), 2.47 (t, J= 7.8 Hz, 2H), 2.88 (t, J= 7.8 Hz, 2H), 3.48-3.50 (m, 1H), 4.77-4.78 (m, 1H), 5.07 (s, 2H), 5.40 (s, 1H), 6.73 (dd, J= 8.3, 2.9 Hz, 1H), 6.84 (d, J= 2.4 Hz, 1H), 7.07 (d, J= 8.3 Hz, 1H). MS (ES) *m/e* 378 (M+1).

Step E: 3-{2-Cyclohexylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester



A 40 mL Carousel tube was charged with 3-(2-cyclohexyl-carbamoyloxymethyl-4-hydroxyphenyl)propionic acid *tert*-butyl ester (0.10 g, 0.26 mmol) in anhydrous DMF (1.0 mL). Toluene-4-sulfonic acid 2-(5-methyl-2-phenyloxazol-4-yl)ethyl ester (0.104g, 0.292 mmol) and cesium carbonate (0.13 g, 0.40 mmol) were added. The mixture was stirred and heated at 55° C under a nitrogen atmosphere for 30 h and was concentrated. The residue was diluted with EtOAc (50 mL) and washed twice with brine (2x), dried (Na_2SO_4), and concentrated. The crude residue was purified using radial chromatography (EtOAc: CH_2Cl_2 2:98 to 5:95) to give a white solid (0.085 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07-1.19 (m, 3H), 1.24-1.38 (m, 2H), 1.42 (s, 9H), 1.56-1.60 (m, 1H), 1.67-1.70 (m, 2H), 1.91-1.93 (m, 2H), 2.37 (s, 3H), 2.46 (t, J= 7.8 Hz, 2H), 2.88 (t, J= 7.8 Hz, 2H), 2.96 (t, J= 7.8 Hz, 2H), 3.48-3.50 (m, 1H), 4.22 (t, J= 6.8 Hz, 2H), 4.69-4.71 (m, 1H), 5.07 (s, 2H), 6.80 (dd, J= 8.3, 2.4 Hz, 1H), 6.90 (d, J= 2.4 Hz, 1H), 7.10 (d, J= 8.3 Hz, 1H), 7.39-7.45 (m, 3H), 7.98 (dd, J= 4.2, 2.2 Hz, 2H). MS (ES) *m/e* 563 (M+1).

Step F: 3-{2-Cyclohexylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid

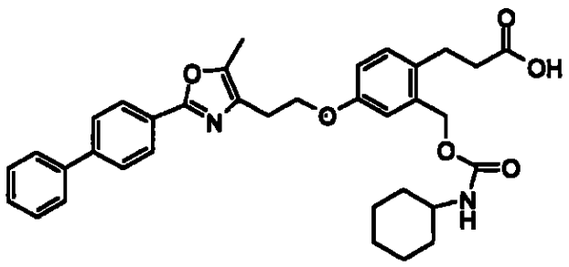
A 25 mL round bottomed flask was charged with 3-{2-cyclohexylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}-propionic acid *tert*-butyl ester (0.080 g, 0.14 mmol) and CH_2Cl_2 (2 mL). Trifluoroacetic acid (2mL) was added, and the solution was stirred at ambient temperature under a nitrogen atmosphere for 1.5 h. The solution was concentrated to give a white solid (0.068 g, 94%) . ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08-1.18 (m 3H), 1.21-1.42 (m, 2H), 1.57 (br s,

1H), 1.66-1.70 (m, 2H), 1.90 (br s, 2H), 2.40 (s, 3H), 2.61 (t, J= 7.7 Hz, 2H), 2.94 (t, J= 7.8 Hz, 2H), 3.01 (t, J= 6.4 Hz, 2H), 3.48 (br s, 1H), 4.22 (t, J= 6.4 Hz, 2H), 4.74 (br s, 1H), 5.07 (s, 2H), 6.79-6.89 (m, 1H), 6.90 (s, 1H), 7.11 (d, J= 8.3 Hz, 1H), 7.44-7.46 (m, 3H), 7.98 (dd, J= 6.7, 2.8 Hz, 2H). MS (ES) *m/e* 507 (M+1).

The following Examples 653 to 661 are prepared by following a substantially similar procedure as described in Example 652.

Example 653

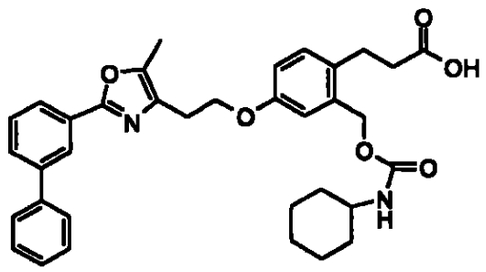
3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-cyclohexylcarbamoyloxymethylphenyl}propionic acid *tert*-butyl ester



MS (ES) *m/e* 639 (M+1).

Example 654

3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-cyclohexylcarbamoyloxymethylphenyl}propionic acid



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14-1.25 (m, 3H), 1.31-1.34 (m, 2H), 1.56-1.66 (m, 1H), 1.69-1.70 (m, 2H), 1.89 (br s, 2H), 2.46 (s, 3H), 2.62 (t, J= 7.6 Hz, 2H), 2.93 (t, J= 7.8 Hz, 2H), 3.11 (t, J= 5.9 Hz, 2H), 3.47 (br s, 1H), 4.24 (t, J= 5.9 Hz, 2H), 4.83 (br s, 1H), 5.08 (s, 2H), 6.80 (d, J= 6.8 Hz, 1H), 6.90 (d, J= 2.9 Hz, 1H), 7.11 (d, J= 8.3 Hz, 1H),

7.41 (d, J= 7.3 Hz, 1H), 7.48 (t, J= 7.6 Hz, 2H), 7.64 (d, J= 7.3 Hz, 2H), 7.74 (d, J= 8.3 Hz, 2H), 8.09 (d, J= 8.3 Hz, 2H). MS (ES) *m/e* 583 (M+1).

Example 655

3-{4-[2-(2-Biphenyl-3-yl-5-methyloxazol-4-yl)ethoxy]-2-cyclohexylcarbamoyloxymethylphenyl}propionic acid *tert*-butyl ester

MS (ES) *m/e* 639 (M+1)

Example 656

3-{4-[2-(2-Biphenyl-3-yl-5-methyloxazol-4-yl)ethoxy]-2-cyclohexylcarbamoyloxymethylphenyl}propionic acid

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26-1.41 (m, 3H), 1.44-1.56 (m, 2H), 1.75 (br s, 1H), 1.84-1.88 (m, 2H), 2.08-2.10 (m, 2H), 2.63 (s, 3H), 2.80 (t, J= 7.8 Hz, 2H), 3.12 (t, J= 7.9 Hz, 2H), 3.27 (t, J= 6.1 Hz, 2H), 3.66 (br s, 4.42 (t, J= 6.1 Hz, 2H), 4.97 (br s, 1H), 5.27 (s, 2H), 7.04 (d, J= 6.4 Hz, 1H), 7.08 (d, J= 2.4 Hz, 1H), 7.30 (d, J= 8.3 Hz, 1H), 7.55-7.76 (m, 4H), 7.85-7.86 (m, 2H), 7.92 (d, J= 7.8 Hz, 1H), 8.15 (d, J= 7.8 Hz, 1H), 8.44 (d, J= 1.5 Hz, 1H). MS (ES) *m/e* 583 (M+1).

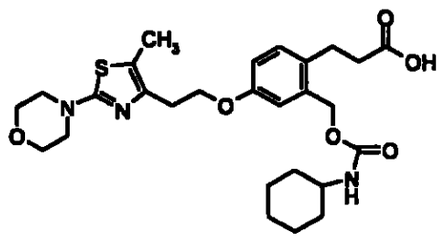
Example 657

3-{2-Cyclohexylcarbamoyloxymethyl-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester

MS (ES) *m/e* 588 (M+1)

Example 658

3-{2-Cyclohexylcarbamoyloxymethyl-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl)ethoxy]phenyl}propionic acid



^{1}H NMR (400 MHz, $CDCl_3$) δ1.11-1.37 (m, 5H), 1.57-1.61 (m, 1H), 1.68-1.72 (m, 2H), 1.90-1.93 (m, 2H), 2.29 (s, 3H), 2.58 (t, J= 7.8 Hz, 2H), 2.90 (t, J= 7.6 Hz, 2H), 3.06 (t, J= 5.1 Hz, 2H), 3.47-3.50 (m, 1H), 3.66 (t, J= 4.6 Hz, 4H), 3.85 (t, J= 4.9 Hz, 4H), 4.20 (t, J= 5.4 Hz, 2H), 5.06 (s,.2H), 6.74 (d, J= 8.3 Hz, 1H), 6.86 (s, 1H), 7.08 (d, J= 8.3 Hz, 1H). MS (ES) *m/e* 532 (M+1).

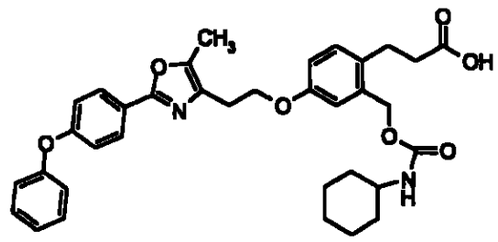
Example 659

3-(2-Cyclohexylcarbamoyloxymethyl-4-{2-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl)propionic acid *tert*-butyl ester

MS (ES) *m/e* 655 (M+1)

Example 660

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

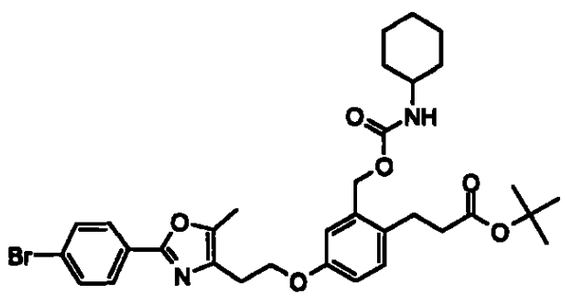


^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15-1.24 (m, 3H), 1.26-1.34 (m, 2H), 1.57 (br s, 1H), 1.67-1.70 (m, 2H), 1.90 (br s, 2H), 2.43 (s, 3H), 2.61 (t, 7.6 Hz, 2H), 2.93 (t, J= 7.3 Hz, 2H), 3.08 (t, J= 5.6 Hz, 2H), 3.47-3.52 (m, 1H), 4.22 (t, J= 5.6 Hz, 1H), 4.84 (br s, 1H,

1H), 6.79 (d, 2.4 Hz, 1H), 6.88 (d, J= 2.4 Hz, 1H), 7.00-7.12 (m, 5H), 7.21 (t, J= 7.6 Hz, 1H), 7.41 (t, J= 7.8 Hz, 2H), 7.99 (d, 8.8 Hz, 2H). MS (ES) *m/e* 599 (M+1).

Example 661

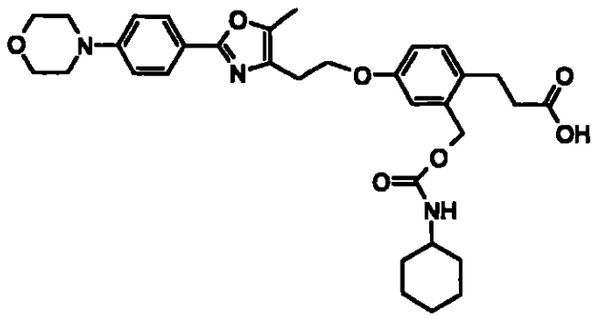
3-(4-{2-[2-(4-Bromophenyl)-5-methyloxazol-4-yl]ethoxy}-2-cyclohexylcarbamoyloxymethylphenyl)propionic acid *tert*-butyl ester



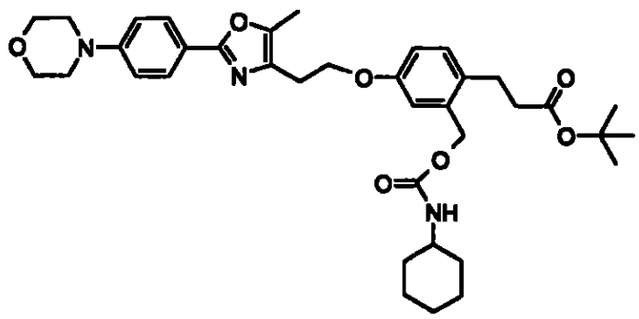
MS (ES) *m/e* 641 (M+1).

Example 662

3-(2-Cyclohexylcarbamoyloxymethyl-4-{2-[5-methyl-2-(4-morpholin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl)propionic acid



Step A: 3-(2-Cyclohexylcarbamoyloxymethyl-4-{2-[5-methyl-2-(4-morpholin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl)propionic acid *tert*-butyl ester



A 1 mL microvial under a nitrogen atmosphere was charged with 3-(4-{2-[2-(4-bromophenyl)-5-methyloxazol-4-yl]ethoxy}-2-cyclohexylcarbamoyloxymethylphenyl)-propionic acid *tert*-butyl ester (0.30 g, 0.468 mmol; Example 39), anhydrous toluene (0.5 mL), and then morpholine (0.053 mL, 0.61 mmol). Tris(dibenzylideneacetone)-dipalladium(0) (0.004 g, 0.0044 mmol), 2-(di-*tert*-butylphosphine)biphenyl (0.006 g, 0.020 mmol), and sodium *tert*-butoxide (0.063g, 0.655 mmol) were added sequentially. The mixture was stirred at ambient temperature under a nitrogen atmosphere for 5 h and was poured into EtOAc (50 mL). The organic layer was washed with brine (2x), dried (Na_2SO_4), and concentrated to a dark yellow oil. This crude product was purified using radial chromatography (EtOAc:hexanes 15:85 to 50:50) to give a yellow oil (0.058 g, 19%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.07-1.18 (m, 3H), 1.29-1.40 (m, 1H), 1.42 (s, 9H), 1.52-1.70 (m, 4H), 1.91-1.93 (m, 2H), 2.34 (s, 3H), 2.46

(t, J= 8.1 Hz, 2H), 2.87 (t, J= 7.8 Hz, 2H), 2.94 (t, J= 6.8 Hz, 2H), 3.24 (t, J= 4.9 Hz, 4H), 3.48-3.50 (m, 1H), 3.86 (t, J= 4.9 Hz, 4H), 4.20 (t, J= 6.6 Hz, 2H), 5.07 (s, 2H), 6.79 (dd, J= 8.6, 2.7 Hz, 1H), 6.85-6.93 (m, 3H), 7.09 (d, J= 8.3 Hz, 1H), 7.87 (dd, J= 11.5, 2.7 Hz, 2H). MS (ES) *m/e* 648 (M+1).

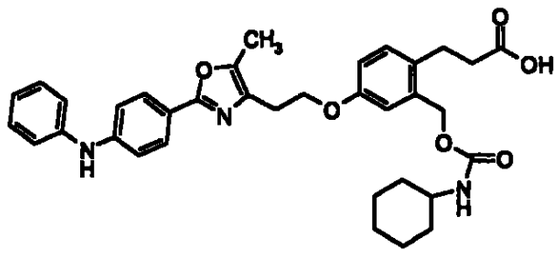
Step B: 3-(2-Cyclohexylcarbamoyloxymethyl-4-{2-[5-methyl-2-(4-morpholin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl)propionic acid

A 15 mL round bottomed flask was charged with 3-(2-cyclohexylcarbamoyloxymethyl-4-{2-[5-methyl-2-(4-morpholin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl)propionic acid (0.058 g, 0.09 mmol) and CH_2Cl_2 (1 mL). Trifluoroacetic acid (0.5 mL) was added, and the solution was stirred at ambient temperature under a nitrogen atmosphere for 1.5 h. The mixture was concentrated to give a yellow solid (0.052 g, 98%) . ^1H NMR (400 MHz, $CDCl_3$) δ 1.03-1.11 (m, 3H), 1.18-1.30 (m, 2H), 1.45-1.50 (m, 1H), 1.60-1.63 (m, 2H), 1.82-1.85 (m, 2H), 2.38 (s, 3H), 2.52 (t, J= 7.6 Hz, 2H), 2.84 (t, J= 7.6 Hz, 2H), 3.04 (t, J= 5.6 Hz, 2H), 3.30 (t, J= 4.9 Hz, 4H), 3.39 (br s, 1H), 3.80 (t, J= 4.9 Hz, 4H), 4.17 (t, J= 5.9 Hz, 2H), 4.86 (br s, 1H), 4.99 (s, 2H), 6.70 (d, J= 8.3 Hz, 1H), 6.81 (d, J= 2.4 Hz, 1H), 7.03 (d, J= 8.3 Hz, 1H), 7.90 (d, J= 9.3 Hz, 2H). MS (ES) *m/e* 592 (M+1).

The following Examples 663 to 664 are prepared by following a substantially similar procedure as described in Example 662.

Example 663

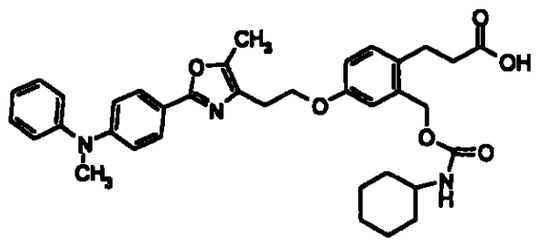
3-(2-Cyclohexylcarbamoyloxymethyl-4-{2-[5-methyl-2-(4-phenylaminophenyl)oxazol-4-yl]ethoxy}phenyl)propionic acid



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.42 (m, 5H), 1.56 (br s, 1H), 1.66-1.69 (m, 2H), 1.89-1.92 (m, 2H), 2.38 (s, 3H), 2.60 (t, J= 7 Hz, 2H), 2.91 (t, J= 7 Hz, 2H), 3.03 (t, J= 5.6 Hz, 2H), 4.22 (t, J= 6.1 Hz, 2H), 4.86 (br s, 1H), 5.06 (s, 2H), 6.78 (d, J= 7.8 Hz, 1H), 6.89 (s, 1H), 7.04-7.10 (m, 4H), 7.16 (d, J= 7.8 Hz, 2H), 7.34 (t, J= 7.8 Hz, 2H), 7.88 (d, J= 8.3 Hz, 2H). MS (ES) *m/e* 598 (M+1).

Example 664

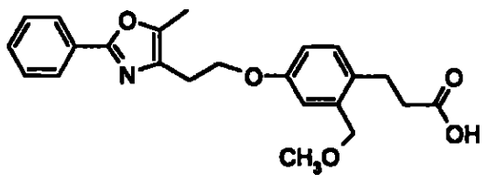
3-[2-Cyclohexylcarbamoyloxymethyl-4-(2-{5-methyl-2-[4-(methylphenylamino)phenyl]oxazol-4-yl}ethoxy)phenyl]propionic acid



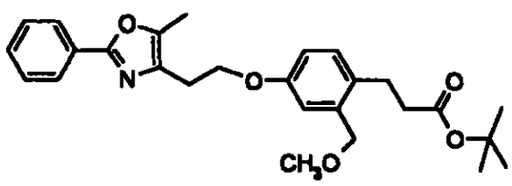
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02-1.35 (m, 5H), 1.56(br s, 1H), 1.67-1.70 (m, 2H), 1.89 (br s, 2H), 2.41 (s, 3H), 2.60 (t, J= 7 Hz, 2H), 2.91 (t, J= 7 Hz, 2H), 3.09 (t, J= 7 Hz, 2H), 3.39 (s, 3H), 3.47 (br s, 1H), 4.24 (t, J= 7 Hz, 2H), 4.95 (br s, 1H), 5.06 (s, 2H), 6.81 (d, J= 8.3 Hz, 2H), 6.89 (s, 1H), 7.09 (d, J= 7.8 Hz, 1H), 7.23 (t, J= 7.6 Hz, 3H), 7.43 (t, J= 7.8 Hz, 3H), 7.87 (d, J= 8.8 Hz, 2H). MS (ES) *m/e* 612 (M+1).

Example 665

3-{2-Methoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



Step A: 3-{2-Methoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl) ethoxy] phenyl} propionic acid *tert*-butyl ester



A 15 mL round bottomed flask was charged with 3-{2-hydroxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester (0.10 g, 0.23 mmol) and methyl iodide (0.21 mL, 2.3 mmol) in anhydrous DMF (1 mL) under a nitrogen atmosphere. The mixture was cooled in an ice bath and treated in one portion with NaH (0.018 g, 0.25 mmol, 60% oil dispersion). The reaction mixture was stirred for 2 h, concentrated, and diluted with EtOAc (40 mL). The organic layer was washed with brine (2x), dried (Na_2SO_4), and concentrated. The crude product was purified using radial chromatography (EtOAc:hexanes 10:90 to 25:75) to give a yellow oil (0.060 g, 58%). MS (ES) *m/e* 648 (M+1).

Step B: 3-{2-Methoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid

A 15 mL round bottomed flask was charged 3-{2-methoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester (0.060 g, 0.13 mmol), CH_2Cl_2 (1.2 mL), and then trifluoroacetic acid (0.6 mL). The solution was stirred at ambient temperature under a nitrogen atmosphere for 16 h and was concentrated. The residue was diluted with CH_2Cl_2 (30 mL) and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give a white solid (0.046 g, 89%). MS (ES) *m/e* 648 (M+1).

The following Examples 666 to 673 are prepared by following a substantially similar procedure as described in Example 665.

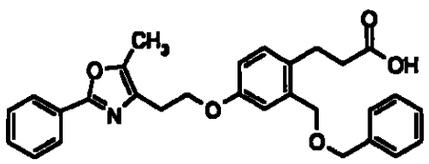
Example 666

3-{2-Benzyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester

MS (ES) *m/e* 528 (M+1)

Example 667

3-{2-Benzyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 472 (M+1).

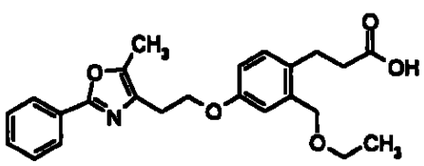
Example 668

3-{2-Ethoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester

MS (ES) *m/e* 466 (M+1)

Example 669

3-{2-Ethoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 410 (M+1).

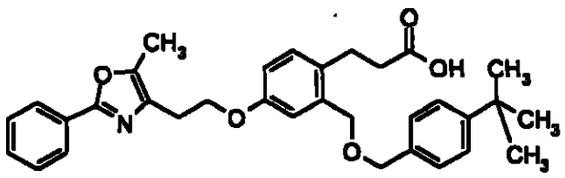
Example 670

3-{2-(4-*tert*-Butyl-benzyloxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester

MS (ES) *m/e* 584 (M+1)

Example 671

3-{2-(4-*tert*-Butyl-benzyloxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 410 (M+1).

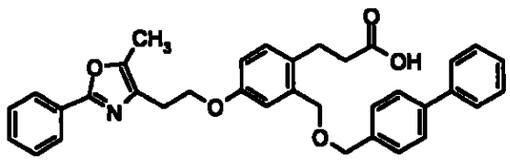
Example 672

3-{2-(Biphenyl-4-ylmethoxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester

MS (ES) *m/e* 604 (M+1)

Example 673

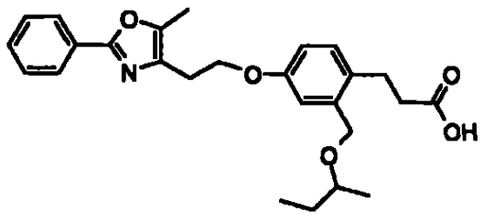
3-{2-(Biphenyl-4-ylmethoxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



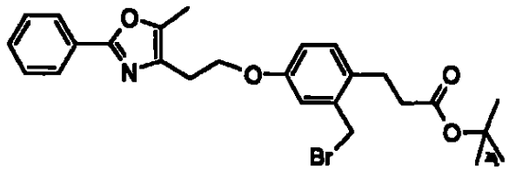
MS (ES) *m/e* 410 (M+1).

Example 674

3-{2-*sec*-Butoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



Step A: 3-{2-Bromomethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid *tert*-butyl ester



A 100 mL round bottomed flask was charged with 3-{2-hydroxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester (1.0 g, 2.29 mmol), anhydrous THF (25 mL), and then triphenylphosphine (1.20 g, 4.57 mmol) and CBr_4 (1.52 g, 4.57 mmol). The yellow mixture was stirred at ambient temperature under a nitrogen atmosphere for 1 h and was poured into EtOAc (100 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified using radial chromatography (EtOAc:hexanes 15:85 to 25:75) to give a colorless oil (0.95 g, 83%). MS (ES) *m/e* 501 (M+1).

Step B: 3-{2-*sec*-Butoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid

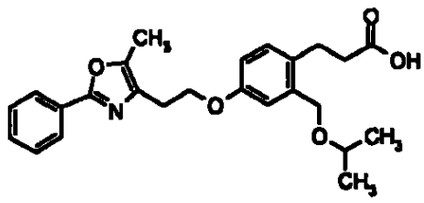
A flame-dried 15 mL round bottomed flask was charged with 2-butanol (0.92 mL, 1.0 mmol), anhydrous DMF (1 mL), and then NaH (0.013 g, 0.2 mmol, 60% oil dispersion). The reaction mixture was cooled in an ice bath for 15 min, and 3-{2-bromomethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester ((0.050 g,0.10 mmol) in anhydrous DMF (0.5 mL) was added. The reaction mixture was stirred under a nitrogen atmosphere for 2 h. A product mixture of free acid and *tert*-butyl ester formed. The reaction was poured into EtOAc (40 mL), washed with

brine (3x), dried (Na_2SO_4), and concentrated. The crude oil was then dissolved directly in CH_2Cl_2 (1 mL) and treated with TFA (1.5 mL). The solution was stirred at ambient temperature for 16 h and concentrated. The crude product residue was purified using radial chromatography (EtOAc:hexanes 15:85 to 1:1) to give a yellow oil (0.012 g, 27%). MS (ES) *m/e* 438 (M+1).

The following Examples 675 to 680 are prepared by following a substantially similar procedure as described in Example 674.

Example 675

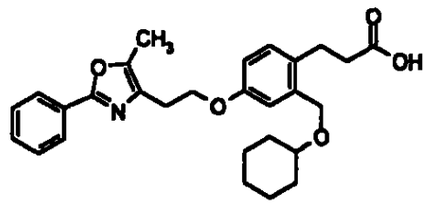
3-{2-Isopropoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-phenyl}propionic acid



MS (ES) *m/e* 424 (M+1).

Example 676

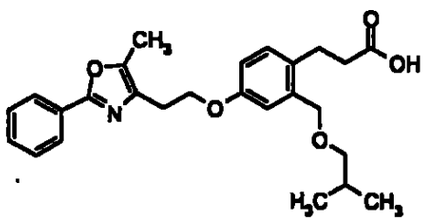
3-{2-Cyclohexyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 464 (M+1).

Example 677

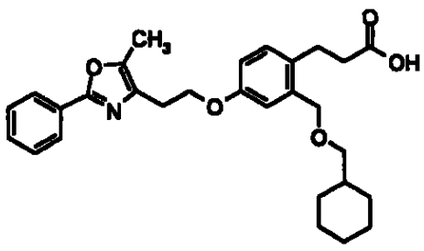
3-{2-Isobutoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 438 (M+1).

Example 678

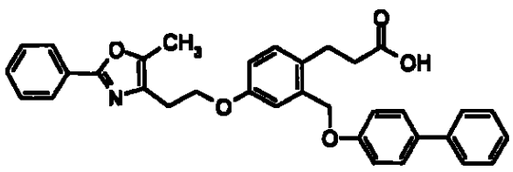
3-{2-Cyclohexylmethoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 478 (M+1).

Example 679

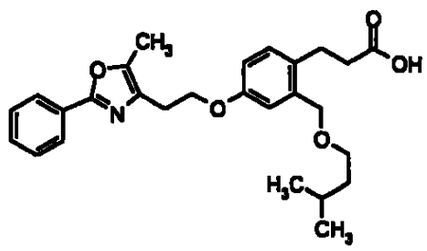
3-{2-(Biphenyl-4-yloxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 534 (M+1).

Example 680

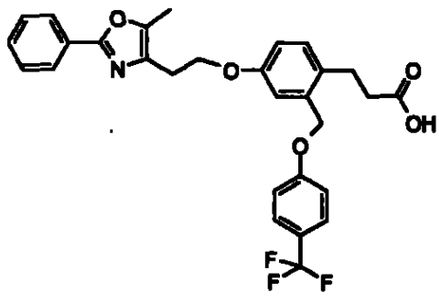
3-{2-(3-Methylbutoxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 452 (M+1).

Example 681

3-[4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-(4-trifluoromethylphenoxymethyl)-phenyl]propionic acid

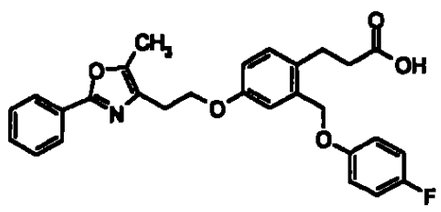


General procedure for parallel synthesis using the DynaVac Carousel apparatus. A 50 mL glass tube with screw cap and nitrogen inlet was charged with 3-{2-bromomethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid *tert*-butyl ester (0.040 g, 0.080 mmol), 4-trifluoromethylphenol (0.019 g 0.12 mmol), anhydrous DMF (0.5 mL), and then cesium carbonate (0.039 g, 0.12 mmol). The mixture was stirred at ambient temperature for 16 h. MS analysis of the reaction indicated formation of the intermediate ester product [MS (ES) *m/e* 582 (M+1)]. The reaction mixture was poured into ether (30 mL). The organic layer was washed with brine (2x), dried (Na_2SO_4), and concentrated. The residue was diluted with CH_2Cl_2 (1 mL) and trifluroacetic acid (0.25 mL) was added. The mixture was stirred at ambient temperature for 1.5 h and was concentrated. The crude product mixture was purified by mass-directed reverse phase HPLC to provide the title compound (0.045 g, 64%). MS (ES) *m/e* 526 (M+1).

The following Examples 682 to 691 are prepared by following a substantially similar procedure as described in Example 681.

Example 682

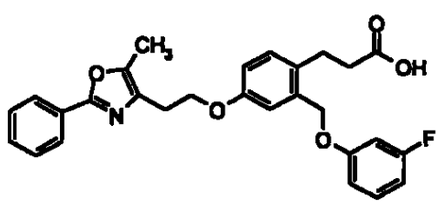
3-{2-(4-Fluorophenoxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 476 (M+1).

Example 683

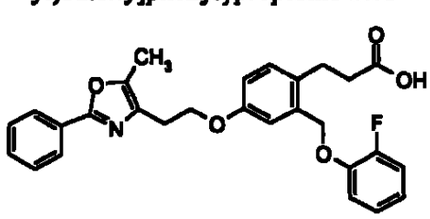
3-{2-(3-Fluorophenoxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 476 (M+1).

Example 684

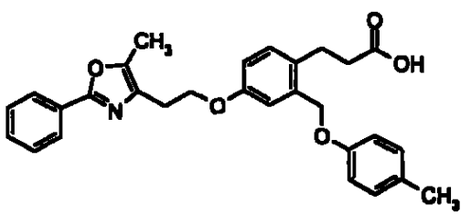
3-{2-(2-Fluorophenoxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 476 (M+1).

Example 685

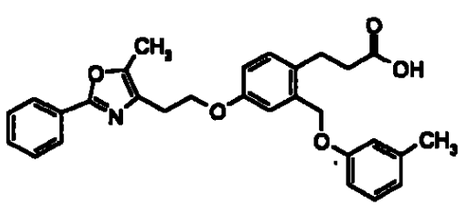
3-{4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-*p*-tolyloxymethylphenyl}propionic acid



MS (ES) *m/e* 472 (M+1).

Example 686

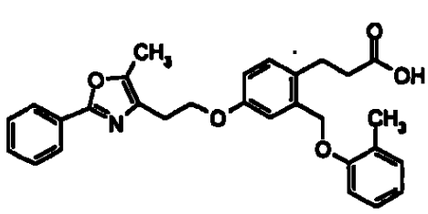
3-{4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-*m*-tolyloxymethylphenyl}propionic acid



MS (ES) *m/e* 472 (M+1).

Example 687

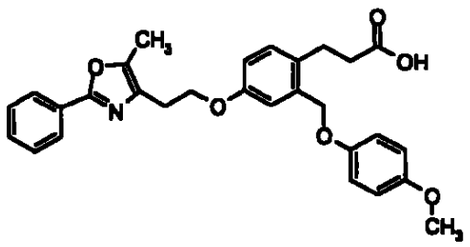
3-{4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-*o*-tolyloxymethylphenyl}propionic acid



MS (ES) *m/e* 472 (M+1).

Example 688

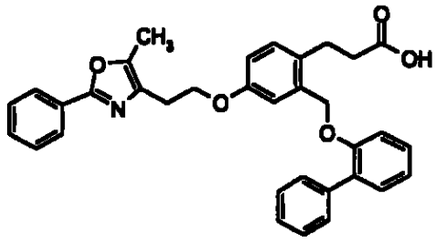
3-{2-(4-Methoxyphenoxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 488 (M+1).

Example 689

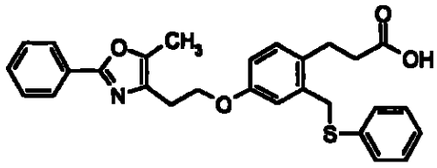
3-{2-(Biphenyl-2-yloxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 534 (M+1).

Example 690

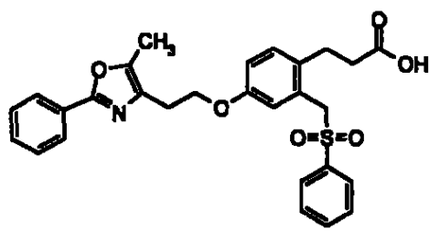
3-{4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-phenylsulfanylmethylphenyl}propionic acid



MS (ES) *m/e* 474 (M+1).

Example 691

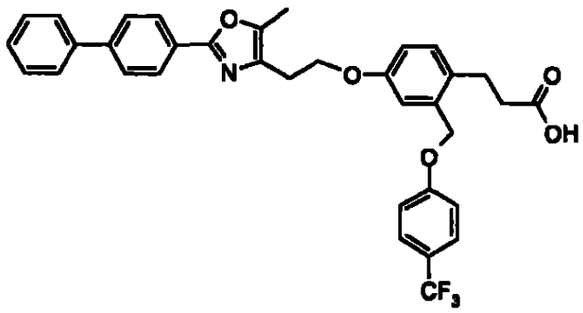
3-{2-Benzenesulfonylmethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid



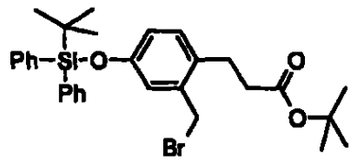
MS (ES) *m/e* 506 (M+1).

Example 692

3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(4-trifluoromethylphenoxy-methyl)-phenyl]-propionic acid



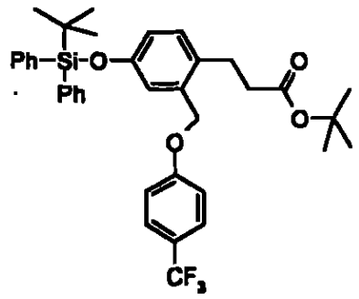
Step A: 3-[2-Bromomethyl-4-(*tert*-butyldiphenylsilanyloxy)phenyl]propionic acid *tert*-butyl ester



A 200 mL round bottomed flask was charged with 3-[4-(*tert*-butyl-diphenylsilanyloxy)-2-hydroxymethylphenyl]propionic acid *tert*-butyl ester (3.03 g, 6.18 mmol), anhydrous THF (75 mL), and then triphenylphosphine (3.24 g, 12.4 mmol) and CBr_4 (4.10 g, 12.4 mmol). The yellow mixture was stirred at ambient temperature under a nitrogen atmosphere for 1 h and was concentrated. The residue was diluted with EtOAc (500 mL). The organic layer was washed with brine (2x), dried (Na_2SO_4), and

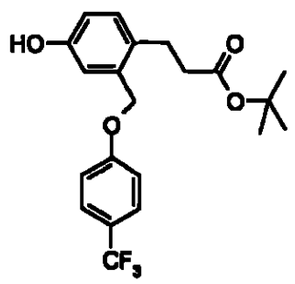
concentrated to a solid. The crude product was purified using a Biotage medium pressure chromatography system (EtOAc:hexanes 10:90) to give a yellow oil (2.95 g, 86%), MS (ES) *m/e* 572 ($M+NH_4$).

Step B: 3-[4-(*tert*-Butyldiphenylsilanyloxy)-2-(4-trifluoromethylphenoxymethyl) phenyl]-propionic acid *tert*-butyl ester



A 50 mL round bottomed flask was charged with 3-[2-bromomethyl-4-(*tert*-butyldiphenylsilanyloxy)phenyl]propionic acid *tert*-butyl ester (1.0 g, 1.81 mmol), anhydrous DMF (10 mL), and then 4-trifluoromethylphenol (0.44 g, 2.7 mmol) and cesium carbonate (0.88 g, 2.7 mmol). The reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 18 h and concentrated. The residue was diluted with EtOAc (100 mL). The organic layer was washed with brine (2x), dried (Na_2SO_4), and concentrated to a yellow oil. The crude residue was purified using radial (EtOAc:hexanes 15:85 to 50:50) to give a yellow oil (0.66 g, 58%). MS (ES) *m/e* 635 (M+1).

Step C: 3-[4-Hydroxy-2-(4-trifluoromethylphenoxymethyl)phenyl]propionic acid *tert*-butyl ester



A 100 mL round bottomed flask was charged with 3-[4-(*tert*-butyldiphenylsilanyloxy)-2-(4-trifluoromethylphenoxymethyl)phenyl]propionic acid *tert*-

butyl ester (0.65 g, 1.02 mmol), anhydrous THF (40 mL), and then tetrabutylammonium fluoride (3.1 mL, 3.1 mmol, 1.0 M in THF). The reaction was stirred under a nitrogen atmosphere for 1.5 h and was concentrated. The residue was diluted with EtOAc (100 mL). The organic layer was washed with brine (2x), dried (Na_2SO_4), and concentrated to an orange oil. The crude oil was purified using radial chromatography (EtOAc:hexanes 15:85) to give a white solid (0.31 g, 77%). MS (ES) *m/e* 395 (M-1).

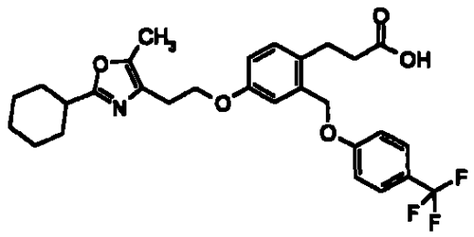
Step D: 3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(4-trifluoromethylphenoxy-methyl)-phenyl]-propionic acid

General procedure for parallel synthesis using the DynaVac Carousel apparatus: A 50 mL glass tube with screw cap and nitrogen inlet was charged with 3-[4-hydroxy-2-(4-trifluoromethylphenoxymethyl)phenyl]propionic acid *tert*-butyl ester (0.050 g, 0.146 mmol), toluene-4-sulfonic acid 2-(2-biphenyl-4-yl-5-methyloxazol-4-yl)ethyl ester (0.078 g, 0.18 mmol), anhydrous DMF (0.5 mL), and then cesium carbonate (0.072 g, 0.22 mmol). The mixture was stirred at ambient temperature for 16 h. MS analysis of the reaction indicated formation of the ester intermediate MS (ES) *m/e* 658 (M+1). The reaction mixture was poured into ether (30 mL). The organic layer was washed with brine (2x), dried (Na_2SO_4), and concentrated. The crude residue was diluted with CH_2Cl_2 (2 mL) and then trifluoroacetic acid (1 mL). The mixture was stirred at ambient temperature for 2 h and concentrated under a stream of N_2. The crude product was purified by mass-directed reverse phase HPLC to provide the title compound (0.053 g, 71%). ^1H NMR (250 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.70 (t, J= 7.7 Hz, 2H), 2.95-3.05 (m, 4H), 4.28 (t, J= 6.6 Hz, 2H), 5.09 (s, 2H), 6.90 (dd, J= 8.5, 2.8 Hz, 1H), 7.01 (d, J= 2.6 Hz, 1H), 7.06 (d, J= 8.6 Hz, 2H), 7.21 (d, J= 8.5 Hz, 1H), 7.41-7.72 (m, 9H), 8.07 (d, J= 8.4 Hz, 2H). MS (ES) *m/e* 602 (M+1).

The following Examples 693 to 697 are prepared by following a substantially similar procedure as described in Example 692.

Example 693

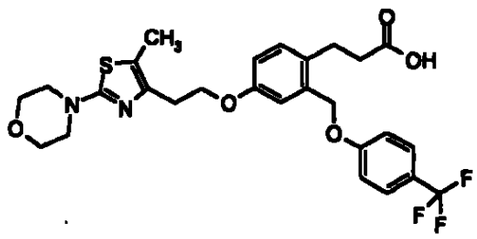
3-[4-[2-(2-Cyclohexyl-5-methyloxazol-4-yl)ethoxy]-2-(4-trifluoromethylphenoxymethyl)phenyl]propionic acid



MS (ES) *m/e* 532 (M+1).

Example 694

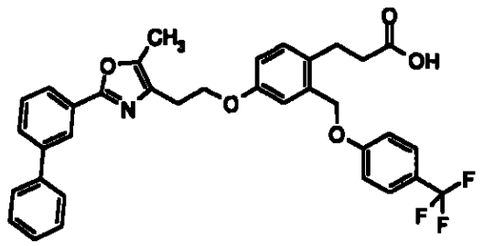
3-[4-[2-(5-Methyl-2-morpholin-4-yl-thiazol-4-yl)ethoxy]-2-(4-trifluoromethylphenoxymethyl)phenyl]propionic acid



MS (ES) *m/e* 551 (M+1).

Example 695

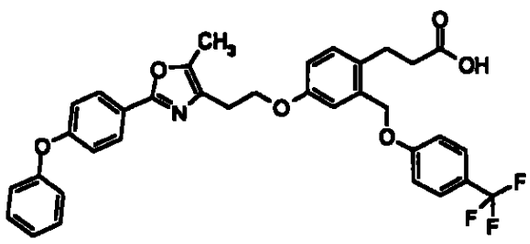
3-[4-[2-(2-Biphenyl-3-yl-5-methyloxazol-4-yl)ethoxy]-2-(4-trifluoromethyl-phenoxymethyl)phenyl]propionic acid



MS (ES) *m/e* 602 (M+1).

Example 696

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



MS (ES) *m/e* 618 (M+1).

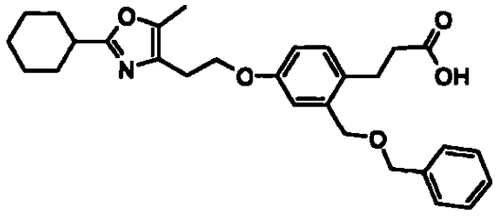
Example 697

3-[4-[4-Methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylmethoxy]-2-(4-trifluoromethylphenoxymethyl)phenyl]propionic acid

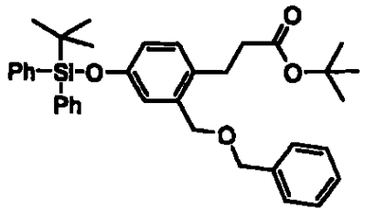
MS (ES) *m/e* 596 (M+1)

Example 698

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

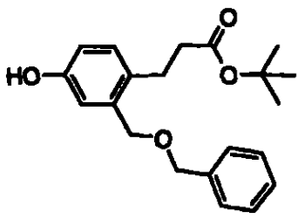


Step A: 3-[2-Benzyloxymethyl-4-(tert-butyl-diphenyl-silanyloxy)-phenyl]-propionic acid tert-butyl ester



A 100 mL round bottomed flask was charged with 3-[4-(*tert*-butyl-diphenylsilanyloxy)-2-hydroxymethylphenyl]propionic acid *tert*-butyl ester (1.52 g, 3.10 mmol), anhydrous DMF (15 mL), and then benzyl bromide (1.84 mL, 15.5 mmol) under a nitrogen atmosphere. The solution was cooled to -10°C, and NaH (0.124 g, 3.10 mmol, 60% oil dispersion) was added. The mixture was stirred for 5 h, and was poured into EtOAc (150 mL). The organic layer was washed with brine (2x), dried (Na_2SO_4), and concentrated to a brown oil. The crude oil was purified using radial chromatography (EtOAc:hexanes 2:98 to 5:95) to give a pale yellow oil (1.04 g, 58%). MS (ES) *m/e* 598 ($M+NH_4$).

Step B: 3-(2-Benzyloxymethyl-4-hydroxy-phenyl)-propionic acid *tert*-butyl ester



A 250 mL round bottomed flask was charged with 3-[2-benzyloxymethyl-4-(*tert*-butyl-diphenyl-silanyloxy)-phenyl]-propionic acid tert-butyl ester (1.03 g, 1.77 mmol), anhydrous THF (60 mL), and then tetrabutylammonium fluoride (5.3 mL, 5.3 mmol, 1.0 M in THF). The reaction mixture was stirred under a nitrogen atmosphere for 1 h, concentrated, and diluted with EtOAc (100 mL). The organic layer was washed with brine (2x), dried (Na_2SO_4), and concentrated to give an oil. The crude oil was purified using radial chromatography (EtOAc:hexanes 10:90 to 50:50) to give a white solid (0.52 g, 86%). MS (ES) *m/e* 343 (M-1).

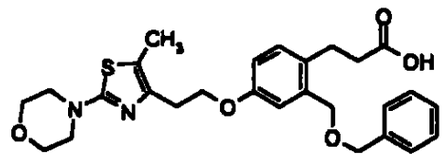
Step C: 3-{2-Benzyloxymethyl-4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

General procedure for the parallel synthesis of analogs using the DynaVac Carousel apparatus: A 50 mL glass tube with screw cap and nitrogen inlet was charged with 3-(2-benzyloxymethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester (0.050 g, 0.146 mmol), toluene-4-sulfonic acid 2-(2-biphenyl-4-yl-5-methyloxazol-4-yl)ethyl ester (0.078 g, 0.18 mmol), anhydrous DMF (0.5 mL), and then cesium carbonate (0.072 g, 0.22 mmol). The mixture was stirred at ambient temperature for 16 h. MS analysis of the reaction indicated that the intermediate ester was formed, MS (ES) *m/e* 534 (M+1). The crude reaction was poured into ether (30 mL), and washed with brine (2x), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was dissolved in CH_2Cl_2 (2 mL) and trifluoroacetic acid was added (1.0 mL). The reaction mixture was stirred at ambient temperature for 2 h and was concentrated under a stream of N_2. The crude product was purified by mass-directed reverse phase HPLC to provide 0.053 g (71%) of 3-{4-[2-(2-Cyclohexyl-5-methyloxazol-4-yl)ethoxy]-2-phenoxymethylphenyl}propionic acid . MS (ES) *m/e* 478 (M+1).

The following Examples 699 to 704 are prepared by following a substantially similar procedure as described in Example 698.

Example 699

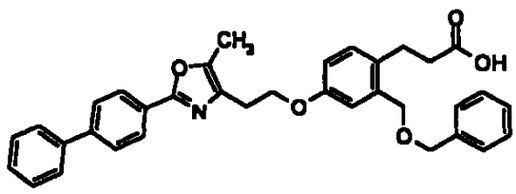
3-{2-Benzyloxymethyl-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 497 (M+1).

Example 670

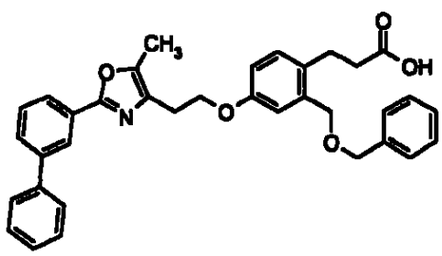
3-{2-Benzyloxymethyl-4-[2-(2-biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]phenyl}propionic acid



MS (ES) *m/e* 548 (M+1).

Example 671

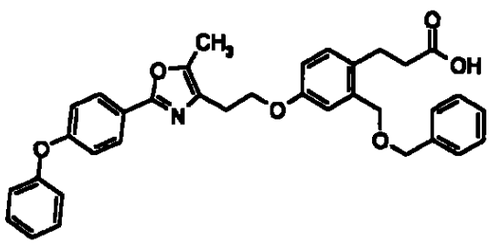
3-{2-Benzyloxymethyl-4-[2-(2-biphenyl-3-yl-5-methyloxazol-4-yl)ethoxy]-phenyl}propionic acid



MS (ES) *m/e* 548 (M+1).

Example 672

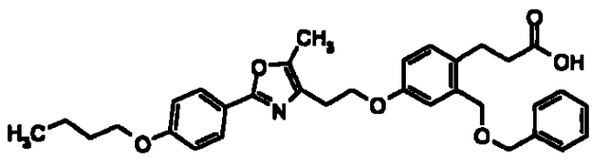
3-(2-Benzyloxymethyl-4-{2-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl)propionic acid



MS (ES) *m/e* 564 (M+1).

Example 673

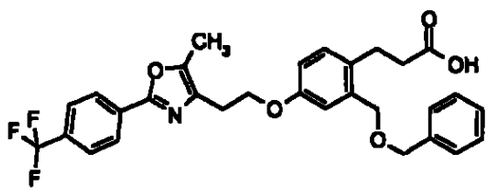
3-(2-Benzyloxymethyl-4-{2-[2-(4-butoxyphenyl)-5-methyloxazol-4-yl]ethoxy}phenyl)propionic acid



MS (ES) *m/e* 544 (M+1).

Example 674

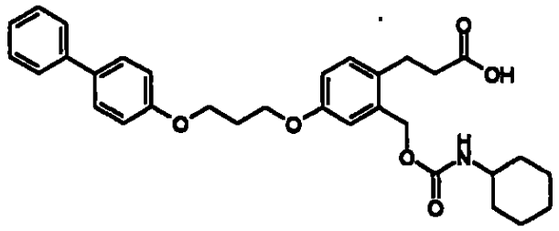
3-(2-Benzyloxymethyl-4-{2-[5-methyl-2-(4-trifluoromethylphenyl)oxazol-4-yl]ethoxy}phenyl)propionic acid



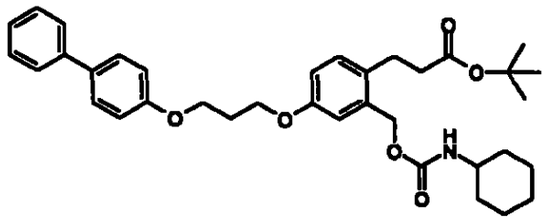
MS (ES) *m/e* 540 (M+1).

Example 705

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-cyclohexylcarbamoyloxymethyl-phenyl}-propionic acid



Step A: 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-cyclohexylcarbamoyloxymethyl-phenyl}-propionic acid *tert*-butyl ester



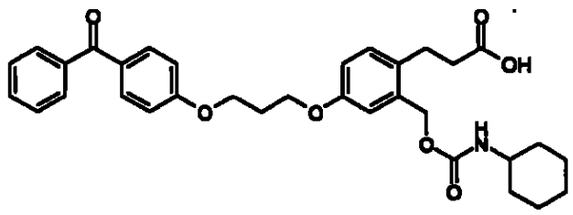
A mixture of 3-(2-cyclohexylcarbamoyloxymethyl-4-hydroxy-phenyl)-propionic acid *tert*-butyl ester (50 mg, 0.13 mmol; Example 652 Step D), 4-(3-bromo-propoxy)-biphenyl (58 mg, 0.2 mmol; *Tetrahedron* 1994, *50*, 3427, and potassium carbonate (53 mg, 0.39 mmol) in acetonitrile (6 mL) was heated at 80°C overnight. Ethyl acetate (20 mL) and H_2O (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by silica gel column chromatography (hexane/ethyl acetate 4/1) to give the title compound (50 mg, 65%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.54 (m, 4H), 7.42 (t, 2H, *J*=7.6), 7.32 (d, 1H, *J*=8.4), 7.12 (d, 1H, *J*=8.3), 6.99 (d, 2H, *J*=8.7), 6.93 (d, 1H, *J*=2.2), 6.82 (dd, 1H, *J*=8.4, 2.7), 5.09 (s, 2H), 4.74 (d, 1H, *J*=7.5), 4.18 (m, 4H), 3.56-3.42 (m, 1H), 2.90 (t, 2H, *J*=7.8), 2.48 (t, 2H, *J*=7.8), 2.28 (qn, 2H, *J*=6.0), 1.95-1.88 (m, 2H), 1.75-1.08 (m, 8H), 1.44 (s, 9H).

Step B: 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-cyclohexylcarbamoyloxymethyl-phenyl}-propionic acid

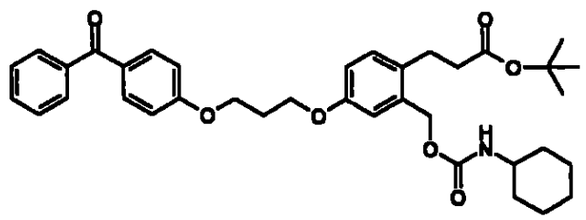
Trifluoroacetic acid (0.032 mL, 0.42 mmol) was added to a solution of 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-2-cyclohexylcarbamoyloxymethyl-phenyl}-propionic acid tert-butyl ester (50 mg, 0.085 mmol) in CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was stirred overnight and concentrated under vacuum to give the title compound (41 mg, 90%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 9.4 (br s, 1H), 7.58-7.49 (m, 4H), 7.42 (m, 2H), 7.32 (m, 1H), 7.13 (d, 1H, *J*=8.3), 7.00-6.93 (m, 3H), 6.84 (dd, 1H, *J*=7.8, 2.7), 5.11 (s, 2H), 4.76 (br s, 1H), 4.17 (m, 4H), 3.57-3.35 (m, 1H), 2.95 (t, 2H, *J*=7.8), 2.63 (t, 2H, *J*=7.8), 2.27 (qn, 2H, *J*=6.0), 1.99-1.05 (m, 10H).

Example 706

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-2-cyclohexylcarbamoyloxymethyl-phenyl}-propionic acid



Step A: 3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-2-cyclohexylcarbamoyloxymethyl-phenyl}-propionic acid *tert*-butyl ester



A mixture of 3-(2-cyclohexylcarbamoyloxymethyl-4-hydroxy-phenyl)-propionic acid *tert*-butyl ester (50 mg, 0.13 mmol; Example 652 Step D), [4-(3-bromo-propoxy)-phenyl]-phenyl-methanone (64 mg, 0.2 mmol, *Bull. Chem. Soc. Jpn.* 1990, *63*, 1342) and potassium carbonate (53 mg, 0.39 mmol) in acetonitrile (6 mL) was heated at 80°C overnight. Ethyl acetate (20 mL) and H_2O (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3x). The

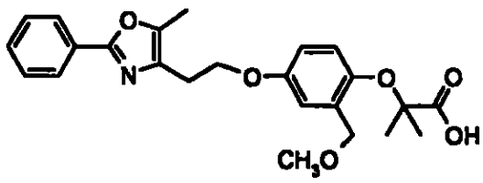
combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by silica gel column chromatography (hexane/ethyl acetate 4/1) to give the title compound (50 mg, 62%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 2H, *J*=8.5), 7.68 (d, 2H, *J*=7.7), 7.48 (d, 1H, *J*=8.4), 7.40 (m, 2H), 7.05 (d, 1H, *J*=8.5), 6.90 (d, 2H, *J*=8.6), 6.85 (s, 1H), 6.74 (dd, 1H, *J*=8.5, 2.2), 5.04 (s, 2H), 4.68 (d, 1H, *J*=7.3), 4.17 (t, 2H, *J*=5.9), 4.09 (t, 2H, *J*=5.9), 3.43 (m, 1H), 2.82 (t, 2H, *J*=7.8), 2.40 (t, 2H, *J*=7.8), 2.21 (qn, 2H, *J*=5.9), 1.85 (m, 2H), 1.67-1.02 (m, 8H), 1.36 (s, 9H).

Step B: 3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-2-cyclohexylcarbamoyloxymethyl-phenyl}-propionic acid

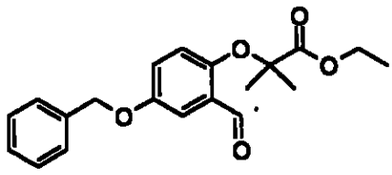
Trifluoroacetic acid (0.031 mL, 0.4 mmol) was added to a solution of 3-{4-[3-(4-benzoyl-phenoxy)-propoxy]-2-cyclohexylcarbamoyloxymethyl-phenyl}-propionic acid tert-butyl ester (50 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was stirred overnight and concentrated under vacuum to give the title compound. (39 mg, 88%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.83-7.72 (m, 4H), 7.57-7.43 (m, 3H), 7.12 (d, 1H, *J*=8.6), 6.98-82 (m, 4H), 5.10 (s, 2H), 4.82 (br s, 1H), 4.23 (t, 2H, *J*=5.9), 4.15 (t, 2H, *J*=5.9), 3.57-3.36 (m, 1H), 2.94 (m, 2H), 2.62 (m, 2H), 2.28 (qn, 2H, *J*=5.9), 1.98-1.02 (m, 10H).

Example 708

2-{2-Methoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid

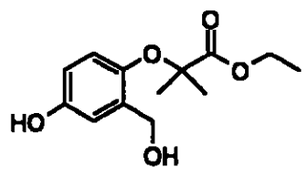


Step A: 2-(4-Benzyloxy-2-formyl-phenoxy)-2-methyl-propionic acid ethyl ester



5-Benzyloxy-2-hydroxy-benzaldehyde (Kappe, T.; Witoszynskyj, T. *Arch. Pharm.*, 1975, *308* (5), 339-346) (169 g, 741 mmol), ethyl bromoisobutyrate (164 mL, 1.11 mol), and cesium carbonate (240 g, 741 mmol) in dry DMF (600 mL) were heated at 80 °C for 15 h. Additional cesium carbonate (5 g) and ethyl bromoisobutyrate (20 mL) were added, and the reaction mixture was heated for 6 h. The reaction mixture was cooled, diluted with EtOAc (4 L), and washed with water (3 x 2 L). The organic layer was dried (Na_2SO_4) and concentrated to a brown oil. The crude product was recrystallized from EtOAc (150 mL) with hexanes until turbid to give the title compound as a pale yellow solid (210 g, 83%): mp 65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.1 Hz), 1.62 (s, 6H), 4.23 (q, 2H, J = 7.1 Hz), 6.81 (d, 1H, J = 8.8 Hz), 7.10 (dd, 1H, J = 4.6, 9.0 Hz), 7.30-7.43 (m, 6H); MS (ES) *m/e* 343.1 [M+1].

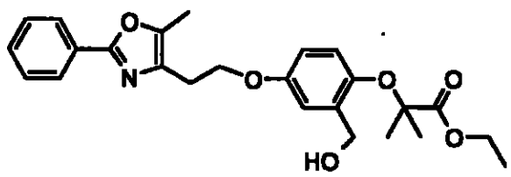
Step B: 2-(4-Hydroxy-2-hydroxymethyl-phenoxy)-2-methyl-propionic acid ethyl ester



2-(4-Benzyloxy-2-formyl-phenoxy)-2-methyl-propionic acid ethyl ester (185 g, 540 mmol) in ethanol (700 mL) was treated with 10% Pd/C (205 g) and hydrogen

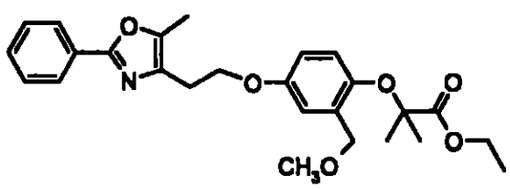
(60 psi) at 50 °C for 2 d. The mixture was filtered through Celite, washed with ethanol (1.5 L), and concentrated. The residue was recrystallized from EtOAc/hexanes to give the title compound (116 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.3 Hz), 1.52 (s, 6H), 2.14 (s, 3H), 4.23 (q, 2H, J = 7.3 Hz), 4.59 (brs, 2H), 6.61-6.68 (m, 2H), 6.77 (d, 1H, J = 2.8 Hz).

Step C: 2-{2-hydroxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid ethyl ester



A 25 mL round bottomed flask under a nitrogen atmosphere was charged with toluene-4-sulfonic acid 2-(5-methyl-2-phenyloxazol-4-yl)ethyl ester (0.77 g, 2.17 mmol), 2-(4-hydroxy-2-hydroxymethylphenoxy)-2-methylpropionic acid ethyl ester (0.5 g, 1.97 mmol), and absolute ethanol (10 mL). Potassium carbonate (0.54 g, 3.94 mmol, 325 mesh) was added, and the reaction was heated to 80° C for 12 h. The mixture was concentrated and the crude residue was diluted with EtOAc (75 mL). The organic layer was washed with brine (2x), dried (Na_2SO_4), and concentrated to an oil. The crude product was purified using radial chromatography (EtOAc:Hex 5:95 to 35:65) to give a colorless oil (0.17 g, 20%). MS (ES) *m/e* 452 (M+1).

Step D: 2-{2-Methoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid ethyl ester



A 15 mL round bottomed flask under a nitrogen atmosphere were charged with 2-{2-hydroxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid ethyl ester (0.075 g, 0.17 mmol), anhydrous DMF (1 mL), and then methyl iodide (0.16 mL, 1.7 mmol). The solution was cooled in an ice bath and was

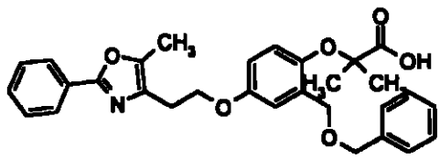
treated with NaH (0.014 g, 0.34 mmol, 60% oil dispersion). The mixture was stirred for 2 h, poured into EtOAc (6 mL) and brine (10 mL), and acidified using dilute sulfuric acid. The organic layer was separated, dried (Na_2SO_4), and concentrated to an oil. The crude product was purified using radial chromatography (EtOAc:Hex 15:85) to give a colorless oil (0.039 g, 51%). MS (ES) *m/e* 454 (M+1).

Step E: 2-{2-Methoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid

A 25 mL round bottomed flask was charged with 2-{2-methoxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid ethyl ester (0.039 g, 0.087 mmol), ethanol (2 mL), and then aqueous 2N NaOH (0.22 mL, 0.44 mmol). The solution was heated at 55° C for 1 h. The mixture was concentrated, acidified using 5% H_2SO_4 (1.5 mL), and partitioned between CH_2Cl_2 (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated and to give a white solid (0.024 g, 66%). MS (ES) *m/e* 426 (M+1).

Example 709

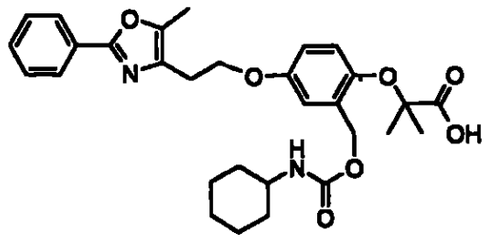
2-{2-Benzyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)-ethoxy]phenoxy}-2-methylpropionic acid



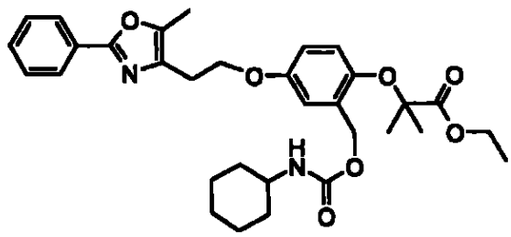
The above compound is prepared by following a substantially similar procedure as described in Example 708. MS (ES) *m/e* 502 (M+1).

Example 710

2-{2-Cyclohexylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid



Step A: 3-{2-Cyclohexylcarbamoyloxymethyl-4-[2-(2-phenyloxazol-4-yl)ethoxy]phenyl}-propionic acid ethyl ester



A 15 mL round bottomed flask under N_2 was charged 2-{2-hydroxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid ethyl ester (0.075 g, 0.17 mmol), cyclohexylisocyanate (0.13 mL, 1.0 mmol), anhydrous CH_2Cl_2 (0.5 mL), and then 1.0 N HCl in ether (0.086 mL, 0.086 mmol). The reaction mixture was stirred at ambient temperature for 18 h and was diluted with CH_2Cl_2 (10 mL). The organic layer was washed with brine, dried (Na_2SO) and concentrated to give 0.10 g of a crude oil, which was used directly in the next step. MS (ES) *m/e* 564 (M+1).

Step B: 3-{2-Cyclohexylcarbamoyloxymethyl-4-[2-(2-phenyloxazol-4-yl)ethoxy]phenyl}-propionic acid

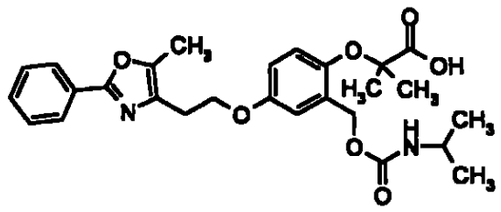
To a 15 mL round bottomed flask was charged with 3-{2-cyclohexylcarbamoyloxymethyl-4-[2-(2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid ethyl ester (0.10 g, 0.17 mmol), ethanol (2 mL), and then 2N NaOH (0.48 mL, 0.96 mmol). The solution was heated at 55°C for 2 h. The mixture was concentrated, acidified using 5% H_2SO_4 (1.5 mL), and partitioned between CH_2Cl_2 (15 mL) and brine (15 mL).

The organic layer was dried (Na_2SO_4), filtered, and concentrated and was concentrated. The crude residue was submitted for mass-directed HPLC purification to give a white solid (0.058 g, 63%). MS (ES) *m/e* 537 (M+1).

The following Examples 711 to 713 are prepared by following a substantially similar procedure as described in Example 710.

Example 711

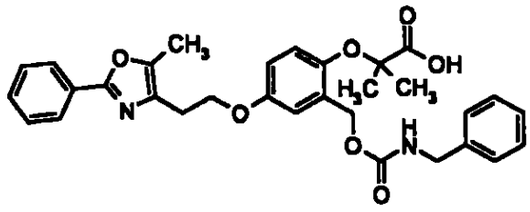
2-{2-Isopropylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid



MS (ES) *m/e* 497 (M+1).

Example 712

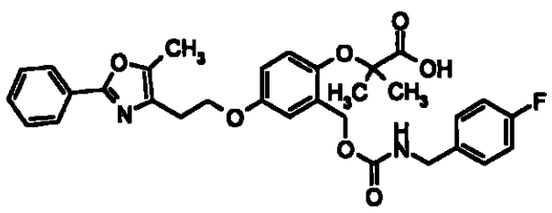
2-{2-Benzylcarbamoyloxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid



MS (ES) *m/e* 545 (M+1).

Example 713

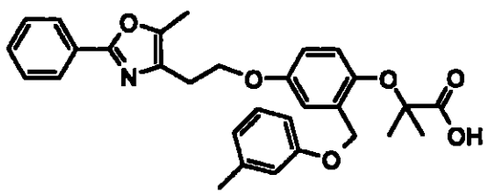
2-{2-(4-Fluorobenzylcarbamoyloxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid



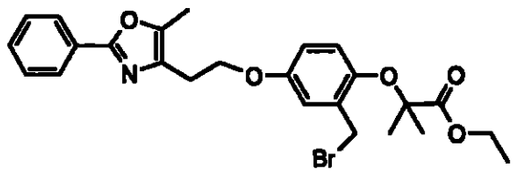
MS (ES) *m/e* 563 (M+1).

Example 714

2-Methyl-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-m-tolyloxymethyl-phenoxy}-propionic acid



Step A: 2-{2-Bromomethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid ethyl ester



A 100 mL round bottomed flask was charged with 2-{2-hydroxymethyl-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid ethyl ester (1.0 g, 2.25 mmol), dissolved in anhydrous THF (75 mL), and then of triphenylphosphine (1.18 g, 4.50 mmol) and CBr_4 (1.49 g, 4.50 mmol). The mixture was stirred at ambient temperature under a nitrogen atmosphere for 1 h and was poured into EtOAc (135 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The crude product was purified using radial chromatography (EtOAc:hexanes 15:85) to give a the title compound as a colorless oil (0.95 g, 76%).

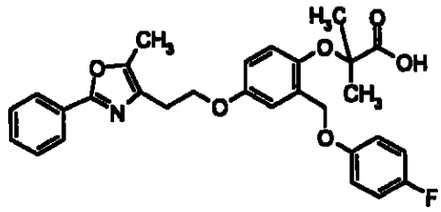
Step B: 2-Methyl-2-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-m-tolyloxymethyl-phenoxy}-propionic acid

General procedure for the parallel synthesis of analogs using the DynaVac Carousel apparatus: A 50 mL glass tube with screw cap and nitrogen inlet was charged with 2-{2-bromomethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methyl-propionic acid ethyl ester (0.040 g, 0.080 mmol), *m*-cresol (0.012 mL, 0.12 mmol), absolute ethanol (1 mL), and then potassium carbonate (0.022 g, 0.16 mmol; 325 mesh). The mixture was heated to 80° C for 4 h. MS analysis of the reaction indicated that 2-methyl-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-2-*m*-tolyloxymethylphenoxy}-propionic acid ethyl ester: MS (ES) *m/e* 530 (M+1) had formed. The reaction mixture was treated with 2N NaOH (0.4 mL), heated at 55°C for 3 h, cooled, and concentrated. The residue was treated with 5N HCl (0.75 mL) and CH_2Cl_2 (1 mL) and was poured onto a 3-mL ChemElute cartridge to remove the aqueous layer. The cartridge was washed with CH_2Cl_2, and the solvent was removed *in vacuo*. The crude residue was purified by mass-directed reverse phase HPLC to provide the title compound (0.032 g, 38%). MS (ES) *m/e* 502 (M+1).

The following Examples 715 to 723 are prepared by following a substantially similar procedure as described in Example 714.

Example 715

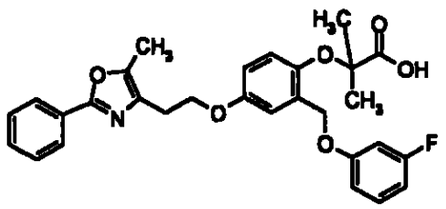
2-{2-(4-Fluorophenoxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid



MS (ES) *m/e* 506 (M+1).

Example 716

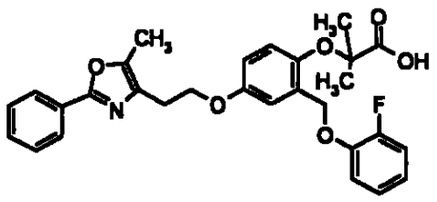
2-{2-(3-Fluorophenoxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid



MS (ES) *m/e* 506 (M+1).

Example 717

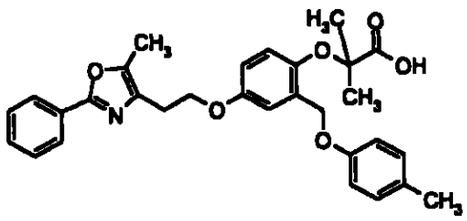
2-{2-(2-Fluorophenoxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid



MS (ES) *m/e* 506 (M+1).

Example 718

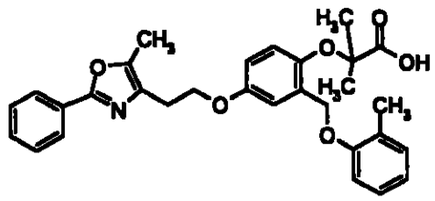
2-Methyl-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-2-*p*-tolyloxymethylphenoxy}propionic acid



MS (ES) *m/e* 502 (M+1).

Example 719

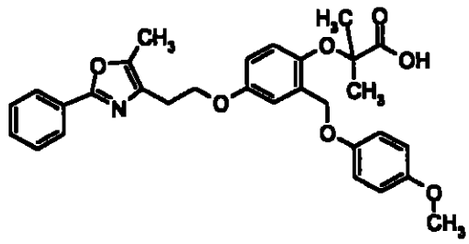
2-Methyl-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-2-*o*-tolyloxymethylphenoxy}propionic acid



MS (ES) *m/e* 502 (M+1).

Example 720

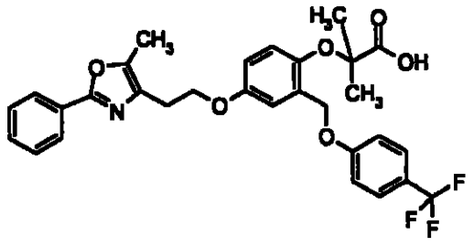
2-{2-(4-Methoxyphenoxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid



MS (ES) *m/e* 518 (M+1).

Example 721

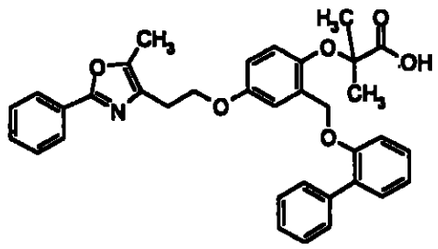
2-Methyl-2-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-2-(4-trifluoromethylphenoxymethyl)phenoxy]propionic acid



MS (ES) *m/e* 556 (M+1).

Example 722

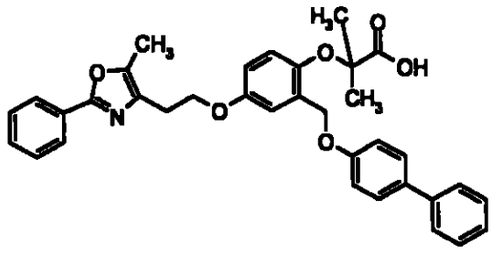
2-{2-(Biphenyl-2-yloxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid



MS (ES) *m/e* 564 (M+1).

Example 723

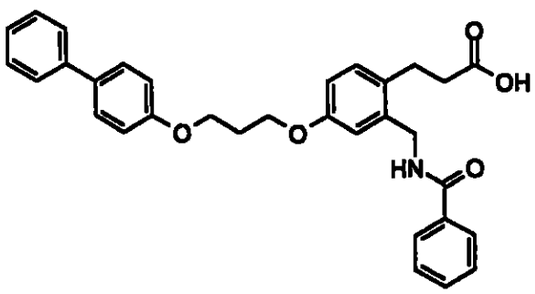
2-{2-(Biphenyl-4-yloxymethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenoxy}-2-methylpropionic acid



MS (ES) *m/e* 564 (M+1).

Example 724

3-{2-(Benzoylaminomethyl)-4-[3-(biphenyl-4-yloxy)propoxy]phenyl} propionic acid



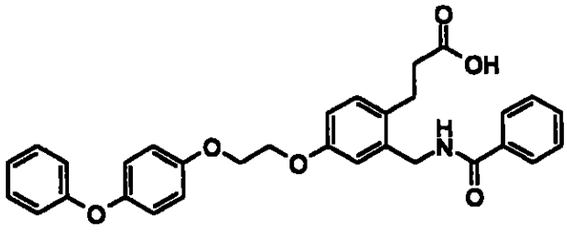
A solution of 4-(3-bromo-propoxy)-biphenyl (291 mg, 1.00 mmol; Preparation 12) and 3-[2-(benzoylamino-methyl)-4-hydroxy-phenyl]-propionic acid tert-

butyl ester (320 mg, 0.90 mmol; Preparation 21) in DMF (5 mL) was treated with K_2CO_3 (100 mg) and heated at 60°C for 48 h. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were dried (Na_2SO_4), concentrated, and purified using silica gel chromatography (10-30% EtOAc/hexanes) to give 3-{2-(benzoylaminomethyl)-4-[3-(biphenyl-4-yloxy)propoxy]phenyl} propionic acid *tert*-butyl ester (450 mg). This material was treated with a mixture of CH_2Cl_2 (1.0 mL)/TFA (0.8 mL)/water (0.1 mL) at ambient temperature for 2 h. The reaction mixture was concentrated and dried under vacuum to afford the title product as a white solid (380 mg, 75%). MS (ES) *m/e* 510.1 (M+1).

The following Examples 725 to 757 are prepared by following a substantially similar procedure as described in Example 724.

Example 725

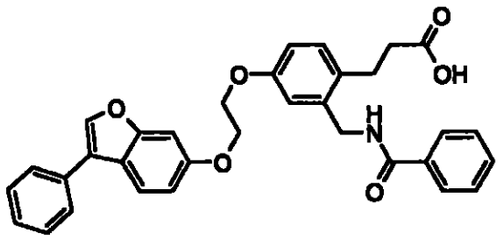
3-{2-(Benzoylaminomethyl)-4-[2-(4-phenoxy-phenoxy)ethoxy]phenyl} propionic acid



MS [ES] m/z 512 (M+1).

Example 726

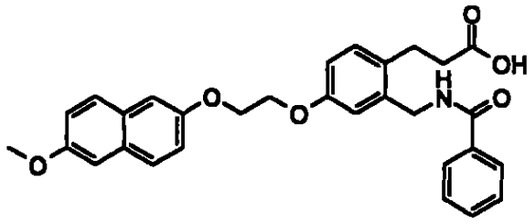
3-{2-(Benzoylaminomethyl)-4-[2-(3-phenylbenzofuran-6-yloxy)ethoxy]-phenyl}-propionic acid



MS [ES] m/z 536 (M+1).

Example 727

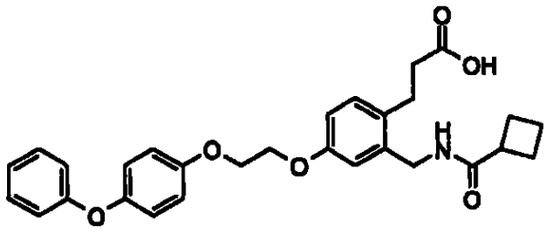
3-{2-(Benzoylaminomethyl)-4-[2-(6-methoxynaphthalen-2-yloxy)ethoxy]-phenyl} propionic acid



MS [ES] m/z 500 (M+1).

Example 728

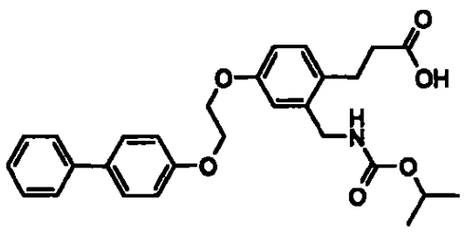
3-{2-[(Cyclobutanecarbonylamino)methyl]-4-[2-(4-phenoxyphenoxy)-ethoxy]phenyl} propionic acid



MS [ES] m/z 490 (M+1).

Example 729

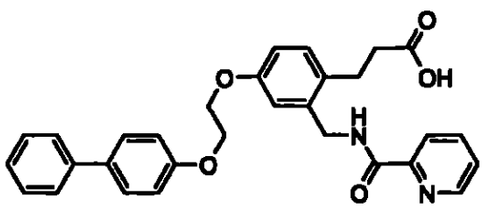
3-[4-[2-(Biphenyl-4-yloxy)ethoxy]-2-(isopropoxycarbonylaminomethyl)-phenyl] propionic acid



MS [ES] m/z 473 (M+1).

Example 730

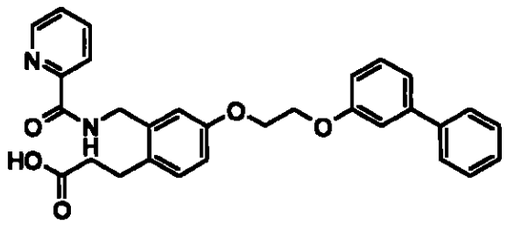
3-(4-[2-(Biphenyl-4-yloxy)ethoxy]-2-{[(pyridine-2-carbonyl)amino]methyl}-phenyl) propionic acid



MS [ES] m/z 497 (M+1).

Example 731

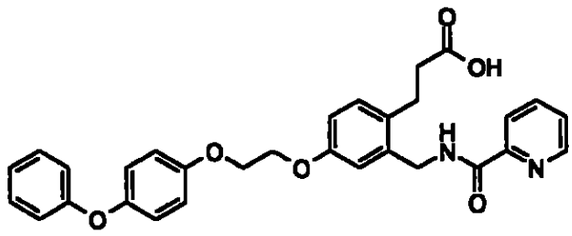
3-(4-[2-(Biphenyl-3-yloxy)ethoxy]-2-{[(pyridine-2-carbonyl)amino]methyl} phenyl)propionic acid



MS [ES] m/z 497 (M+1).

Example 732

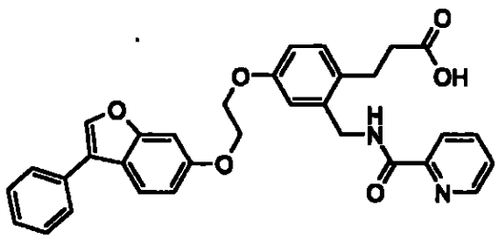
3-(4-[2-(4-Phenoxy-phenoxy)ethoxy]-2-{[(pyridine-2-carbonyl)amino]-methyl}phenyl) propionic acid



MS [ES] m/z 501 (M+1).

Example 733

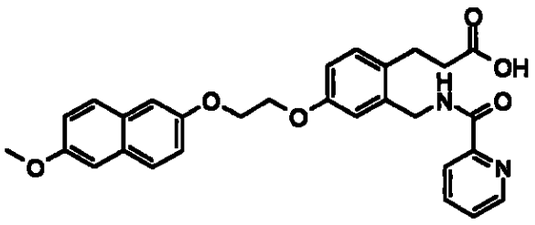
3-(4-[2-(3-Phenylbenzofuran-6-yloxy)ethoxy]-2-{[(pyridine-2-carbonyl)-amino]methyl}phenyl) propionic acid



MS [ES] m/z 537 (M+1).

Example 734

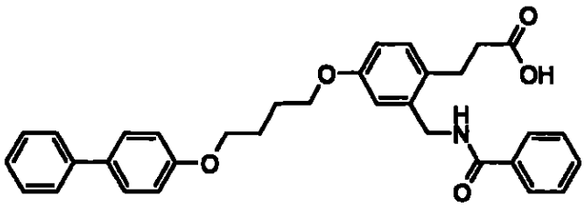
3-(4-[2-(6-Methoxynaphthalen-2-yloxy)ethoxy]-2-{[(pyridine-2-carbonyl)-amino]methyl}phenyl) propionic acid



MS [ES] m/z 501 (M+1).

Example 735

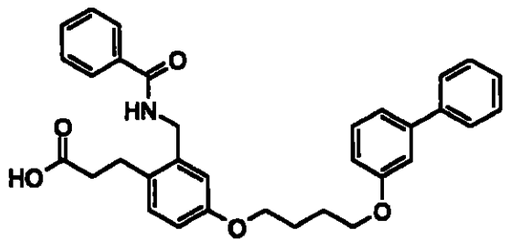
3-{2-(Benzoylaminomethyl)-4-[4-(biphenyl-4-yloxy)butoxy]phenyl} propionic acid:



MS [ES] m/z 524 (M+1).

Example 736

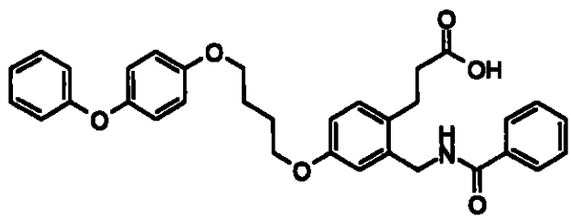
3-{2-(Benzoylaminomethyl)-4-[4-(biphenyl-3-yloxy)butoxy]phenyl} propionic acid:



MS [ES] m/z 524 (M+1).

Example 737

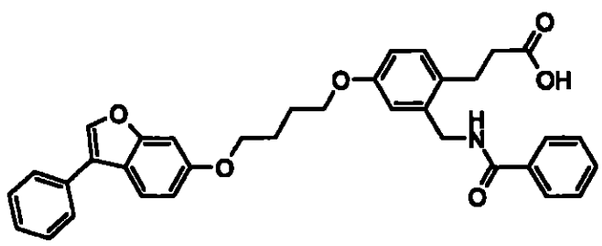
3-{2-(Benzoylaminomethyl)-4-[4-(4-phenoxyphenoxy)butoxy]phenyl} propionic acid:



MS [ES] m/z 540 (M+1).

Example 738

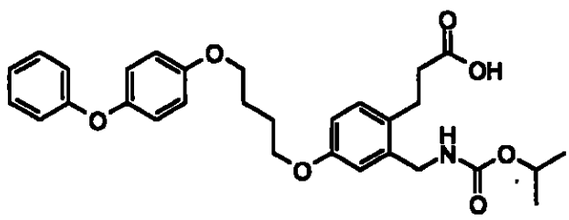
3-{2-(Benzoylaminomethyl)-4-[4-(3-phenylbenzofuran-6-yloxy)butoxy] phenyl}-propionic acid



MS [ES] m/z 564 (M+1).

Example 739

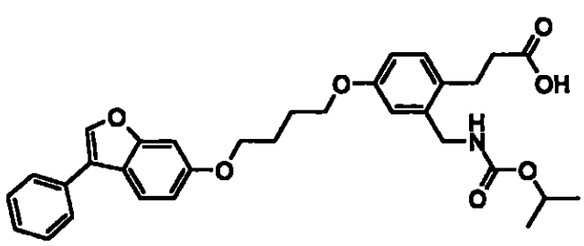
3-{2-(Isopropoxycarbonylaminomethyl)-4-[4-(4-phenoxyphenoxy)butoxy]phenyl} propionic acid



MS [ES] m/z 522 (M+1).

Example 740

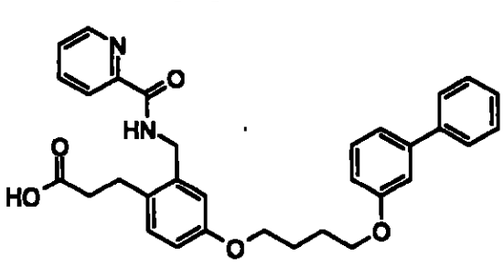
3-{2-(Isopropoxycarbonylaminomethyl)-4-[4-(3-phenylbenzofuran-6-yloxy)butoxy]phenyl} propionic acid



MS [ES] m/z 546 (M+1).

Example 741

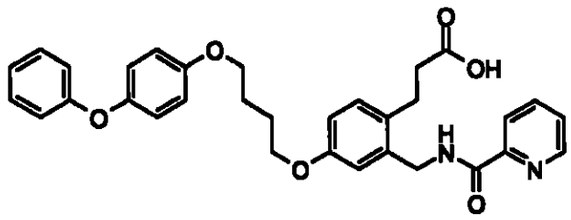
3-(4-[4-(Biphenyl-3-yloxy)butoxy]-2-{[(pyridine-2-carbonyl)amino]methyl}-phenyl) propionic acid



MS [ES] m/z 525 (M+1).

Example 742

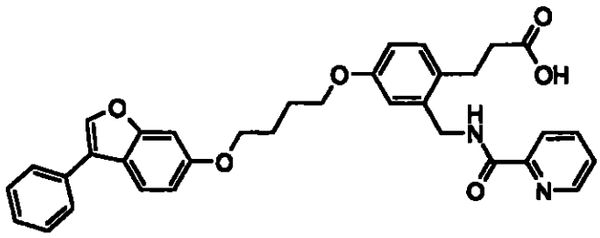
3-(4-[4-(4-Phenoxyphenoxy)butoxy]-2-{[(pyridine-2-carbonyl)amino]-methyl}phenyl) propionic acid



MS [ES] m/z 541 (M+1).

Example 743

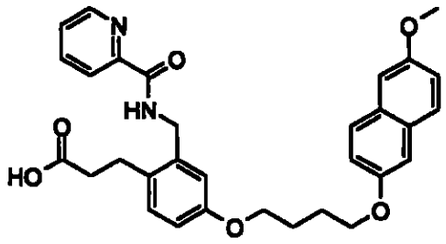
3-(4-[4-(3-Phenylbenzofuran-6-yloxy)butoxy]-2-{[(pyridine-2-carbonyl)-amino]methyl} phenyl) propionic acid



MS [ES] m/z 565 (M+1).

Example 744

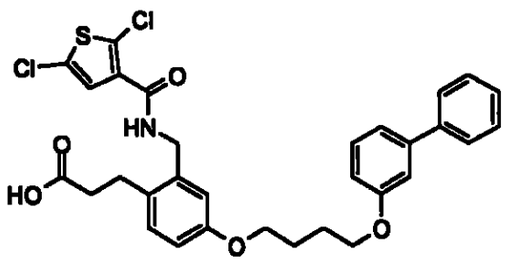
3-(4-[4-(6-Methoxynaphthalen-2-yloxy)butoxy]-2-{[(pyridine-2-carbonyl)-amino]methyl}phenyl) propionic acid



MS [ES] m/z 529 (M+1).

Example 745

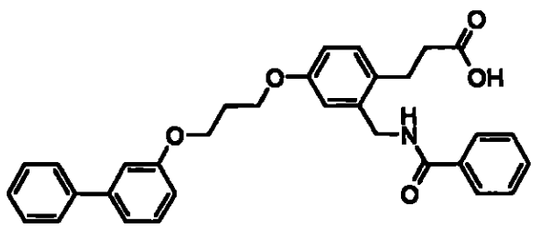
3-(4-[4-(Biphenyl-3-yloxy)butoxy]-2-{[(2,5-dichlorothiophene-3-carbonyl)-amino]methyl}phenyl) propionic acid



MS [ES] m/z 599 (M+1).

Example 746

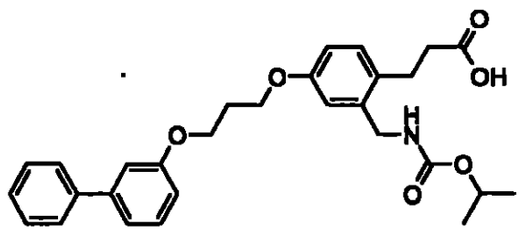
3-{2-(Benzoylaminomethyl)-4-[3-(biphenyl-3-yloxy)propoxy]phenyl} propionic acid:



MS [ES] m/z 510 (M+1).

Example 747

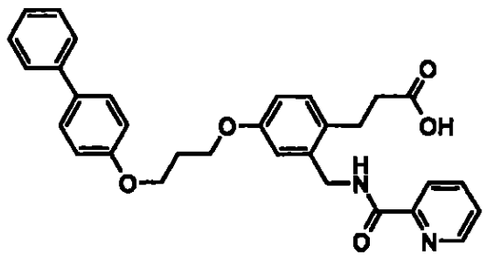
3-[4-[3-(Biphenyl-3-yloxy)propoxy]-2-(isopropoxycarbonylaminomethyl)-phenyl] propionic acid



MS [ES] m/z 492 (M+1).

Example 748

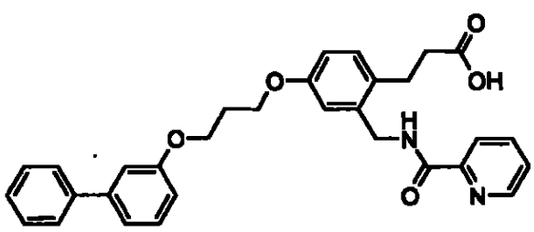
3-(4-[3-(Biphenyl-4-yloxy)propoxy]-2-{[(pyridine-2-carbonyl)amino]methyl}-phenyl) propionic acid



MS [ES] m/z 511 (M+1).

Example 749

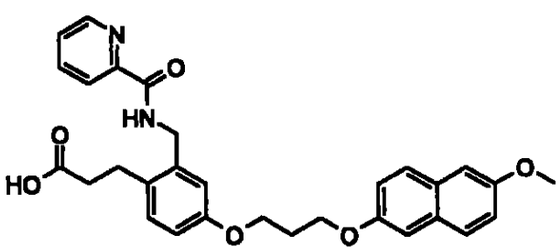
3-(4-[3-(Biphenyl-3-yloxy)propoxy]-2-{[(pyridine-2-carbonyl)amino]methyl} phenyl) propionic acid



MS [ES] m/z 511 (M+1).

Example 750

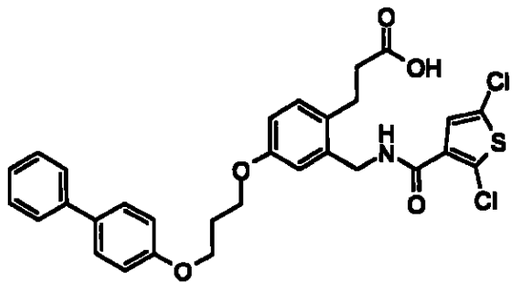
3-(4-[3-(6-Methoxynaphthalen-2-yloxy)propoxy]-2-{[(pyridine-2-carbonyl)-amino]methyl}phenyl) propionic acid



MS [ES] m/z 515 (M+1).

Example 751

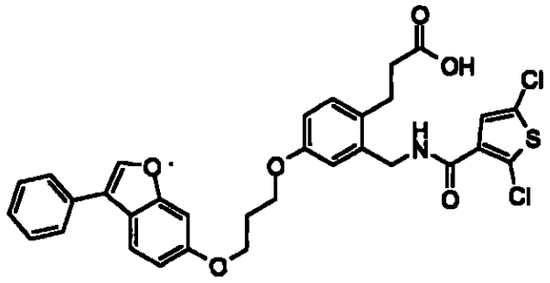
3-(4-[3-(Biphenyl-4-yloxy)propoxy]-2-{[(2,5-dichlorothiophene-3-carbonyl)-amino]methyl}phenyl) propionic acid



MS [ES] m/z 585 (M+1).

Example 752

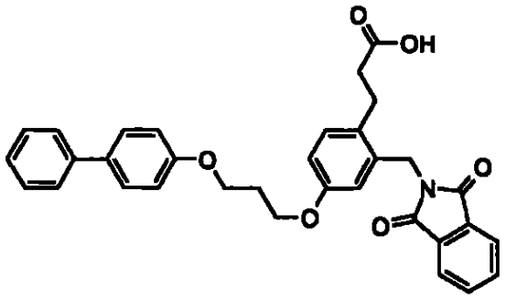
3-{2-{[(2,5-Dichlorothiophene-3-carbonyl)amino]methyl}-4-[3-(3-phenyl-benzofuran-6-yloxy)propoxy]phenyl} propionic acid



MS [ES] m/z 625 (M+1).

Example 753

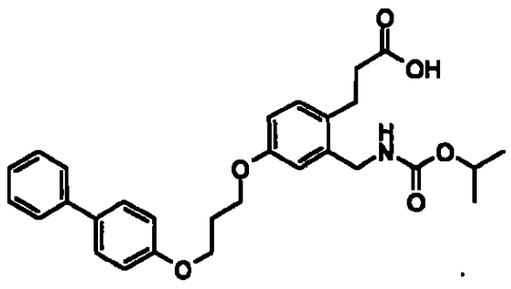
3-[4-[3-(Biphenyl-4-yloxy)propoxy]-2-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)phenyl] propionic acid



MS [ES] m/z 536 (M+1).

Example 754

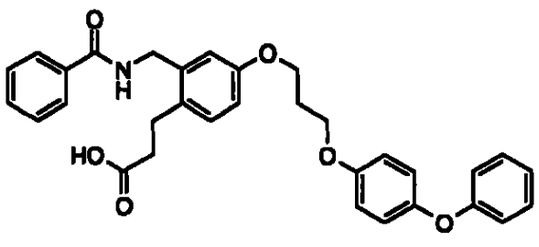
3-[4-[3-(Biphenyl-4-yloxy)propoxy]-2-(isopropoxycarbonylaminomethyl)-phenyl] propionic acid



MS [ES] m/z 492 (M+1).

Example 755

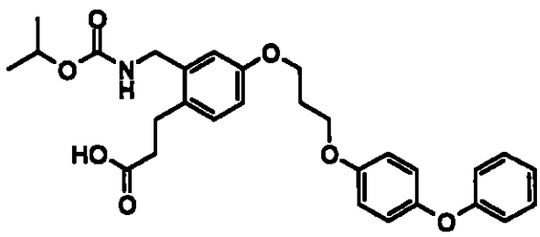
3-{2-(Benzoylaminomethyl)-4-[3-(4-phenoxyphenoxy)propoxy]phenyl} propionic acid



MS [ES] m/z 526 (M+1).

Example 756

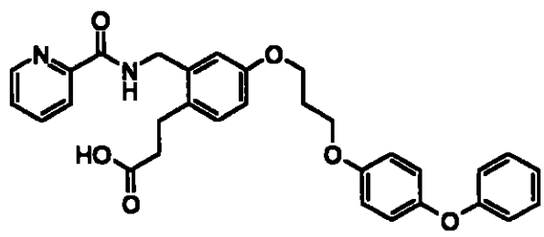
3-{2-(Isopropoxycarbonylaminomethyl)-4-[3-(4-phenoxyphenoxy)propoxy]-phenyl} propionic acid



MS [ES] m/z 508 (M+1).

Example 757

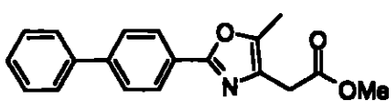
3-(4-[3-(4-Phenoxyphenoxy)propoxy]-2-{[(pyridine-2-carbonyl)amino]-methyl}phenyl) propionic acid



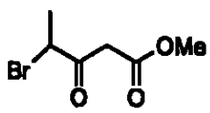
MS [ES] m/z 527 (M+1).

Example 758

(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-acetic acid methyl ester



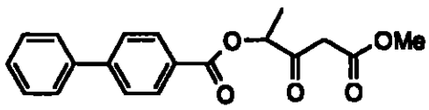
Step 1: 4-Bromo-3-oxo-pentanoic acid methyl ester



A solution of bromine (28.3 g, 0.177 mol) in chloroform (30 mL) was added dropwise over 2 h to a solution of methyl propionylacetate (23.5 g, 0.177 mol) in chloroform (155 mL) at 0-5 °C. The mixture was stirred for 30 min, and the cooling bath

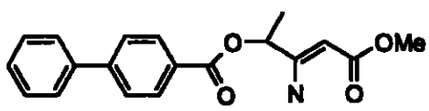
was removed. The mixture was stirred for 18 h, and ice water (200 mL) was added. The organic layer was collected and washed with cold water (2 x 200 mL), 10% aqueous sodium thiosulfate (2 x 200 mL) and brine (200 mL). The filtered solution was dried (Na_2SO_4) and concentrated to 36.5 g of the title compound as a clear liquid.

Step 2: Biphenyl-4-carboxylic acid 3-methoxycarbonyl-1-methyl-2-oxo-propyl ester



A mixture of biphenyl-4-carboxylic acid (800 g, 4.03 mol) in acetone (4.6 L) was treated with triethylamine (0.6 L, 4.3 mol, 1.07eq) dropwise over 13 min while maintaining the temperature at 15-30 °C. 4-Bromo-3-oxo-pentanoic acid methyl ester (880 g, 4.21 mol, 1.04 eq) was added dropwise over 21 min at 15-30 °C. The mixture was stirred overnight at room temperature. Water (9.6 L) was added dropwise over 85 minutes at 15-30 °C. The mixture was stirred for 2 h. The precipitated product was collected by filtration and washed twice with water (1 L). The product was dried under vacuum at 50 °C to afford 1291 g (98% yield, 96% HPLC purity) of the title compound.

Step 3: Biphenyl-4-carboxylic acid 2-amino-3-methoxycarbonyl-1-methyl-allyl ester



A mixture of biphenyl-4-carboxylic acid 3-methoxycarbonyl-1-methyl-2-oxo-propyl ester (1275 g, 3.9 mol, 1 eq) and ammonium acetate (640 g, 8.3 mol) in ethanol (10 L) was heated with stirring at 70-75 °C until the keto ester compound is completely consumed (1-2 h). The mixture was then kept at 0-5 °C for 1.5 h. The precipitated solid was collected by filtration and washed with hexanes (2.5 L). The product was dried overnight under vacuum at 50 °C to obtain 1244 g (90% yield, 98% HPLC purity) of the title compound.

Step 4: (2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-acetic acid methyl ester

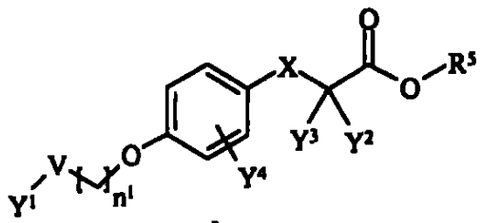
A mixture of biphenyl-4-carboxylic acid 2-amino-3-methoxycarbonyl-1-methyl-allyl ester (566 g, 1.74 mol, 1 eq) and ammonium acetate (283 g, 3.67 mol) in glacial

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acetic acid (11.3 L) was heated at reflux for 2 h, cooled, and concentrated. The residue was coevaporated with toluene (2 x 2.5 L) and EtOAc (2.5 L). The mixture was diluted with EtOAc (6.6 L) and transferred with EtOAc (2.2 L) to a bottom outlet separation flask. The mixture was washed twice with water (2.2 L), saturated aqueous $NaHCO_3$ (1.1 L), and brine (2 x 2.2 L). The organic layer was dried (Na_2SO_4, 550 g), filtered with the aid of EtOAc (1.1 L), and concentrated. The residue was dissolved in isopropanol (2 L) at 50°C and allowed to cool overnight at room temperature. The mixture was kept at 0°C to 5°C for 1 h. The precipitated solid was broken up and collected by filtration. The solid was washed with cold isopropanol (4 x 0.55 L) and dried overnight in a vacuum oven at 50°C to yield 428 g of the title compound (72% from Step 2).

WHAT IS CLAIMED IS:

1. A compound of formula I,



I

and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof, wherein:

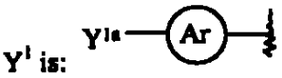
n^1 is 2, 3, 4 or 5;

V is a bond or O;

X is CH_2 or O;

p is 0 or 1;

m is 1-4;

Y^1 is:  wherein,

 is: aryl or heteroaryl,

wherein aryl and heteroaryl are optionally substituted with one or more groups independently selected from the group consisting of:

hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, haloalkyl and haloalkyloxy;

Y^{1a} is: hydrogen,

$(C_0$-$C_3)$alkyl-aryl,

C(O)-aryl,

heteroaryl,

cycloalkyl,

heterocycloalkyl,

aryloxy,

$NR^5(CH_2)_mOR^5$,

aryl-Z-aryl,
aryl-Z-heteroaryl,
aryl-Z-cycloalkyl,
aryl-Z-heterocycloalkyl,
heteroaryl-Z-aryl,
heteroaryl-Z-heterocycloalkyl or
heterocycloalkyl-Z-aryl,
wherein aryl, cycloalkyl, aryloxy, heteroaryl, and heterocycloalkyl are optionally substituted with one or more substituents independently selected from the group consisting of:

halo,
hydroxyl,
nitro,
cyano,
C_1-C_6 alkyl,
C_1-C_6 alkoxy optionally substituted with $N(R^5)_2$,
haloalkyl,
$N(R^5)_2$,
$N[C(O)R^5]_2$,
$N[S(O)_2R^5]_2$,
$NR^5S(O)_2R^5$,
$NR^5C(O)R^5$,
$NR^5C(O)OR^5$,
$C(O)N(R^5)_2$,
$C(O)OR^5$ and
$C(O)R^5$;

Z is: a bond,
-oxygen-
$-C(O)NR^5-$
$-NR^5C(O)-$,
$-NR^5C(O)O-$,

-C(O)-,
-NR^5-,
-$[O]_p(CH_2)_m$-,
-$(CH_2)_m[O]_p$-,
-$NR^5(CH_2)_m$- or
- $(CH_2)_m NR^5$-;

Y^2 and Y^3 are each independently:
hydrogen,
C_1-C_6 alkyl or
C_1-C_6 alkoxy;

Y^4 is: $(C_1$–$C_3)$alkyl-$NR^5C(O)$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1$–$C_3)$alkyl-$NR^5C(O)$-$(C_2$-$C_5)$alkenyl-Y^7,
$(C_1$–$C_3)$alkyl-$NR^5C(O)$-$(C_2$-$C_5)$alkynyl-Y^7;
$(C_1$–$C_3)$alkyl-$NR^5C(O)O$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1$–$C_3)$alkyl-$NR^5C(O)NR^5$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1$–$C_3)$alkyl-$NR^5C(S)NR^5$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_0$–$C_3)$alkyl-$C(O)NR^5$-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1$–$C_3)$alkyl-$OC(O)NY^{10}Y^{11}$,
$(C_1$-$C_3)$alkyl-$NY^{10}Y^{11}$,
$(C_1$–$C_3)$alkyl-O-$(C_0$-$C_5)$alkyl-Y^7,
$(C_1$–$C_3)$alkyl-S-$(C_0$-$C_5)$alkyl-Y^7 or
CN;

Y^7 is: hydrogen,
aryl,
heteroaryl,
C_1-C_{12} alkyl,
C_1-C_6 alkoxy,
cycloalkyl,
heterocycloalkyl,

aryloxy,
C(O)-heteroaryl or
SR^6,
wherein alkyl, aryl, aryloxy, alkoxy, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more groups independently selected from R^7:

Y^{10} and Y^{11} are each independently:
hydrogen,
aryl,
heteroaryl,
C_1-C_{10} alkyl,
cycloalkyl,
$SO_2(R^6)$; or
Y^{10} and Y^{11} together are a 5- to 10-membered heterocycloalkyl ring or heterocycloalkyl ring fused with aryl, and the heterocycloalkyl ring optionally containing one or more heteroatoms selected from N, O or S; and wherein, aryl, heteroaryl, heterocycloalkyl and alkyl are optionally substituted with one or more substituents independently selected from R^7;

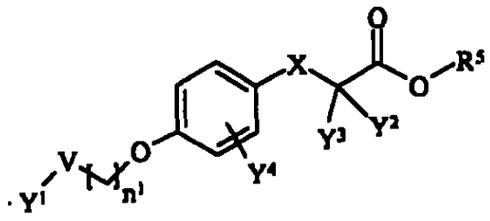
R^5 is: hydrogen or C_1-C_6 alkyl;

R^6 is: hydrogen,
C_1-C_{10} alkyl,
cycloalkyl,
aryl, or
heteroaryl,
wherein alkyl, cycloalkyl, aryl and heteroaryl are optionally substituted with one or more substituents independently selected from R^7;

R^7 is: halo,
nitro,
oxo,
cyano,

hydroxyl,
benzyl,
phenyl,
phenoxy,
heteroaryl,
$C(O)R^6$,
C_1-C_{10} alkyl,
C_1-C_6 alkoxy,
C_1-C_6 haloalkyl,
C_1-C_6 haloalkyloxy,
$O(CH_2)_m$-phenyl,
$(CH_2)_mOC(O)$-aryl,
$C(O)OR^5$,
$S(O)_2R^5$,
$S(O)_2N(R^5)_2$,
SR^5 or
$N(R^5)_2$,
wherein phenyl and phenoxy are optionally substituted with one or more groups independently selected from halo or trifluoromethyl.

2. A compound represented by the following structural formula Ia:



Ia

or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein:

Y^1 is an unsubstituted or substituted group selected from the group consisting of: aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aryl-C_1-C_4 alkyl, heteroaryl-C_1-C_4 alkyl, cycloalkyl-C_1-C_4 alkyl, and t-butyl;

Y^2 is selected from the group consisting of:
H, C_1-C_{10} alkyl, cycloalkyl,(C_1-C_{10} alkyl)-Y^5 , O-Y^6;

Y^5 is selected from the group consisting of:

an aryl, substituted aryl group, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, $-CSR^4$, and $-C(S)NR^6R^7$;

Y^6 is selected from the group consisting of:

an aliphatic group, a substituted aliphatic group, an aryl, substituted aryl group, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, $-CSR^4$, and $-C(S)NR^6R^7$;

R^4, R^6 and R^7 are each independently selected from the group consisting of:

H, an aliphatic group, a substituted aliphatic group, an aryl group and a substituted aryl group;

Y^3 is selected from the group consisting of:

H, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and (C_1-C_{10} alkyl)-R^8; R^8 is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

R^5 is selected from the group consisting of:

H, aliphatic group, a substituted aliphatic group, heteroaryl, substituted heteroaryl, an aryl, a substituted aryl, and (C_1-C_{10} alkyl)-R^9;

R^9 is selected from the group consisting of

aryl, substituted aryl, heteroaryl, and substituted heteroaryl, aminoalkyl, and cycloalkyl;

V is a bond or O;

X is CH_2 or O;

Y^4 is selected from the group consisting of:

-(C_1-C_3)alkyl-O-W-Y^7, $-C(O)NY^8Y^9$, -(C_1–C_3)alkyl-$NY^{10}Y^{11}$, and -(C_1–C_3)alkyl$N(Y^{13})$W-(C_0-C_3)alkyl-Y^{14};

W is selected from the group consisting of:

a bond, $-CONY^{12}$, -C(O)-, $-OCH_2$-, C_1-C_6 alkyl, $-CO_2$-, $-CHOY^{15}$-, $-CSNY^{16}$ and $-SO_2$-;

Y^7 is selected from the group consisting of:

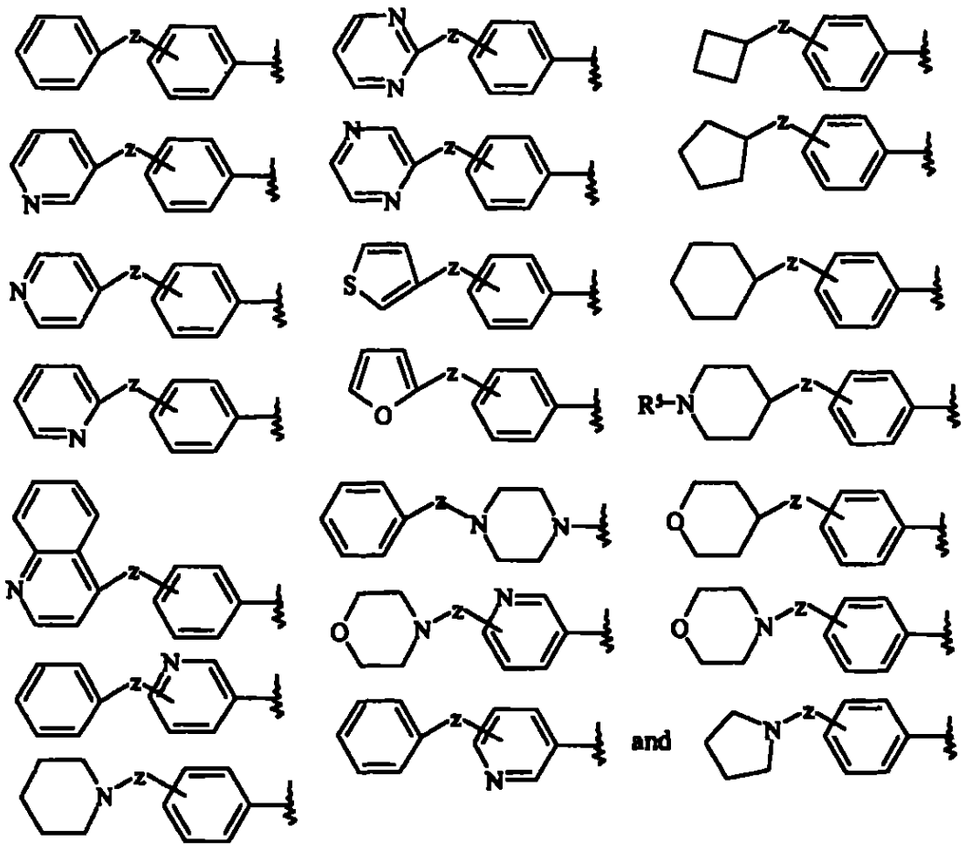
aryl, substituted aryl, heteroaryl, substituted heteroaryl, aliphatic, branched aliphatic and substituted (C_1-C_{10}) alkyl;

Y^8, Y^9, Y^{10}, Y^{11}, Y^{12}, Y^{13}, Y^{14}, Y^{15}, and Y^{16} are each independently selected from the group consisting of:

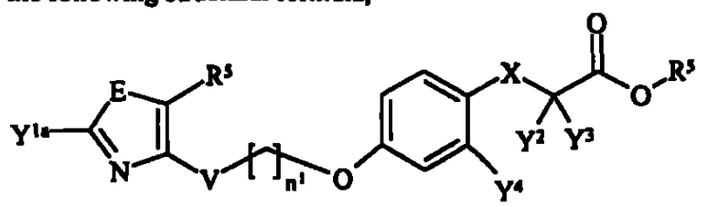
aryl, substituted aryl, heteroaryl, substituted heteroaryl, aliphatic, branched aliphatic and substituted (C_1-C_{10}) alkyl; and

n^1 is 2, 3, 4 or 5.

3. The compound of Claim 1, wherein Y^{1a} is selected from the group consisting of: aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aryloxy,

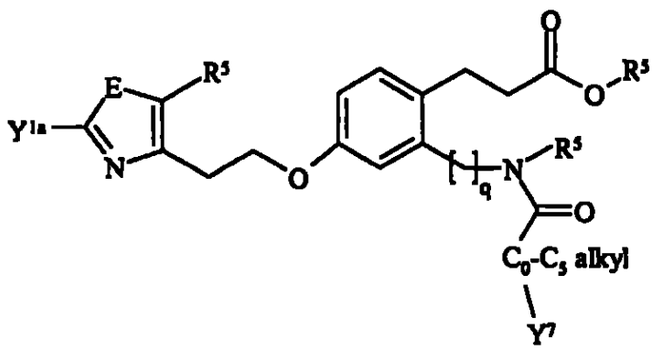


4. The compound of Claim 1 or 2, wherein the compound is represented by the following structural formula,



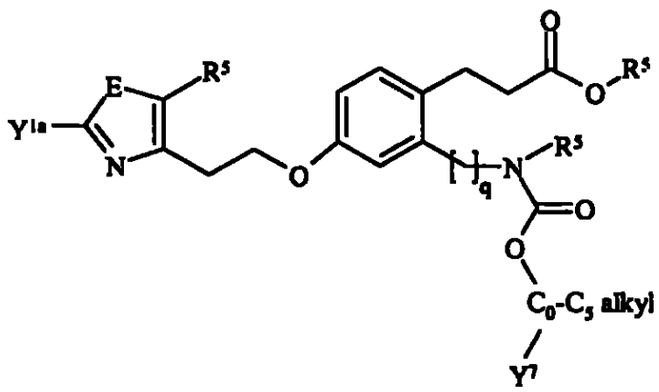
wherein E is O or S.

5. The compound of Claim 4, wherein the compound is represented by the following structural formula,



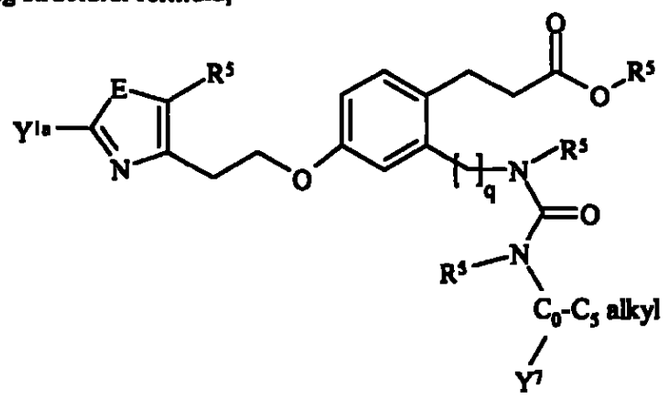
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

6. The compound of Claim 4, wherein the compound is represented by the following structural formula,



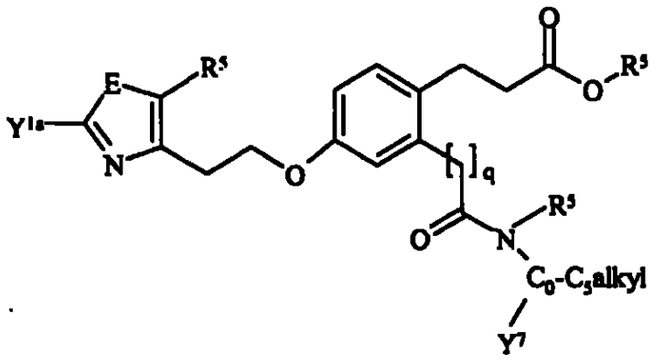
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

7. The compound of Claim 4, wherein the compound is represented by the following structural formula,



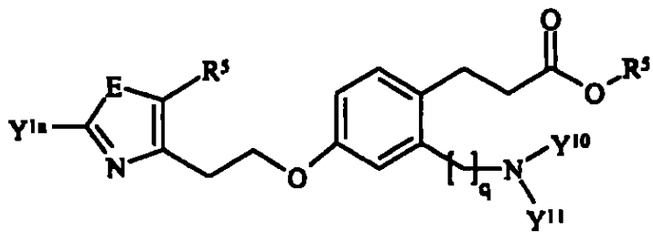
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

8. The compound of Claim 4, wherein the compound is represented by the following structural formula,



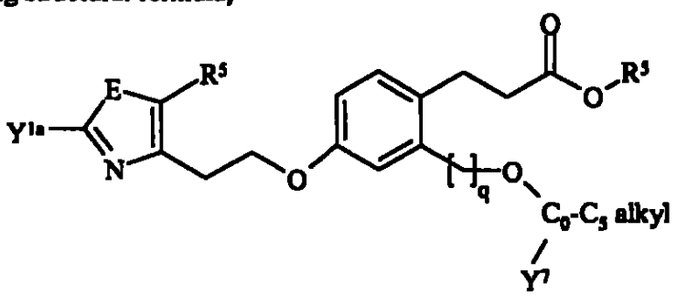
wherein q is 0 or 1; and each R^5 is independently hydrogen or methyl.

9. The compound of Claim 4, wherein the compound is represented by the following structural formula,



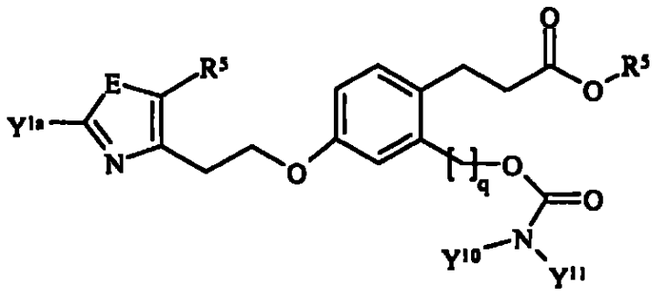
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

10. The compound of Claim 4, wherein the compound is represented by the following structural formula,



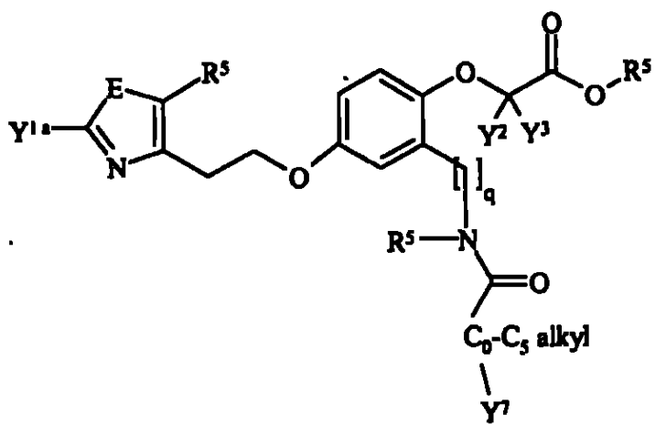
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

11. The compound of Claim 4, wherein the compound is represented by the following structural formula,



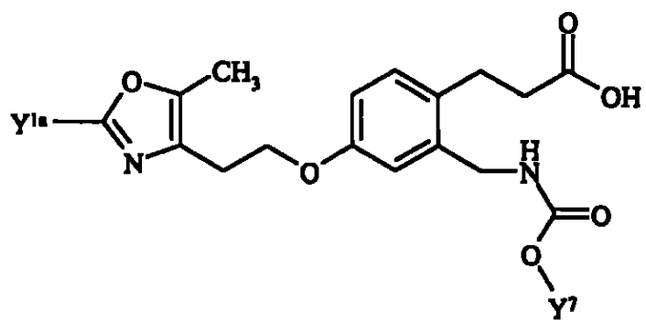
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

12. The compound of Claim 4, wherein the compound is represented by the following structural Formula,

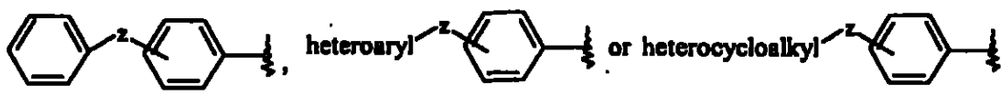


wherein q is 1 or 2; and each R^5, Y^2 and Y^3 are independently hydrogen or methyl.

13. The compound of Claim 4 represented by the following structural formula,

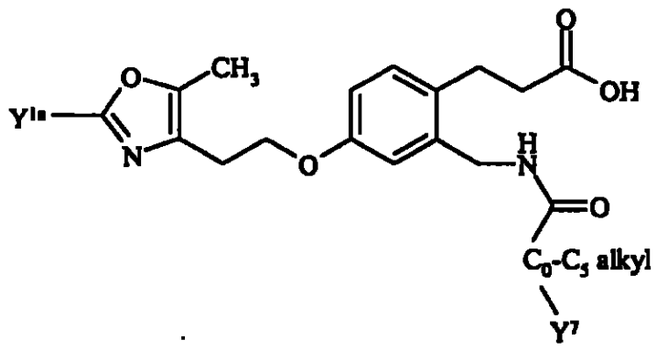


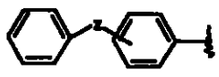
wherein Y^{1a} is optionally substituted phenyl, naphthyl,



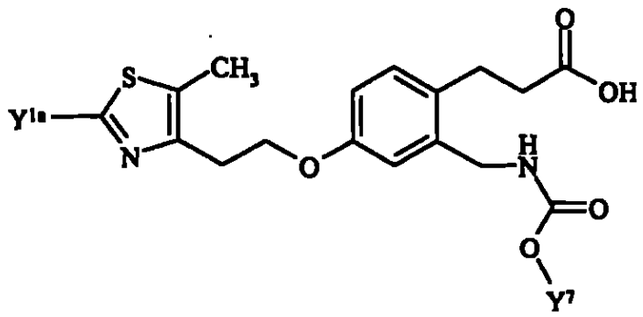
and Z is a bond, oxygen, -NH-, -N(CH_3)-, -NHC(O)- or -C(O)NH-.

14. The compound of Claim 4 represented by the following structural formula,



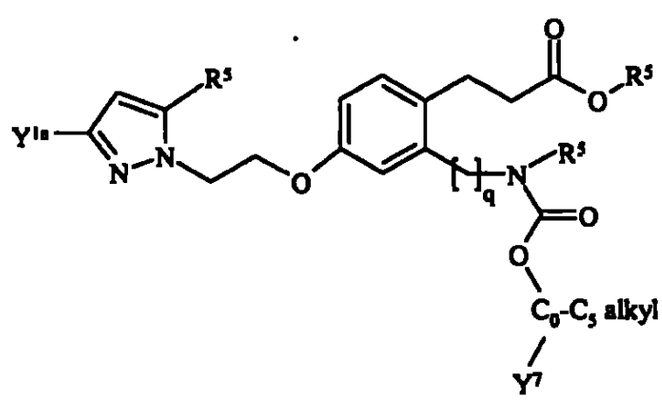
wherein Y^{1a} is optionally substituted phenyl, naphthyl or  and Z is a bond, oxygen, -NH-, -N(CH_3)-, -NHC(O)- or -C(O)NH-.

15. The compound of Claim 4 represented by the following structural formula,



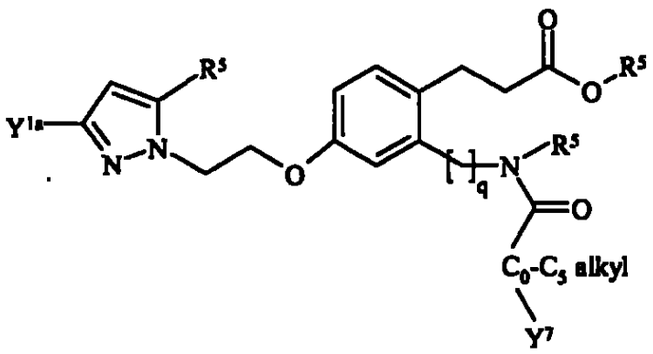
wherein Y^{1a} is optionally substituted aryl, heteroaryl, heterocycloalkyl, heteroaryl-Z-heterocycloalkyl or heteroaryl-Z-aryl.

16. The compound of Claim 1 represented by the following structural formula,



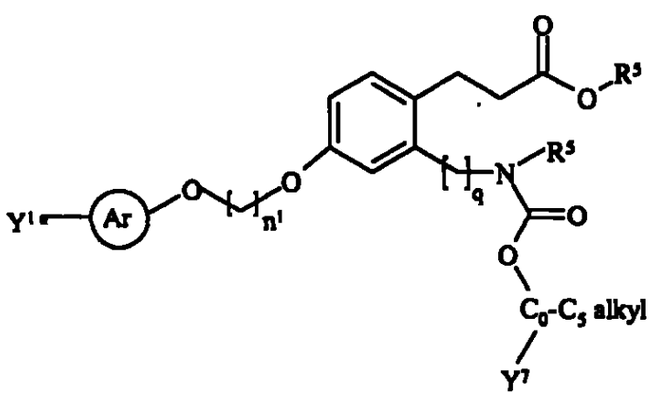
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

17. The compound of Claim 1 represented by the following structural formula,



wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

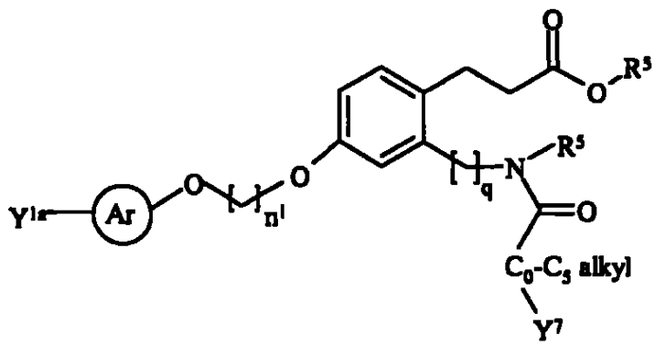
18. The compound of Claim 1 represented by the following structural formula,



wherein,

Y^{1a} is hydrogen, aryl, heteroaryl, or aryloxy; q is 1 or 2; and n^1 is 2, 3, or 4.

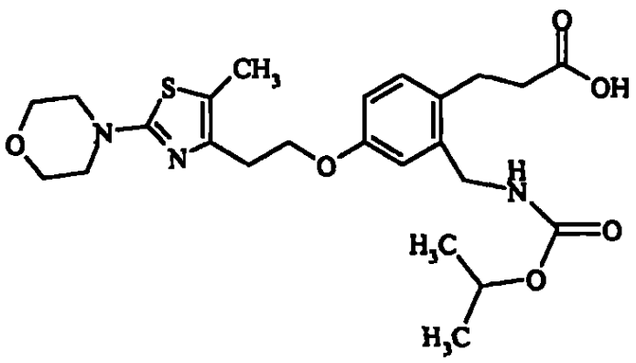
19. The compound of Claim 1 represented by the following structural formula,



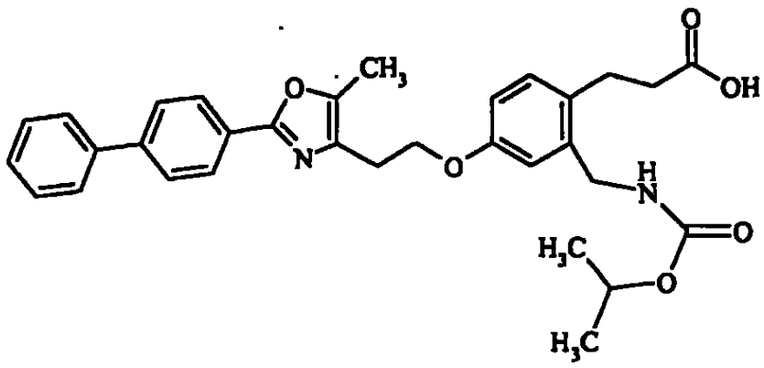
wherein,

Y^{1a} is hydrogen, aryl, heteroaryl or aryloxy; q is 1 or 2; and n^1 is 2, 3, or 4.

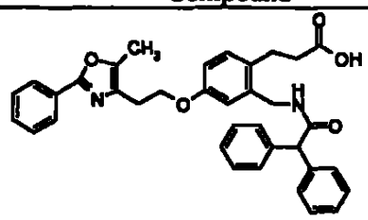
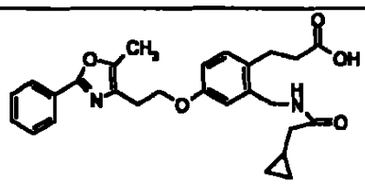
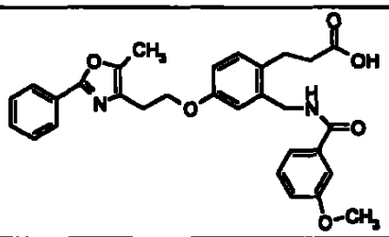
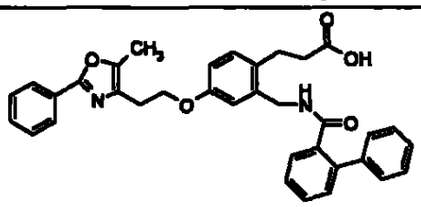
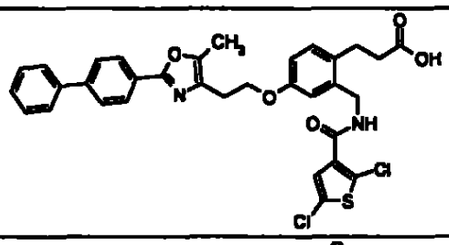
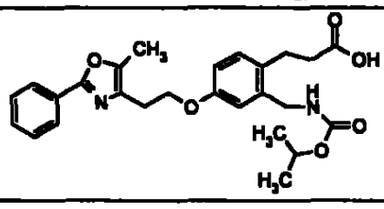
20. The compound of Claim 1 or 2 represented by a following structural formula,

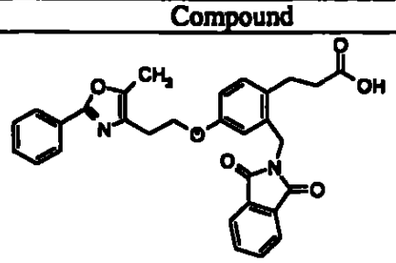
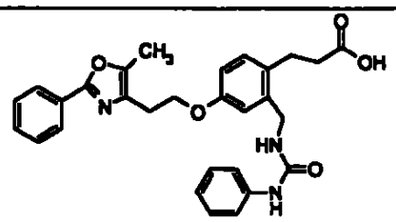
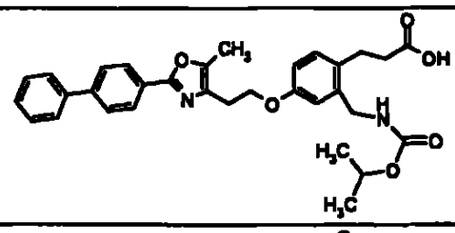
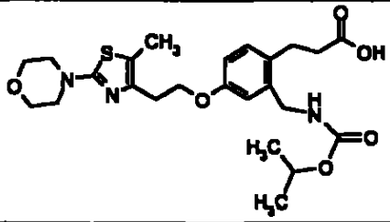
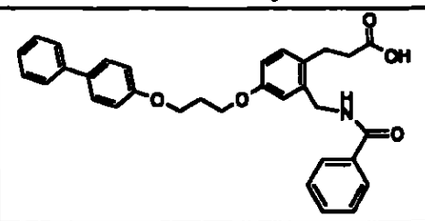
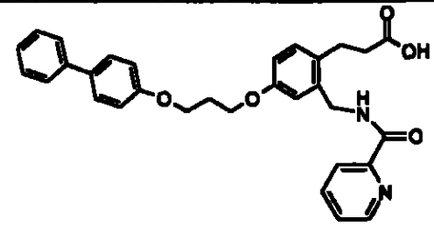


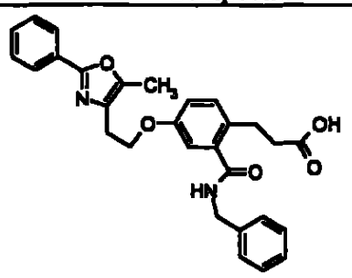
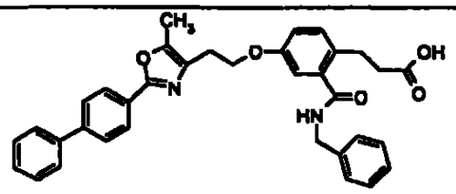
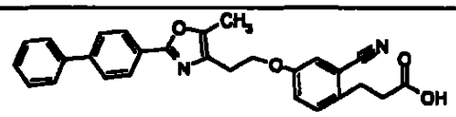
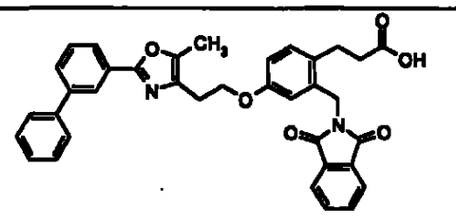
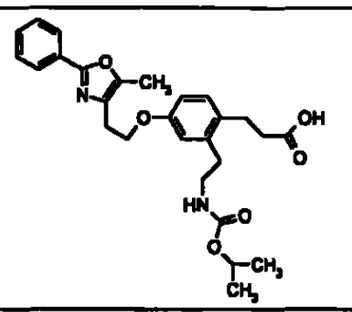
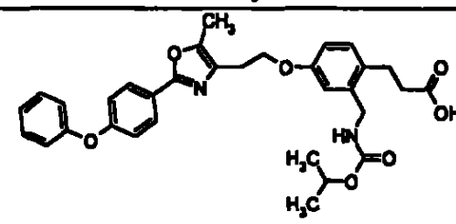
21. The compound of Claim 1 or 2 represented by a following structural formula,

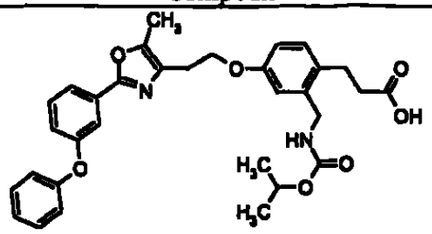
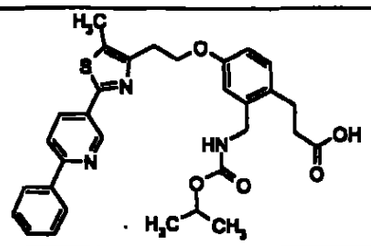
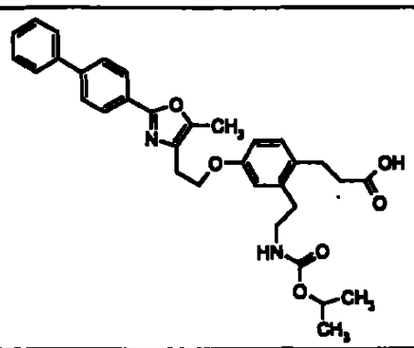
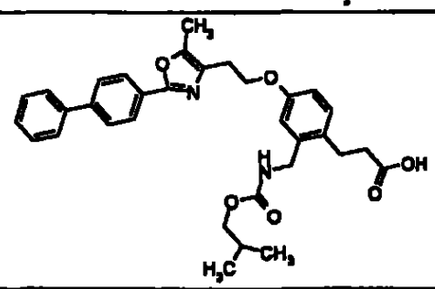
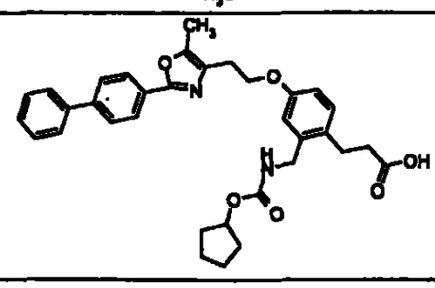


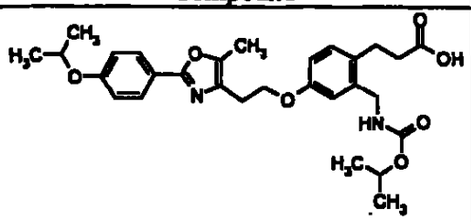
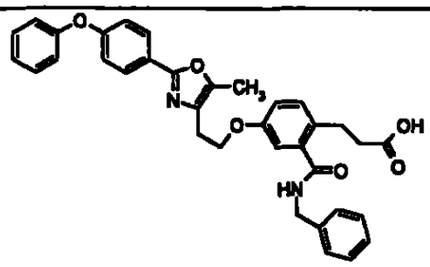
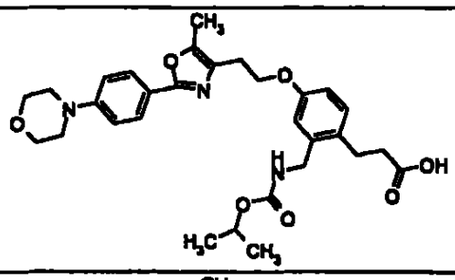
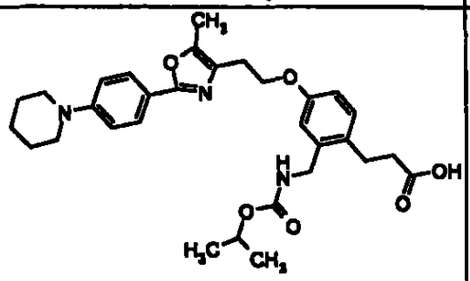
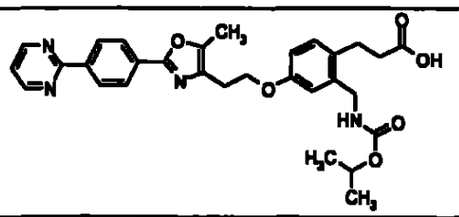
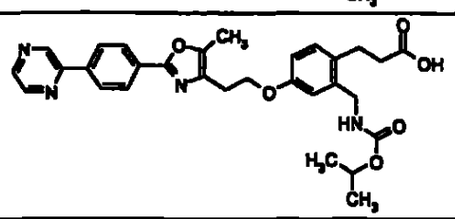
22. A compound selected from the group consisting of:

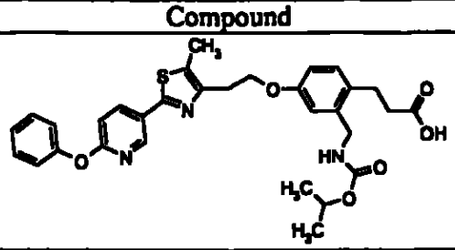
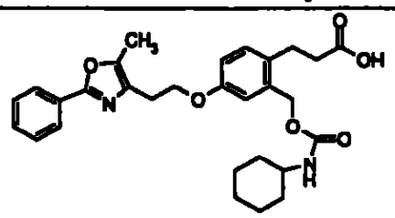
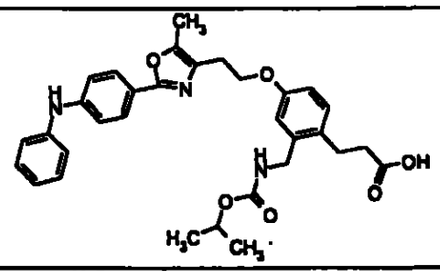
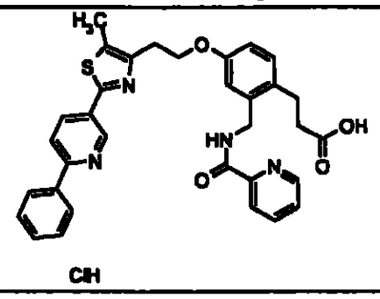
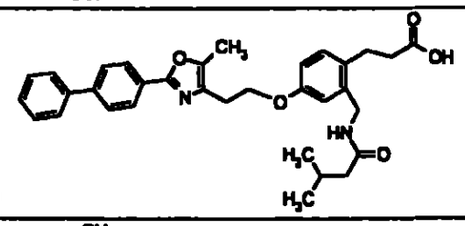
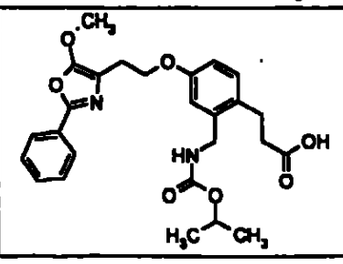
No.	Compound	Name
1		3-{2-(Diphenylacetyl-aminomethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
2		3-{2-[(2-Cyclopropylacetylamino)methyl] -4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid
3		3-{2-[(3-Methoxybenzoylamino) methyl]-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
4		3-{2-{[(Biphenyl-2-carbonyl) amino]methyl}-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
5		3-(4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-{[(2,5-dichlorothiophene-3-carbonyl)amino]methyl}phenyl) propionic acid
6		3-{2-(Isopropoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid

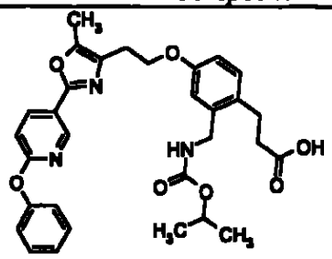
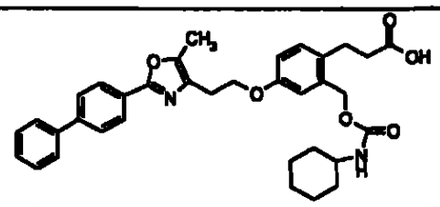
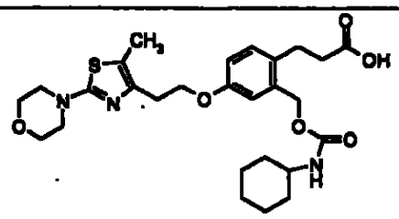
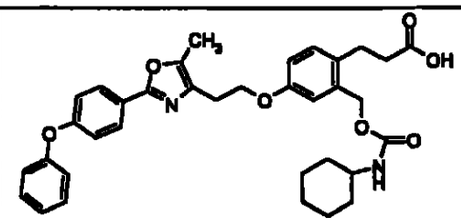
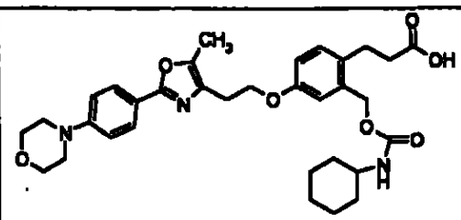
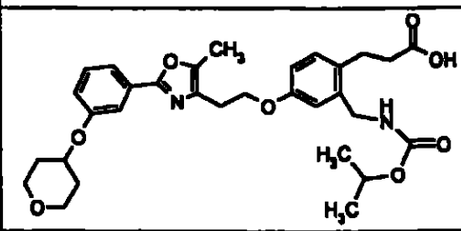
No.	Compound	Name
7		3-{2-(1,3-Dioxo-1,3-dihydroisoindol-2-ylmethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid
8		3-{4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-[(3-phenylureido)methyl] phenyl} propionic acid
9		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(isopropoxycarbonyl-aminomethyl)phenyl] propionic acid
10		3-{2-(Isopropoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl) ethoxy]phenyl} propionic acid
11		3-{2-(Benzoylaminomethyl)-4-[3-(biphenyl-4-yloxy)propoxy] phenyl} propionic acid
12		3-(4-[3-(Biphenyl-4-yloxy) propoxy]-2-{[(pyridine-2-carbonyl)amino]methyl}phenyl) propionic acid

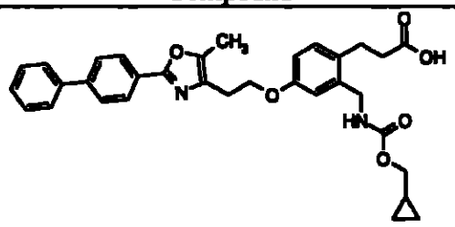
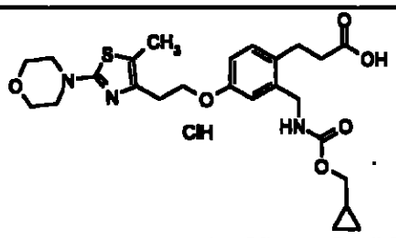
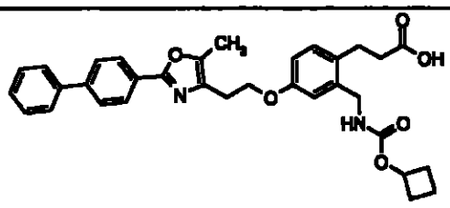
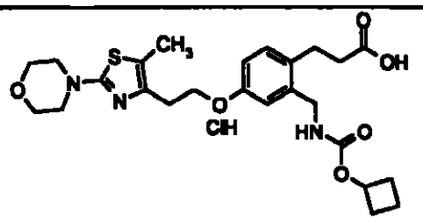
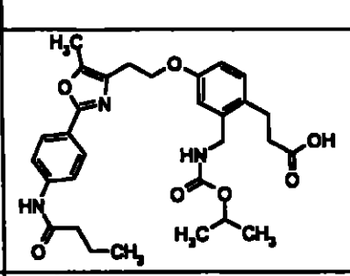
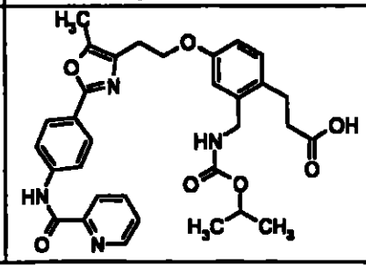
No.	Compound	Name
13		3-{2-Benzylcarbamoyl-4-[2-(5-methyl-2-phenyloxazol-4-yl) ethoxy]phenyl} propionic acid
14		3-{2-Benzylcarbamoyl-4-[2-(2-biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]phenyl} propionic acid
15		3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-cyanophenyl} propionic acid
16		3-[4-[2-(2-Biphenyl-3-yl-5-methyloxazol-4-yl)ethoxy]-2-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)phenyl] propionic acid
17		3-{2-(2-Isopropoxycarbonyl-aminoethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
18		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid

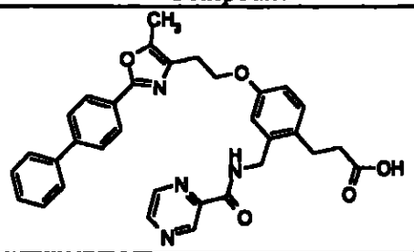
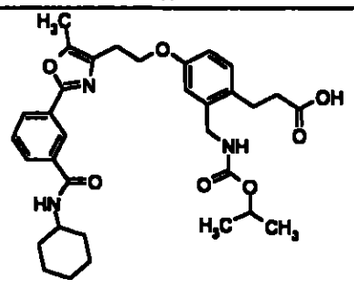
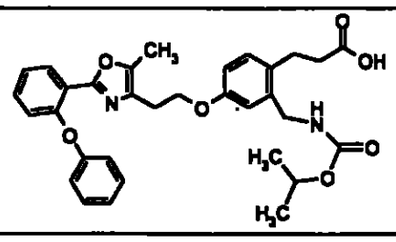
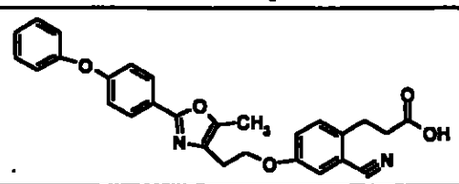
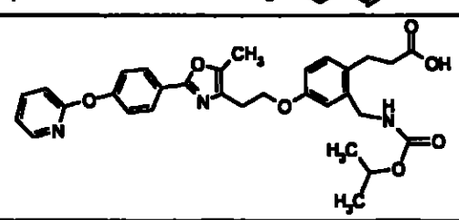
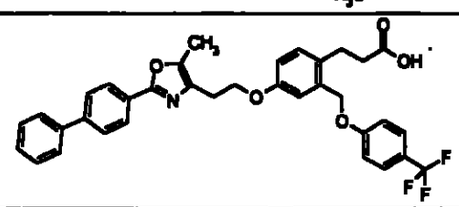
No.	Compound	Name
19		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(3-phenoxyphenyl)oxazol-4-yl] ethoxy}phenyl) propionic acid
20		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(6-phenylpyridin-3-yl)thiazol-4-yl]ethoxy}phenyl) propionic acid
21		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(2-isopropoxycarbonylaminoethyl) phenyl] propionic acid
22		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(isobutoxycarbonyl-aminomethyl)phenyl] propionic acid
23		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(cyclopentyloxycarbonyl-aminomethyl)phenyl] propionic acid

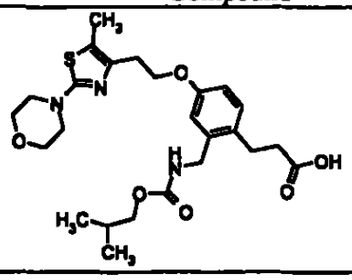
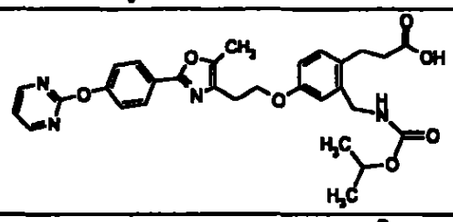
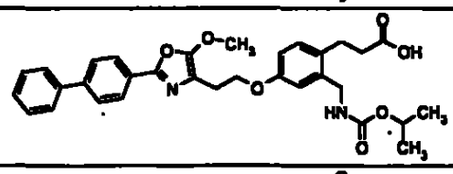
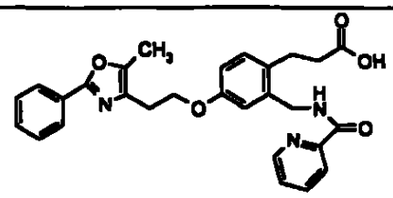
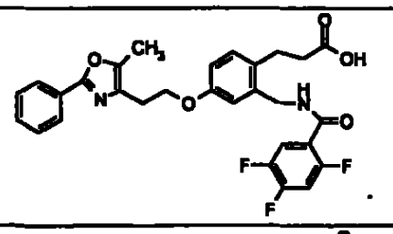
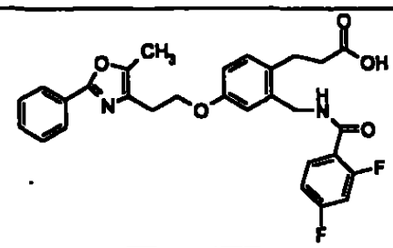
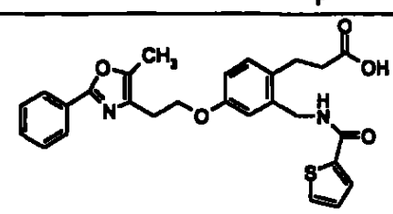
No.	Compound	Name
24		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[2-(4-isopropoxyphenyl)-5-methyloxazol-4-yl]ethoxy} phenyl) propionic acid
25		3-(2-Benzylcarbamoyl-4-{2-[5-methyl-2-(4-phenoxyphenyl) oxazol-4-yl]ethoxy}phenyl) propionic acid
26		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-morpholin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
27		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-piperidin-1-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
28		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-pyrimidin-2-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
29		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-pyrazin-2-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid

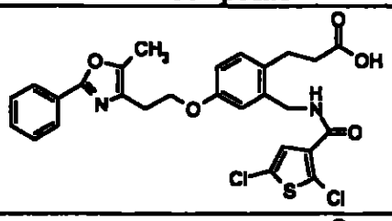
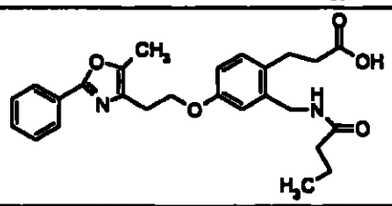
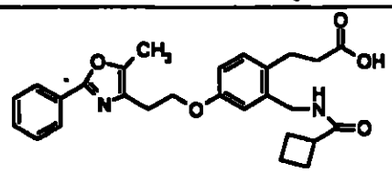
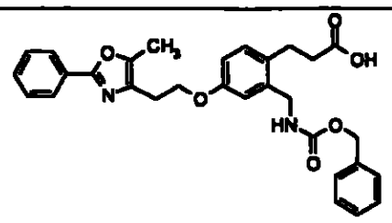
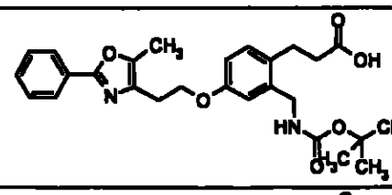
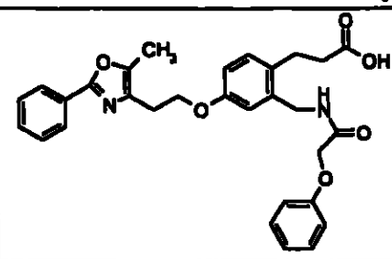
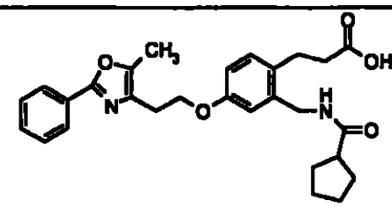
No.	Compound	Name
30		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(6-phenoxypyridin-3-yl)thiazol-4-yl]ethoxy}phenyl) propionic acid
31		3-{2-Cyclohexylcarbamoyl-oxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
32		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-phenylaminophenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
33		3-(4-{2-[5-Methyl-2-(6-phenylpyridin-3-yl)thiazol-4-yl]ethoxy}-2-{[(pyridine-2-carbonyl)amino]methyl}phenyl) propionic acid HCl salt
34		3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-[(3-methylbutyrylamino) methyl]phenyl} propionic acid
35		3-{2-(Isopropoxycarbonyl-aminomethyl)-4-[2-(5-methoxy-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid

No.	Compound	Name
36		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(6-phenoxypyridin-3-yl)oxazol-4-yl]ethoxy}phenyl) propionic acid
37		3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-cyclohexylcarbamoyloxymethyl phenyl} propionic acid
38		3-{2-Cyclohexylcarbamoyl-oxymethyl-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl) ethoxy]phenyl} propionic acid
39		3-(2-Cyclohexylcarbamoyl-oxymethyl-4-{2-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-yl] ethoxy}phenyl) propionic acid
40		3-(2-Cyclohexylcarbamoyl-oxymethyl-4-{2-[5-methyl-2-(4-morpholin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
41		3-[2-(Isopropoxycarbonyl-aminomethyl)-4-(2-{5-methyl-2-[3-(tetrahydropyran-4-yloxy) phenyl]oxazol-4-yl} ethoxy) phenyl] propionic acid

No.	Compound	Name
42		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(cyclopropylmethoxycarbonylaminomethyl)phenyl] propionic acid
43		3-{2-(Cyclopropylmethoxy-carbonylaminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl)ethoxy]phenyl} propionic acid HCl salt
44		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(cyclobutoxycarbonylaminomethyl)phenyl]propionic acid HCl salt
45		3-{2-(Cyclobutoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl) ethoxy]phenyl} propionic acid HCl salt
46		3-[4-{2-[2-(4-Butyrylaminophenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonyl-aminomethyl)phenyl] propionic acid
47		3-{2-(Isopropoxycarbonyl-amino-methyl)-4-[2-(5-methyl-2-{4-[(pyridine-2-carbonyl)-amino]-phenyl}-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

No.	Compound	Name
48		3-(4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-{[(pyrazine-2-carbonyl) amino]methyl}phenyl) propionic acid
49		3-[4-{2-[2-(3-Cyclohexylcarbamoylphenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonyl-aminomethyl)phenyl] propionic acid
50		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(2-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
51		3-(2-Cyano-4-{2-[5-methyl-2-(4-phenoxy-phenyl)-oxazol-4-yl]-ethoxy}-phenyl) propionic acid
52		3-[2-(Isopropoxycarbonyl-aminomethyl)-4-(2-{5-methyl-2-[4-(pyridin-2-yloxy)phenyl] oxazol-4-yl}ethoxy)phenyl] propionic acid
53		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(4-trifluoromethylphenoxymethyl)phenyl] propionic acid

No.	Compound	Name
54		3-{2-(Isobutoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl) ethoxy]phenyl} propionic acid
55		3-[2-(Isopropoxycarbonyl-aminomethyl)-4-(2-{5-methyl-2-[4-(pyrimidin-2-yloxy)phenyl] oxazol-4-yl}ethoxy)phenyl] propionic acid
56		3-[4-[2-(2-Biphenyl-4-yl-5-methoxyoxazol-4-yl)ethoxy]-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid
57		3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid
58		3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(2,4,5-trifluoro-benzoylamino)-methyl]-phenyl}-propionic acid
59		3-{2-[(2,4-Difluoro-benzoylamino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
60		3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{[(thiophene-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid

No.	Compound	Name
61		3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{[(thiophene-2-carbonyl)-amino]-methyl}-phenyl)-proprionic acid
62		3-{2-(Butyrylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
63		3-{2-[(Cyclobutanecarbonyl-amino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
64		3-{2-(Benzyloxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
65		3-{2-(tert-Butoxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
66		3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(2-phenoxy-acetylamino)-methyl]-phenyl}-propionic acid
67		3-{2-[(Cyclopentanecarbonyl-amino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one compound of Claims 1-22 or a pharmaceutically acceptable salt, solvate or hydrate thereof.

24. A pharmaceutical composition comprising (1) a compound of Claim 1 or 2, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof; (2) a second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acryl CoA:cholestrol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin; and (3) a pharmaceutically acceptable carrier.

25. A method of modulating a peroxisome proliferator activated receptor (PPAR), comprising the step of contacting the receptor with at least one compound of Claims 1-22, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

26. The method of Claim 25, wherein the peroxisome proliferator activated receptor is an alpha-receptor.

27. The method of Claim 25, wherein the peroxisome proliferator activated receptor is a gamma-receptor.

28. A method for treating or preventing a peroxisome proliferator activated receptor-gamma mediated disease or condition comprising the step of administering an effective amount of at least one compound of Claim 1 or 2.

29. A method for lowering blood-glucose comprising the step of administering an effective amount of at least one compound of Claim 1 or 2.

30. A method of treating or preventing disease or condition selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of at least one compound of Claim 1 or 2.

31. A method of treating or preventing diabetes mellitus in a mammal comprising the step of administering to a mammal a therapeutically effective amount of at least one compound of Claim 1 or 2.

32. A method of treating or preventing cardiovascular disease in a mammal comprising the step of administering to a mammal a therapeutically effective amount of at least one compound of Claim 1 or 2, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

33. A method of treating or preventing syndrome X in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of Claim 1 or 2, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

34. A method of treating or preventing disease or condition selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of at least one compound of Claim 1 or 2 and an effective amount of second therapeutic agent selected from the group consisting of: insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acryl CoA:cholestrol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin.

35. Use of a compound of Claim 1 or 2 and pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, for the manufacture of a medicament for the treatment of a condition modulated by a PPAR.

(12) SOLICITUD INTERNACIONAL PUBLICADA EN VIRTUD DEL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual
Oficina Internacional

(43) Fecha de Publicación Internacional
19 de diciembre 2002 (19.12.2002)

(Código de Barras)
WIPO
OMPI

(10) Número de Publicación Internacional
WO 02/100403 A1

PCT

(51) Clasificación Internacional de Patente : A61K 31/42 C07D 263/32, A61P 3/10, C07D 231/12, A61K 31/422, 31/428, 31/427, C07D 233/88, 277/24, 277/24, 277/38, C07C 271/24, 271/22, 233/87, 233/63, C07D 413/12, 417/14, 413/14, 413/04, 413/10, 417/14, 417/04, 213/81, 307/83.

(21) Número de Solicitud Internacional: PCT /US02/15143

(22) Fecha de Presentación Internacional: 24 de mayo de 2002(24.05.2002)

(25) Idioma de presentación: Inglés

(26) Idioma de publicación: Inglés

(30) Datos de prioridad:

60 / 296,701 7 de junio de 2001 (07.06.2001) US

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(81) Estados Designados (*fase nacional*) : EA, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Estados Designados (*fase regional*) : Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Patente Euroasiática: (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Publicada:
- *Con informe de búsqueda internacional*

Para los códigos de dos letras y otras abreviaturas, véanse las "Notas Directrices sobre Códigos y Abreviaturas" que aparecen al principio de cada ejemplar de la Gaceta PCT.

(54) Título: MODULADORES DE RECEPTORES ACTIVADOS DEL PROLIFERADOR DE PEROXISOMA (PPAR)

(57) Resumen: La presente invención se refiere a un compuesto de fórmula I, y sales, solvatos, hidratos o estereoisómeros farmacéuticamente aceptables del mismo, son útiles en el tratamiento del síndrome X, diabetes tipo II, hiperglucemia, hiperlipidemia, obesidad, coagulopatía, hipertensión, arteriosclerosis y otros trastornos relacionados con el síndrome X así como enfermedades cardiovasculares

MODULADORES DE RECEPTORES ACTIVADOS POR EL PROLIFERADOR DE PEROXISOMAS

CAMPO DE LA INVENCIÓN

La presente invención se refiere a compuestos agonistas del receptor activado por el proliferador de peroxisomas (PPAR), que son útiles para el tratamiento y/o la prevención de trastornos modulados por un PPAR.

ANTECEDENTES DE LA INVENCIÓN

Los receptores activados por el proliferador de peroxisomas (PPAR) son miembros de la familia génica de receptores nucleares que se activan por ácidos grasos y metabolitos de ácidos grasos. Los PPAR pertenecen a una subserie de receptores nucleares que funcionan como heterodímeros con el receptor del ácido 9-*cis* retinoico (RXR). En especies que varían de *Xenopus* a seres humanos se han encontrado tres subtipos, designados PPARα, PPARγ y PPARδ.

PPARα es el principal subtipo en el hígado y ha facilitado el análisis del mecanismo mediante el cual los proliferadores de peroxisomas ejercen sus efectos pleiotrópicos. PPARα se activa por varios ácidos grasos de cadena media y larga, y está implicado en la estimulación de la oxidación β de ácidos grasos. PPARα también está implicado en la actividad de fibratos y ácidos grasos en roedores y seres humanos. Los derivados del ácido fíbrico tales como clofibrato, fenofibrato, bezafibrato, ciprofibrato, beclofibrato y etofibrato, así como gemfibrozil, producen una reducción sustancial de los triglicéridos en plasma junto con una reducción moderada del colesterol de lipoproteínas de baja densidad (LDL), y se usan particularmente para el tratamiento de la

hipertrigliceridemia.

PPARγ es el subtipo principal en tejido adiposo y está implicado en la activación del programa de diferenciación de adipocitos. PPARγ no está implicado en la estimulación de la proliferación de peroxisomas en el hígado. Existen dos isómeros de PPARγ: PPARγ1 y PPARγ2, que difieren únicamente en que PPARγ2 contiene 28 aminoácidos adicionales presentes en el extremo amino terminal. Las secuencias de ADN para los receptores de PPARγ se describen en Elbrecht, y col, BBRC 224;431-437 (1996). Aunque los proliferadores de peroxisomas, incluyendo los fibratos y ácidos grasos, activan la actividad transcripcional de PPAR, sólo se han identificado derivados de prostaglandina J_2 como ligandos naturales para PPARγ, que también unen los agentes antidiabéticos diazolidinodionas con alta afinidad. Las funciones fisiológicas de PPARα y PPARγ en lípidos y en el metabolismo de carbohidratos quedaron sin cubrir una vez que se reconoció que eran los receptores para los fármacos de fibrato y glitazona, respectivamente.

Los receptores PPARα y PPARγ se han implicado en la diabetes mellitus, enfermedad cardiovascular, obesidad y enfermedad gastrointestinal, tal como enfermedad inflamatoria del intestino y otras enfermedades relacionadas con la inflamación. Tales enfermedades relacionadas con la inflamación incluyen, pero sin limitación, enfermedad de Alzheimer, enfermedad de Crohn, artritis reumatoide, psoriasis y lesión por isquemia-reperfusión.

En contraste, no se ha indicado que PPARδ (también denominado PPARβ y NUC1) sea el receptor para ninguna clase conocida de moléculas farmacológicas, y su papel en la fisiología de mamíferos sigue sin definirse. El

gen del receptor nuclear humano PPARδ (hPPARδ) se ha clonado a partir de una biblioteca de ADNc de células de osteosarcoma humano y se describe con detalle en A. Schmidt y col, *Molecular Endocrinology*, 6:1634-1641 (1991).

La diabetes es una enfermedad en la que está alterada la capacidad de un mamífero para regular los niveles de glucosa en sangre porque el mamífero tiene una capacidad reducida para convertir la glucosa en glucógeno para almacenarlo en células musculares y hepáticas. En la diabetes de tipo I, esta capacidad reducida para almacenar la glucosa se produce por una reducción de la producción de insulina. La "diabetes de tipo II" o "diabetes mellitus no dependiente de insulina" (NIDDM) es la forma de diabetes, que se debe a una resistencia profunda al efecto estimulador o regulador de la insulina en el metabolismo de la glucosa y de los lípidos en los principales tejidos sensibles a la insulina, músculo, hígado y tejido adiposo. Esta resistencia a la respuesta a la insulina ocasiona una activación de insulina insuficiente en la ingesta de glucosa, oxidación y almacenamiento en el músculo y una represión inadecuada de la lipolisis por la insulina en el tejido adiposo y de la producción y secreción de glucosa en el hígado. Cuando estas células se desensibilizan a la insulina, el cuerpo intenta compensarlo produciendo niveles de insulina anormalmente altos, produciéndose hiperinsulemia. La hiperinsulemia se asocia con hipertensión y un peso corporal elevado. Como la insulina está implicada en la promoción de la absorción celular de glucosa, aminoácidos y triglicéridos de la sangre por células sensibles a la insulina, la insensibilidad a la insulina puede dar lugar a niveles elevados de triglicéridos y LDL (conocido como colesterol "malo"), que son factores de riesgo en enfermedades cardiovasculares. La constelación de síntomas que incluyen hiperinsulemia

combinada con hipertensión, elevado peso corporal, elevados triglicéridos y elevado LDL se conoce como Síndrome X.

La hiperlipidemia es una afección que se caracteriza por un aumento anormal de los lípidos en suero, tales como colesterol, triglicéridos y fosfolípidos. Estos lípidos no circulan libremente en solución en el plasma, sino que se unen a proteínas y se transportan como complejos macromoleculares denominados lipoproteínas. Una forma de hiperlipidemia es la hipercolesterolemia, caracterizada por la existencia de niveles elevados de colesterol LDL. A menudo, el tratamiento inicial de la hipercolesterolemia es una dieta baja en grasa y colesterol junto con un ejercicio físico apropiado. La intervención del fármaco se inicia si los propósitos de disminuir el LDL no se consiguen por la dieta y el ejercicio solos. Es deseable disminuir los niveles elevados de colesterol LDL y aumentar los niveles de colesterol HDL. Generalmente, se ha descubierto que el aumento de los niveles de HDL está asociado con un menor riesgo de enfermedad cardíaca coronaria (CHD). Véase Gordon, y col, *Am. J. Med.*, 62, 707-714 (1977); Stampfer, y col, *N. England J. Med.*, 325, 373-381 (1991); y Kannel, y col, *Ann. Internal Med.*, 90, 85-91 (1979). Un ejemplo de un agente que aumenta el HDL es el ácido nicotínico, pero las cantidades necesarias para conseguir este aumento de HDL están asociadas con efectos no deseados, tales como rubores.

Actualmente existen varios tratamientos disponibles para tratar la diabetes mellitus, pero estos tratamientos siguen siendo insatisfactorios y tienen limitaciones. Aunque el ejercicio físico y la reducción en la ingesta dietética de calorías mejorarán el estado diabético, la aceptación de esta estrategia puede ser escasa debido a los estilos de vida sedentarios y al

exceso de consumo de alimentos, en particular de alimentos de alto contenido de grasas. Por lo tanto, a menudo es necesario el tratamiento con hipoglucemiantes, tales como sulfonilureas (por ejemplo, clorpropamida, tolbutamida, tolazamida y acetohexamida) y biguanidas (por ejemplo, fenformin y metformin) según progresa la enfermedad. Las sulfonilureas estimulan las células β del páncreas para secretar más insulina conforme progresa la enfermedad. Sin embargo, la respuesta de las células β falla con el tiempo y es necesario el tratamiento con inyecciones de insulina. Además, tanto el tratamiento con sulfonilurea como con inyección de insulina tienen el efecto secundario amenazador para la vida del coma hipoglucémico y, de esta forma, los pacientes que usan estos tratamientos deben controlar cuidadosamente la dosificación.

Está bien establecido que la mejora del control glucémico en pacientes con diabetes (tipo I y tipo II) va acompañada por una disminución de las complicaciones microvasculares (DCCT y UKPDS). Debido a la dificultad de mantener un control glucémico adecuado a lo largo del tiempo en pacientes con diabetes de tipo II, está aumentando el uso de sensibilizadores de insulina en la terapia de la diabetes de tipo II. También existen cada vez más indicios de que el antagonista de PPARγ, un sensibilizador de insulina, puede tener efectos beneficiosos en el tratamiento de la diabetes de tipo II más allá de sus efectos en la mejora del control glucémico.

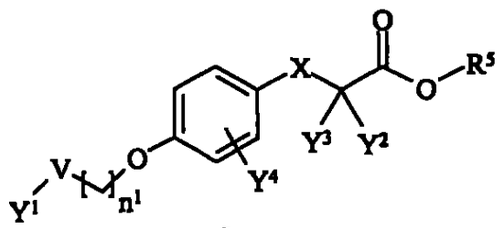
En la última década ha surgido una clase de compuestos conocidos como tiazolidinodionas (por ejemplo, Patentes de Estados Unidos Nº 5.089.517; 4.342.771; 4.367.234; 4.340.605; y 5.306.726) como agentes antidiabéticos eficaces que, como se ha demostrado, aumentan la sensibilidad

de tejidos sensibles a la insulina, tales como músculo esquelético, hígado y tejido adiposo, a la insulina. Al aumentar la sensibilidad a la insulina en lugar de la cantidad de insulina en la sangre, se reduce la probabilidad de coma hipoglucémico. Aunque se ha demostrado que las diazolidinodionas aumentan la sensibilidad a la insulina uniéndose a receptores PPARγ, este tratamiento también produce efectos secundarios no deseados tales como aumento de peso y, con respecto a troglitazona, toxicidad hepática.

En vista de lo anterior, existe la necesidad de nuevos agentes farmacéuticos que modulen estos receptores para prevenir, tratar y/o aliviar estas enfermedades o afecciones y reducir al mismo tiempo los efectos secundarios de los tratamientos actuales.

SUMARIO DE LA INVENCIÓN

La presente invención se refiere a un compuesto de nuevos antagonistas del receptor activado del proliferador de peroxisomas que tiene la fórmula estructural I,



I

y sales, solvatos, hidratos o estereoisómeros farmacéuticamente aceptables del mismo, donde:

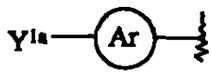
n^1 es 2, 3, 4 ó 5;

V es un enlace o O;

X es CH_2 o O;

p es 0 ó 1;

m es 1-4;

Y^1 es:  donde,

 es: arilo o heteroarilo,

donde arilo y heteroarilo están opcionalmente sustituidos con uno o más grupos seleccionados independientemente entre el grupo compuesto por:

hidrógeno, *alquilo C1-C6*, *alcoxi* C1-C6, halo, haloalquilo y haloalquiloxi;

Y^{1a} es: hidrógeno,

alquilo (C0-C3)-arilo,

C(O)-arilo,

heteroarilo,

cicloalquilo,

heterocicloalquilo,

ariloxi,

$NR^5(CH_2)_mOR^5$,

aril-Z-arilo,

aril-Z-heteroarilo,

aril-Z-cicloalquilo,

aril-Z-heterocicloalquilo,

heteroaril-Z-arilo,

heteroaril-Z-heterocicloalquilo o

heterocicloalquil-Z-arilo,

donde arilo, cicloalquilo, ariloxi, heteroarilo, y heterocicloalquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre el grupo compuesto por:

halo,

hidroxilo,

nitro,

ciano,

alquilo C1-C6,

alcoxi C1-C6 opcionalmente sustituido con $N(R^5)_2$,

haloalquilo,

$N(R^5)_2$,

$N[C(O)R^5]_2$,

$N[S(O)_2R^5]_2$,

$NR^5S(O)_2R^5$,

$NR^5C(O)R^5$,

$NR^5C(O)OR^5$,

$C(O)N(R^5)_2$,

$C(O)OR^5$ y

$C(O)R^5$;

Z es: un enlace,

-oxígeno-

$-C(O)NR^5-$

$-NR^5C(O)-$,

$-NR^5C(O)O-$,

-C(O)-,

-NR^5-,

-$[O]_p(CH_2)_m$-,

-$(CH_2)_m[O]_p$-,

-$NR^5(CH_2)_m$- o

- $(CH_2)_mNR^5$-;

cada uno de Y^2 e Y^3 es independientemente:

hidrógeno,

alquilo C1-C6 o

alcoxi C1-C6;

Y^4 es: alquil (C1-C3)-NR^5C(O)-alquil (C0-C5)-Y^7,

alquil (C1-C3)-NR^5C(O)-alquenil (C2-C5)-Y^7,

alquil (C1-C3)-NR^5C(O)-alquinil (C2-C5)-Y^7;

alquil (C1-C3)-NR^5C(O)O-alquil (C0-C5)-Y^7,

alquil (C1-C3)-NR^5C(O)NR^5-alquil (C0-C5)-Y^7,

alquil (C1-C3)-NR^5C(S)NR^5-alquil (C0-C5)-Y^7,

alquil (C0-C3)-C(O)NR^5-alquil (C0-C5)-Y^7,

alquil (C1-C3)-OC(O)$NY^{10}Y^{11}$,

alquil (C1-C3)-$NY^{10}Y^{11}$,

alquil (C1-C3)-O-alquil (C0-C5)-Y^7,

alquil (C1-C3)-S-alquil (C0-C5)-Y^7 o

CN;

Y^7 es: hidrógeno,

arilo,

heteroarilo,

alquilo C1-C12,

490

alcoxi C1-C6,

cicloalquilo,

heterocicloalquilo,

ariloxi,

C(O)-heteroarilo o

SR^6,

donde alquilo, arilo, ariloxi, alcoxi, heteroarilo, cicloalquilo, y heterocicloalquilo están opcionalmente sustituidos con uno o más seleccionados independientemente entre R^7:

cada uno de Y^{10} e Y^{11} es independientemente entre:

hidrógeno,

arilo,

heteroarilo,

alquilo C1-C10,

cicloalquilo,

$SO_2(R^6)$; o

Y^{10} e Y^{11} conjuntamente son un anillo heterocicloalquilo de 5 a 10 miembros o un anillo heterocicloalquilo condensado con arilo, y el anillo heterocicloalquilo contiene opcionalmente uno o más heteroátomos seleccionados entre N, O o S; y donde,

arilo, heteroarilo, heterocicloalquilo y alquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre R^7;

R^5 es: hidrógeno o alquilo C1-C6;

R^6 es: hidrógeno,

alquilo C1-C10,

cicloalquilo,

arilo, o

heteroarilo,

donde alquilo, cicloalquilo, arilo y heteroarilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre R^7;

R^7 es: halo,

nitro,

oxo,

ciano,

hidroxilo,

bencilo,

fenilo,

fenoxi,

heteroarilo,

$C(O)R^6$,

alquilo C1-C10,

alcoxi C1-C6,

haloalquilo C1-C6,

haloalcoxi C1-C6,

$O(CH_2)_m$-fenilo,

$(CH_2)_mOC(O)$-arilo,

$C(O)OR^5$,

$S(O)_2R^5$,

$S(O)_2N(R^5)_2$,

SR^5 o

$N(R^5)_2$,

donde fenilo y fenoxi están opcionalmente sustituidos con uno o más seleccionados independientemente entre halo o trifluorometilo.

Los compuestos de la presente invención son útiles en el tratamiento o prevención de enfermedades o afecciones relacionadas con hipertrigliceridemia, dislipidemia, diabetes de Tipo II, diabetes de Tipo I, hipertrigliceridemia, síndrome X, resistencia a insulina, fallo cardíaco, dislipidemia diabética, hiperlipidemia, hipercolesterolemia, hipertensión, obesidad, anorexia, bulimia, anorexia nerviosa, enfermedades cardiovasculares y otras enfermedades en las que la resistencia a insulina es un componente.

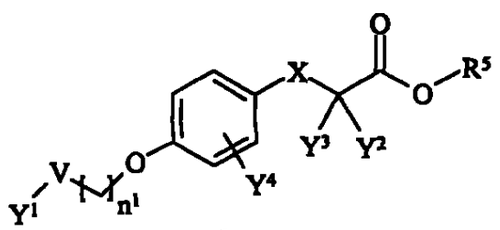
En una realización, la presente invención también se refiere a composiciones farmacéuticas que comprenden al menos un compuesto de la presente invención, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo y un vehículo farmacéuticamente aceptable. Dentro del alcance de la invención también se incluye una composición farmacéutica que contiene un agente terapéutico adicional así como al menos un compuesto de la presente invención, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo y un vehículo farmacéuticamente aceptable.

En otra realización, la presente invención se refiere a un procedimiento de modulación del receptor activado del proliferador de peroxisomas, poniendo en contacto el receptor con al menos un compuesto de Fórmula I, y sales, solvatos e hidratos farmacéuticamente aceptables del mismo.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Los compuestos de la presente invención se refieren a agonistas del receptor activado del proliferador de peroxisomas (PPAR), que son útiles para el tratamiento y/o prevención de trastornos modulados por un PPAR.

Una realización de la presente invención es un compuesto de fórmula estructural I:



I

y sales, solvatos, hidratos o estereoisómeros farmacéuticamente aceptables de los mismos, donde:

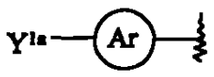
n^1 es 2, 3, 4 ó 5;

V es un enlace o O;

X es CH_2 o O;

p es 0 ó 1;

m es 1-4;

Y^1 es:  donde,

 es: arilo o heteroarilo,

donde arilo y heteroarilo están opcionalmente sustituidos con uno o más grupos seleccionados independientemente entre el grupo compuesto por:

hidrógeno, alquilo C1-C6, alcoxi C1-C6, halo, haloalquilo y haloalquiloxi;

Y^{1a} es: hidrógeno,

alquilo (C0-C3)-arilo,

C(O)-arilo,

heteroarilo,

cicloalquilo,

heterocicloalquilo,

ariloxi,

$NR^5(CH_2)_mOR^5$,

aril-Z-arilo,

aril-Z-heteroarilo,

aril-Z-cicloalquilo,

aril-Z-heterocicloalquilo,

heteroaril-Z-arilo,

heteroaril-Z-heterocicloalquilo o

heterocicloalquil-Z-arilo,

donde arilo, cicloalquilo, ariloxi, heteroarilo, y heterocicloalquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre el grupo compuesto por:

halo,

hidroxilo,

nitro,

ciano,

alquilo C1-C6,

alcoxi C1-C6 opcionalmente sustituido con $N(R^5)_2$,

haloalquilo,

$N(R^5)_2$,

$N[C(O)R^5]_2$,

$N[S(O)_2R^5]_2$,

$NR^5S(O)_2R^5$,

$NR^5C(O)R^5$,

$NR^5C(O)OR^5$,

$C(O)N(R^5)_2$,

$C(O)OR^5$ y

$C(O)R^5$;

Z es: un enlace,

-oxígeno-

$-C(O)NR^5-$

$-NR^5C(O)-$,

$-NR^5C(O)O-$,

-C(O)-,

$-NR^5-$,

$-[O]_p(CH_2)_m-$,

$-(CH_2)_m[O]_p-$,

$-NR^5(CH_2)_m-$ o

$-(CH_2)_mNR^5-$;

cada uno de Y^2 e Y^3 es independientemente:

hidrógeno,

alquilo C1-C6 o

alcoxi C1-C6;

Y^4 es: alquil (C1-C3)-NR^5C(O)-alquil (C0-C5)-Y^7,
alquil (C1-C3)-NR^5C(O)-alquenil (C2-C5)-Y^7,
alquil (C1-C3)-NR^5C(O)-alquinil (C2-C5)-Y^7;
alquil (C1-C3)-NR^5C(O)O-alquil (C0-C5)-Y^7,
alquil (C1-C3)-NR^5C(O)NR^5-alquil (C0-C5)-Y^7,
alquil (C1-C3)-NR^5C(S)NR^5-alquil (C0-C5)-Y^7,
alquil (C0-C3)-C(O)NR^5-alquil (C0-C5)-Y^7,
alquil (C1-C3)-OC(O)$NY^{10}Y^{11}$,
alquil (C1-C3)-$NY^{10}Y^{11}$,
alquil (C1-C3)-O-alquil (C0-C5)-Y^7,
alquil (C1-C3)-S-alquil (C0-C5)-Y^7 o
CN;

Y^7 es: hidrógeno,
arilo,
heteroarilo,
alquilo C1-C12,
alcoxi C1-C6,
cicloalquilo,
heterocicloalquilo,
ariloxi,
C(O)-heteroarilo o
SR^6,
donde alquilo, arilo, ariloxi, alcoxi, heteroarilo, cicloalquilo, y heterocicloalquilo están opcionalmente sustituidos con uno o más seleccionados independientemente entre R^7:

cada uno de Y^{10} e Y^{11} es independientemente:

hidrógeno,

arilo,

heteroarilo,

alquilo C1-C10,

cicloalquilo,

$SO_2(R^6)$; o

Y^{10} e Y^{11} conjuntamente son un anillo heterocicloalquilo de 5 a 10 miembros o un anillo heterocicloalquilo condensado con arilo, y el anillo heterocicloalquilo contiene opcionalmente uno o más heteroátomos seleccionados entre N, O o S; y donde,

arilo, heteroarilo, heterocicloalquilo y alquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre R^7;

R^5 es: hidrógeno o alquilo C1-C6;

R^6 es: hidrógeno,

alquilo C1-C10,

cicloalquilo,

arilo, o

heteroarilo,

donde alquilo, cicloalquilo, arilo y heteroarilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre R^7;

R^7 es: halo,

nitro,

oxo,

ciano,

hidroxilo,

bencilo,

fenilo,

fenoxi,

heteroarilo,

$C(O)R^6$,

alquilo C1-C10,

alcoxi C1-C6,

haloalquilo C1-C6,

haloalcoxi C1-C6,

$O(CH_2)_m$-fenilo,

$(CH_2)_mOC(O)$-arilo,

$C(O)OR^5$,

$S(O)_2R^5$,

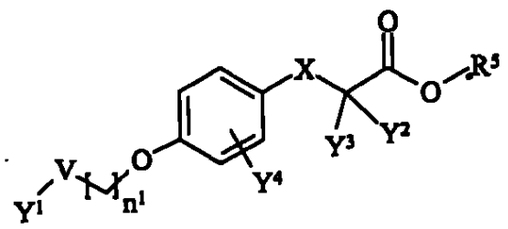
$S(O)_2N(R^5)_2$,

SR^5 o

$N(R^5)_2$,

donde fenilo y fenoxi están opcionalmente sustituidos con uno o más seleccionados independientemente entre halo o trifluorometilo.

Una realización de la presente invención también incluye un compuesto representado por la Fórmula estructural Ia:



Ia

o una sal, hidrato o solvato farmacéuticamente aceptable del mismo, donde:

Y^1 es un grupo sin sustituir o sustituido seleccionado entre el grupo compuesto por:

arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aril-alquilo C1-C4, heteroaril-alquilo C1-C4, cicloalquil-alquilo C1-C4, y t-butilo;

Y^2 se selecciona entre el grupo compuesto por:

H, alquilo C1-C10, cicloalquilo, (alquilo C1-C10)-Y^5 , O-Y^6;

Y^5 se selecciona entre el grupo compuesto por:

un grupo arilo, arilo sustituido, -COR^4, -$COOR^4$, -$CONR^6R^7$,-CSR^4 , y -$C(S)NR^6R^7$;

Y^6 se selecciona entre el grupo compuesto por:

un grupo alifático, un grupo alifático sustituido, un grupo arilo, arilo sustituido, -COR^4, -$COOR^4$, -$CONR^6R^7$, -CSR^4, y -$C(S)NR^6R^7$;

cada uno de R^4, R^6 y R^7 se seleccionan independientemente entre el grupo compuesto por:

H, un grupo alifático, un grupo alifático sustituido, un grupo arilo y un grupo arilo sustituido;

Y^3 se selecciona entre el grupo compuesto por:

H, un grupo alifático, un grupo alifático sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, y (alquilo C1-C10)-R^8; R^8 se selecciona entre

el grupo compuesto por arilo, arilo sustituido, heteroarilo, y heteroarilo sustituido; y

R^5 se selecciona entre el grupo compuesto por:

H, un grupo alifático, un grupo alifático sustituido, heteroarilo, heteroarilo sustituido, un arilo, un arilo sustituido, y (alquilo C1-C10)-R^9;

R^9 se selecciona entre el grupo compuesto por:

arilo, arilo sustituido, heteroarilo, y heteroarilo sustituido, aminoalquilo, y cicloalquilo;

V es un enlace o O;

X es CH_2 o O;

Y^4 se selecciona entre el grupo compuesto por:

-alquil (C1-C3)-O-W-Y^7, -C(O)NY^8Y^9, -alquil (C1-C3)-$NY^{10}Y^{11}$, y

-alquil (C1-C3)-N(Y^{13})W-alquil (C0-C5)-Y^{14} ;

W se selecciona entre el grupo compuesto por:

un enlace, -$CONY^{12}$, -C(O)-, -OCH_2-, alquilo C1-C6, -CO_2-, -$CHOY^{15}$-, -$CSNY^{16}$ y

-SO_2-;

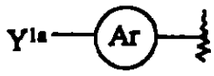
Y^7 se selecciona entre el grupo compuesto por:

arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, un grupo alifático, un grupo alifático ramificado y alquilo (C1-C10) sustituido;

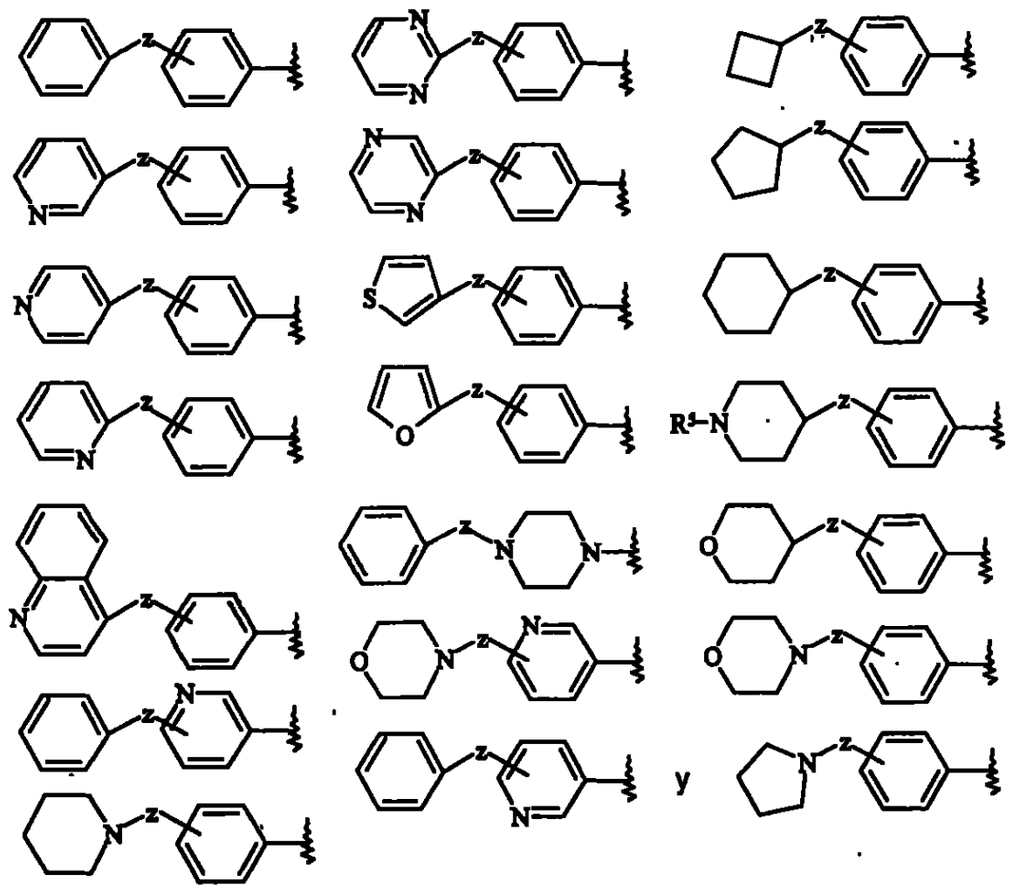
cada uno de Y^8, Y^9, Y^{10}, Y^{11}, Y^{12}, Y^{13}, Y^{14}, Y^{15}, e Y^{16} se selecciona independientemente entre el grupo compuesto por:

arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, un grupo alifático, un grupo alifático ramificado y alquilo (C1-C10) sustituido; y n^1 are 2, 3, 4 ó 5.

El sustituyente Y^1 del compuesto representado por la fórmula Ia incluye

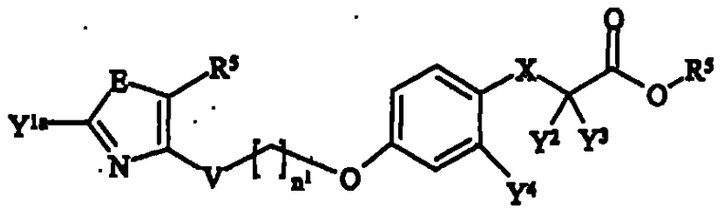
 donde Y^{1a} y  son como se han definido anteriormente en la fórmula I, y el grupo sustituyente incluye los sustituyentes mencionados anteriormente y como se han definido en la realización.

El compuesto de la presente invención como se ha definido anteriormente, donde Y^{1a} se selecciona entre el grupo compuesto por: arilo, heteroarilo, cicloalquilo, heterocicloalquilo, ariloxi,



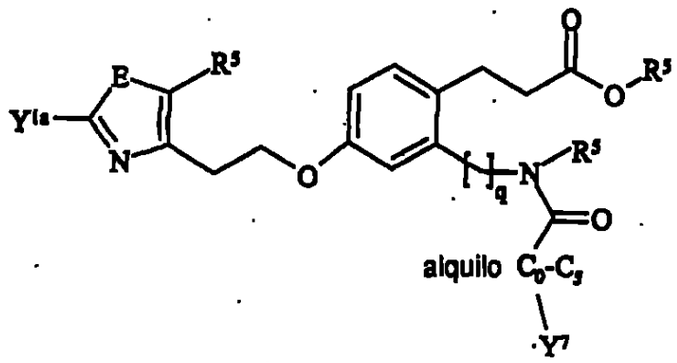
y

Una realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



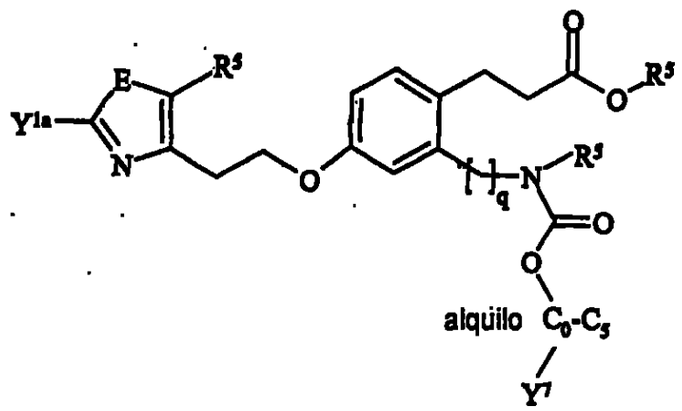
donde E es O o S.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



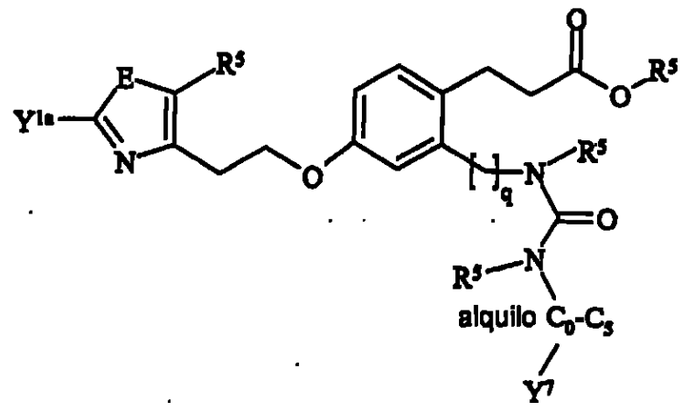
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



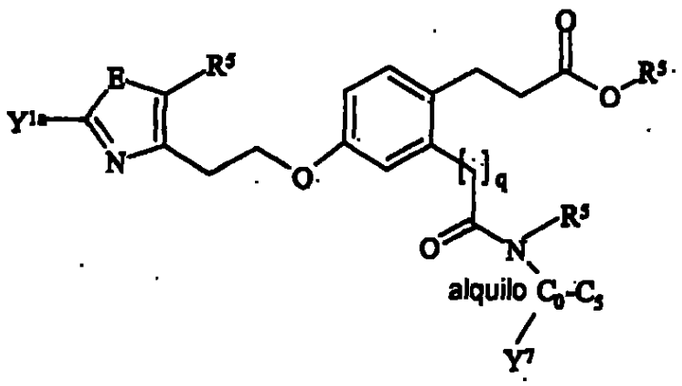
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



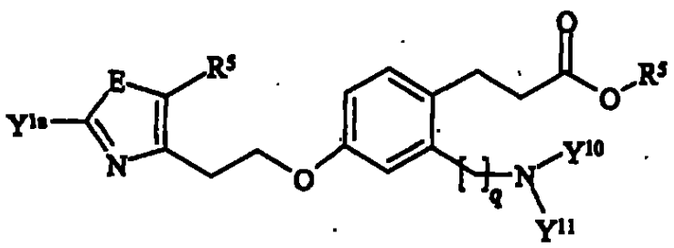
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



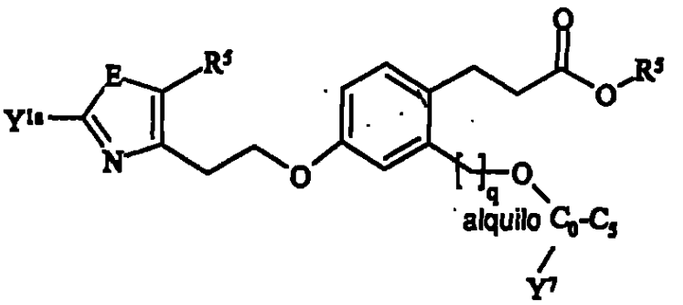
donde q es 0 ó 1; y cada R^5 es independientemente hidrógeno o metilo.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



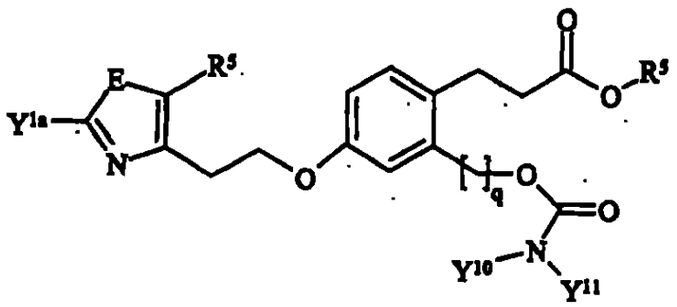
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



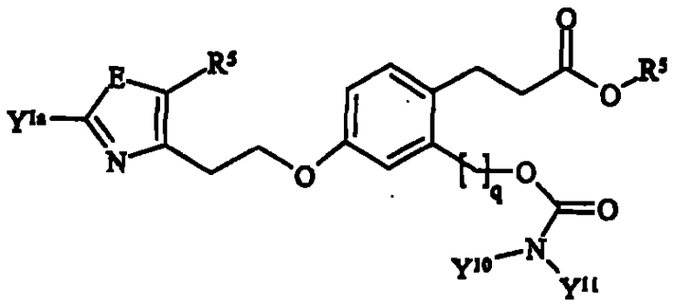
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



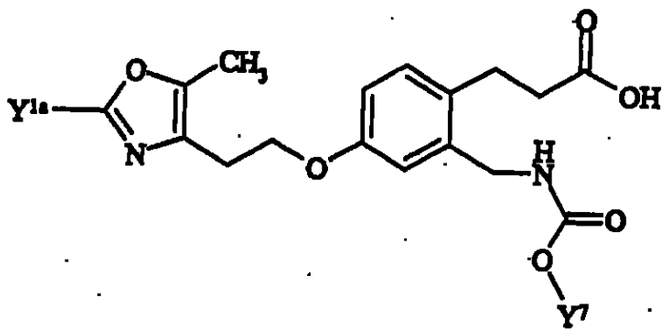
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,

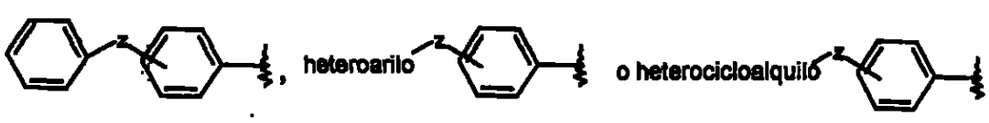


donde q es 1 ó 2; y cada R^5, Y^2 y Y^3 son independientemente hidrógeno o metilo.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,

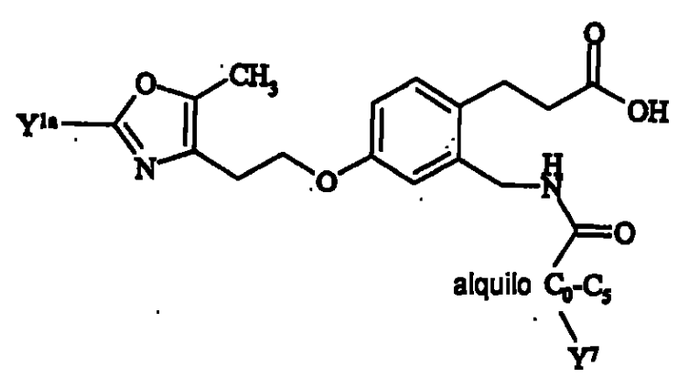


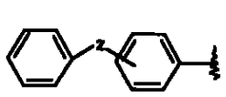
donde Y^{1a} es fenilo opcionalmente sustituido, naftilo,



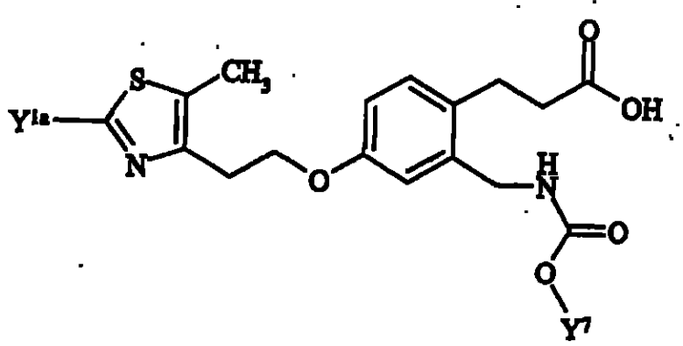
y Z es un enlace, oxígeno, -NH-, -$N(CH_3)$-, -NHC(O)- o -C(O)NH-.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



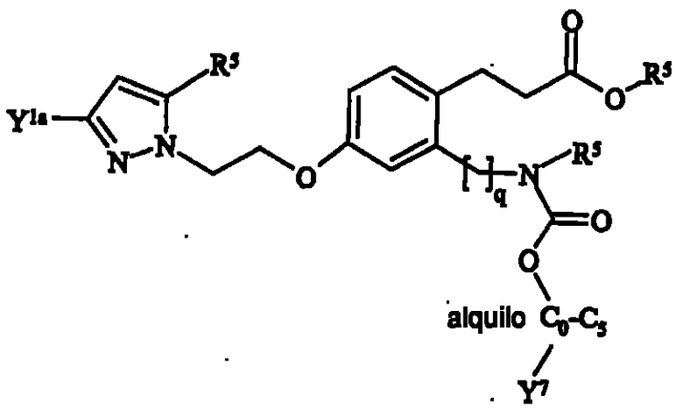
donde Y^{1a} es fenilo opcionalmente sustituido, naftilo o  y Z es un enlace, oxígeno, -NH-, -$N(CH_3)$-, -NHC(O)- o -C(O)NH-.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



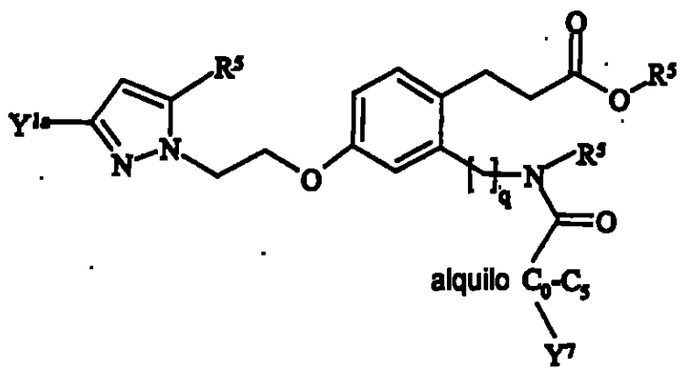
donde Y^{1a} es arilo opcionalmente sustituido, heteroarilo, heterocicloalquilo, heteroaril-Z-heterocicloalquilo o heteroaril-Z-arilo.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



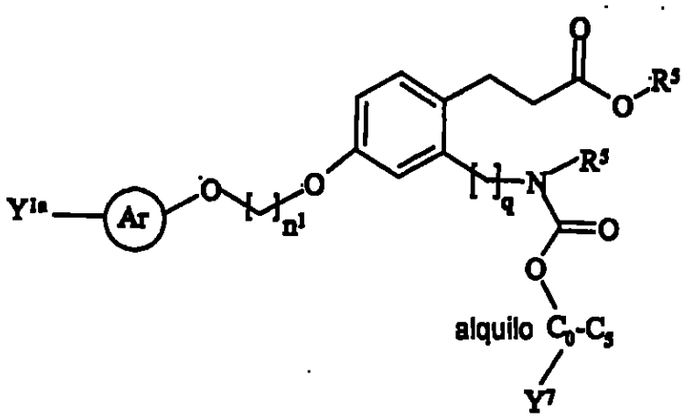
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



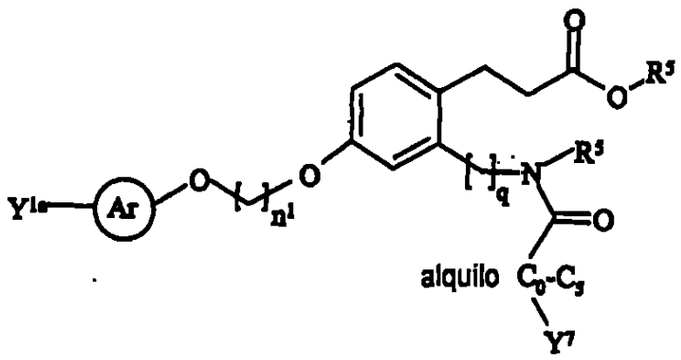
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,



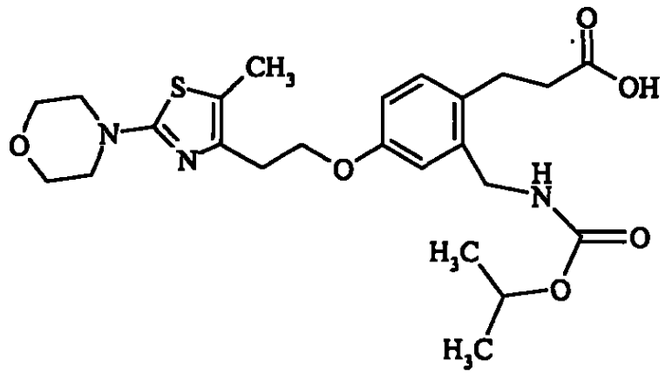
donde, Y^{1a} es hidrógeno, arilo, heteroarilo, o ariloxi; q es 1 ó 2; y n^1 es 2, 3, o 4.

Otra realización preferida de la presente invención es un compuesto representado por la siguiente fórmula estructural,

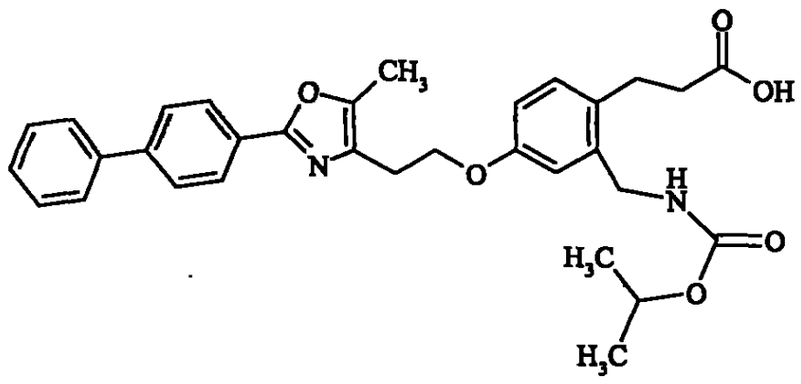


donde, Y^{1a} es hidrógeno, arilo, heteroarilo o ariloxi; q es 1 ó 2; y n^1 es 2, 3, o 4.

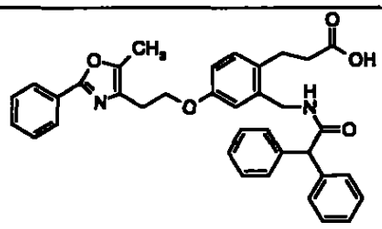
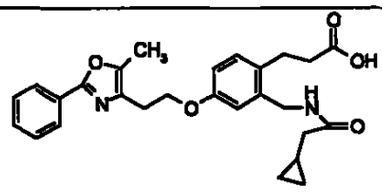
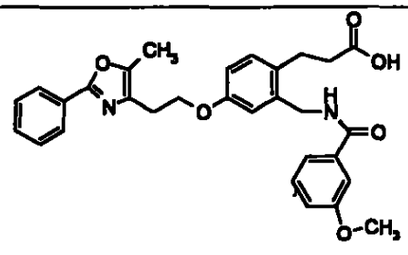
Un compuesto preferido es un compuesto representado por la siguiente fórmula estructural,

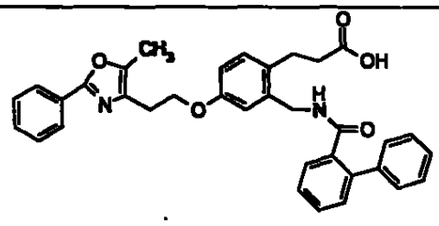
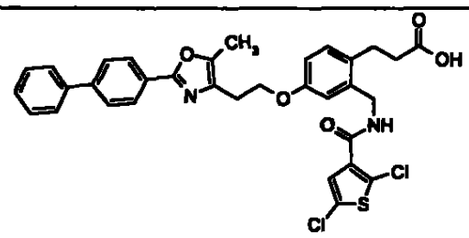
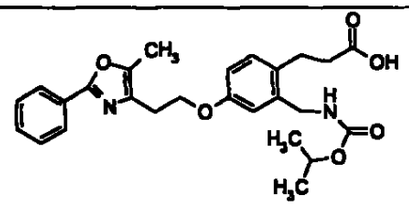
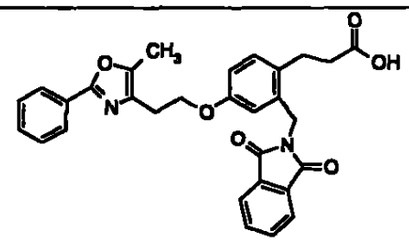
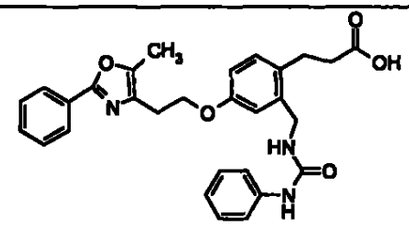


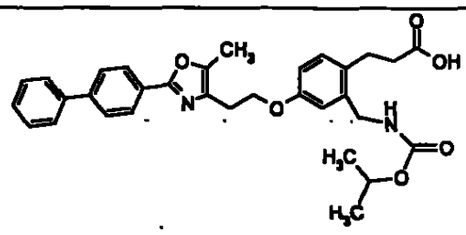
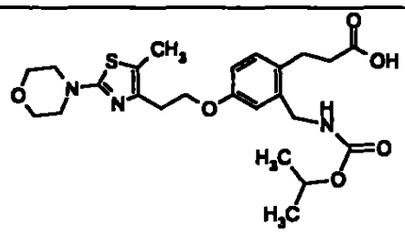
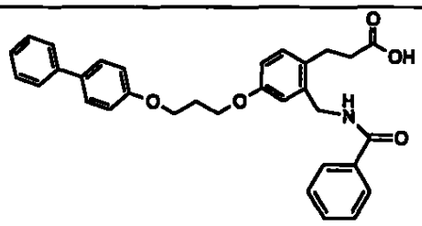
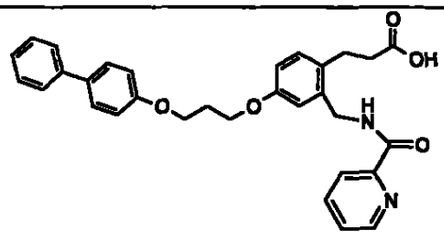
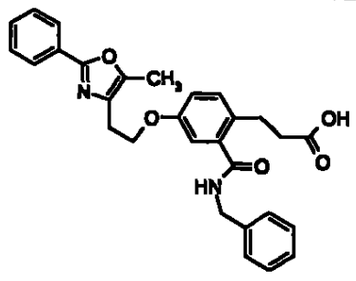
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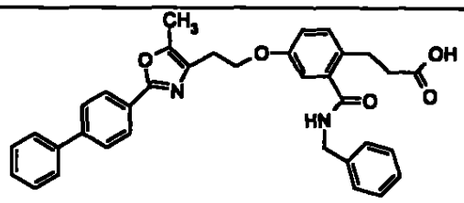
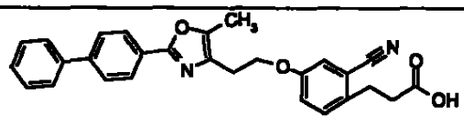
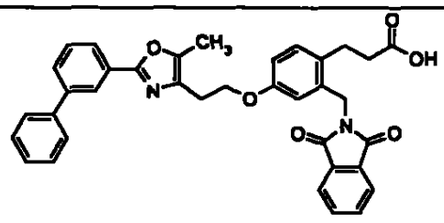
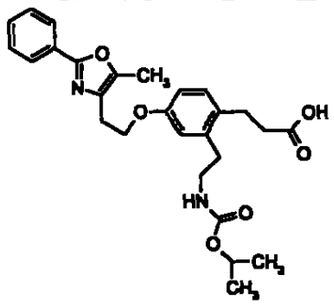
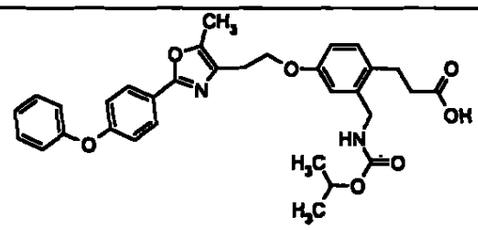


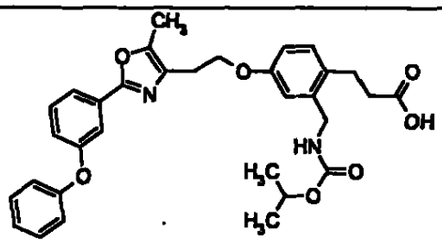
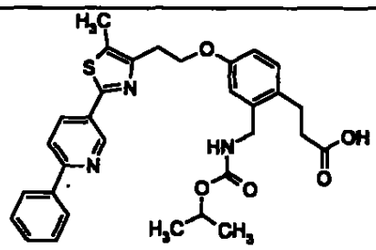
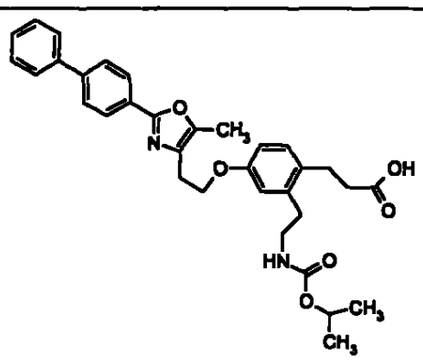
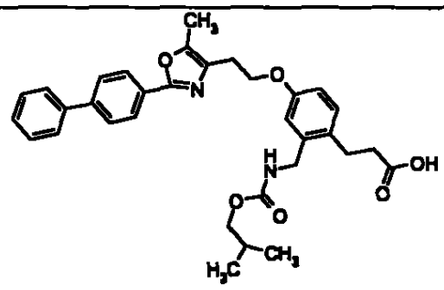
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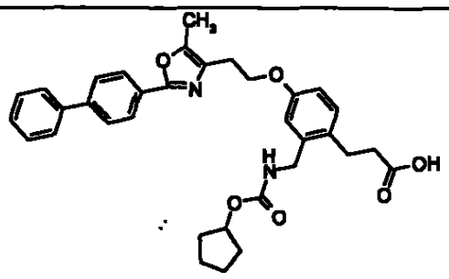
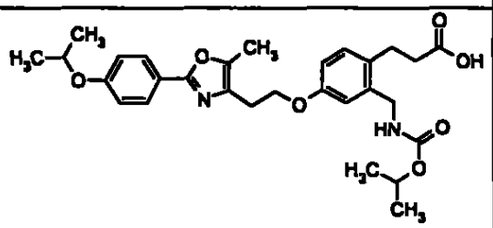
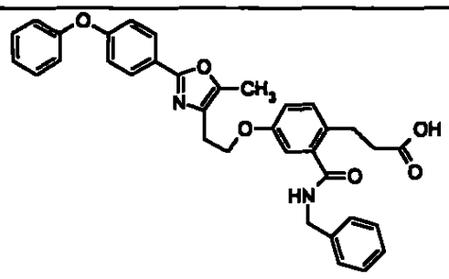
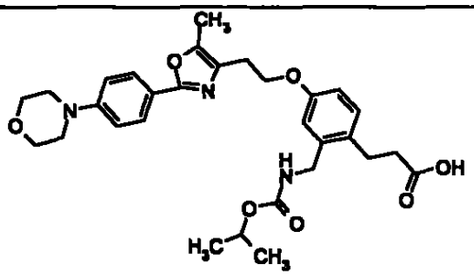
No.	Compuesto	nombre
1		ácido 3-{2-(difenilacetil-aminometil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
2		Ácido 3-{2-[(2-ciclopropilacetilamino) metil]-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
3		Ácido 3-{2-[(3-metoxibenzoilamino) metil]-4-[2-(5-metil-2-feniloxazol-4-il)etoxi] fenil} propiónico

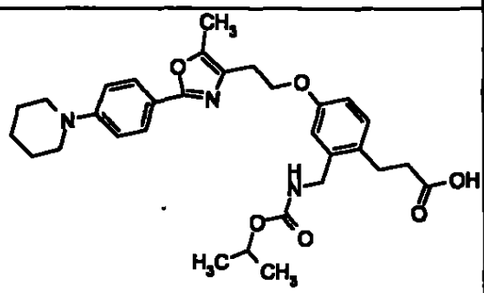
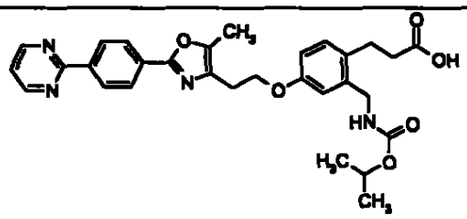
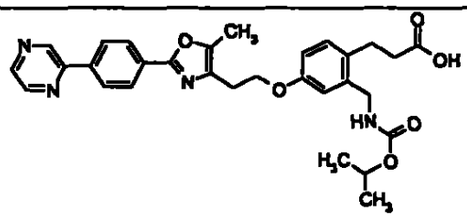
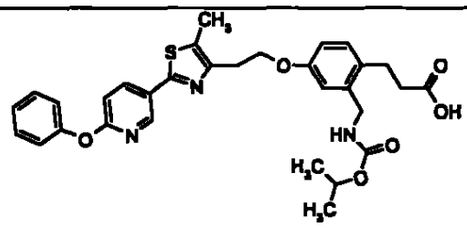
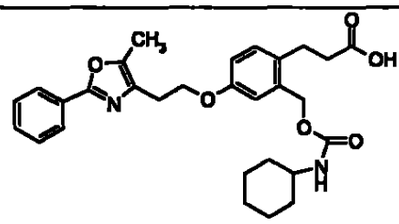
No.	Compuesto	nombre
4		Ácido 3-{2-{[(bifenil-2-carbonil) amino]metil}-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
5		Ácido 3-(4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-{[(2,5-diclorotiofeno-3-carbonil)amino]metil}fenil) propiónico
6		Ácido 3-{2-(isopropoxicarbonil-aminometil)-4-[2-(5-metil-2-feniloxazol-4-il) etoxi] fenil} propiónico
7		Ácido 3-{2-(1,3-dioxo-1,3-dihidroisoindol-2-ilmetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
8		Ácido 3-{4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-[(3-fenilureido)metil] fenil} propiónico

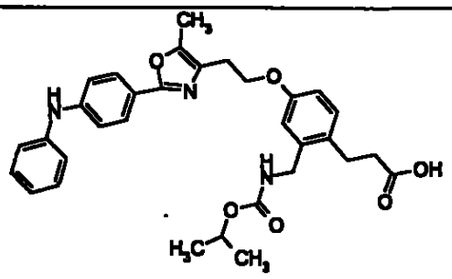
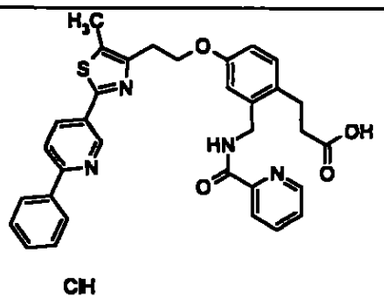
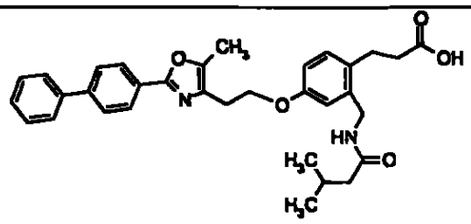
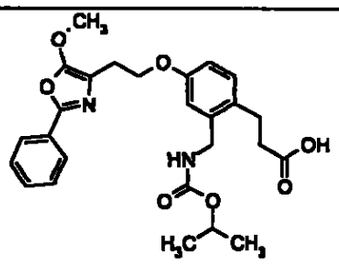
No.	Compuesto	nombre
9		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(isopropoxicarbonilaminometil)fenil] propiónico
10		Ácido 3-{2-(isopropoxicarbonil-aminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il) etoxi]fenil} propiónico
11		Ácido 3-{2-(benzoilaminometil)-4-[3-(bifenil-4-iloxi)propoxi] fenil} propiónico
12		Ácido 3-(4-[3-(bifenil-4-iloxi) propoxi]-2-{[(piridina-2-carbonil)amino]metil}fenil) propiónico
13		Ácido 3-{2-bencilcarbamoil-4-[2-(5-metil-2-feniloxazol-4-il) etoxi]fenil} propiónico

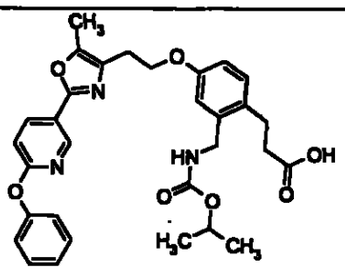
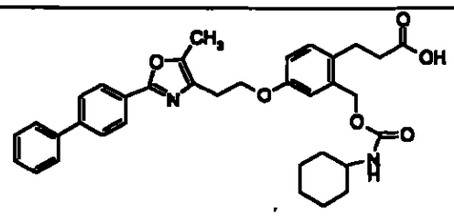
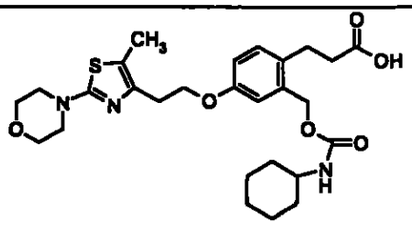
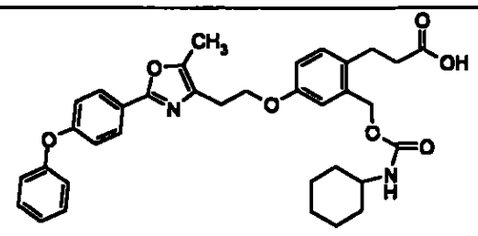
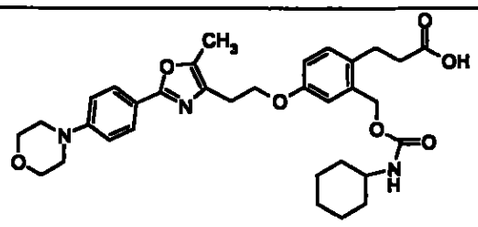
No.	Compuesto	nombre
14		Ácido 3-{2-bencilcarbamoil-4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]fenil} propiónico
15		Ácido 3-{4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-cianofenil} propiónico
16		Ácido 3-[4-[2-(2-bifenil-3-il-5-metiloxazol-4-il)etoxi]-2-(1,3-dioxo-1,3-dihidroisoindol-2-ilmetil)fenil] propiónico
17		Ácido 3-{2-(2-isopropoxicarbonil-aminoetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
18		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico

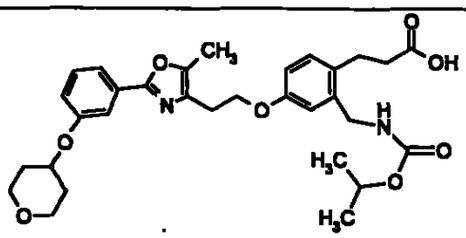
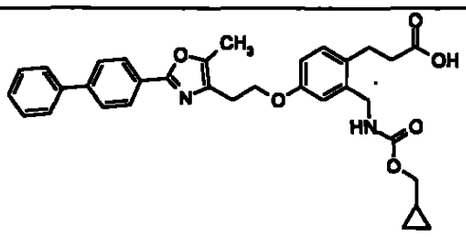
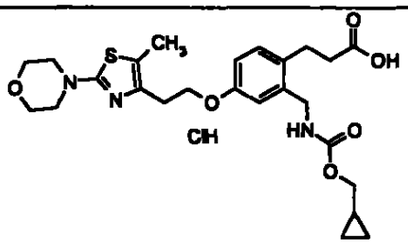
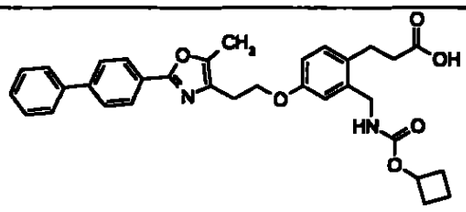
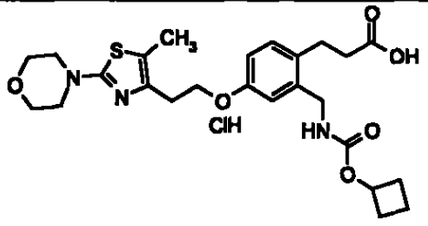
No.	Compuesto	nombre
19		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-(2-[5-metil-2-(3-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico
20		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-(2-[5-metil-2-(6-fenilpiridin-3-il)tiazol-4-il]etoxi}fenil) propiónico
21		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(2-isopropoxicarbonilaminoetil) fenil] propiónico
22		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(isobutoxicarbonilaminometil) fenil] propiónico

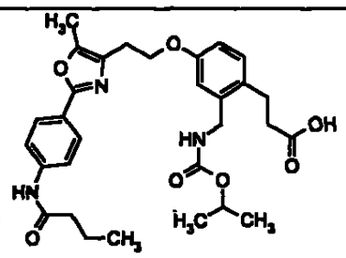
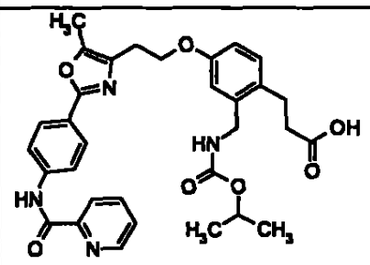
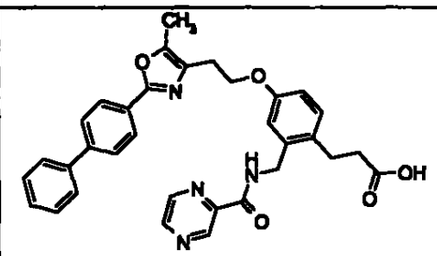
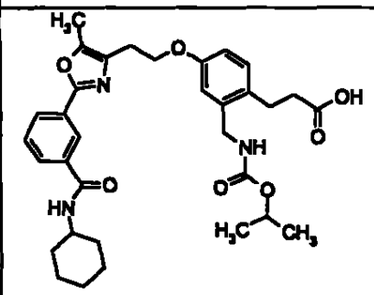
No.	Compuesto	nombre
23		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(ciclopentiloxicarbonil-aminometil)fenil] propiónico
24		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[2-(4-isopropoxifenil)-5-metiloxazol-4-il]etoxi} fenil) propiónico
25		Ácido 3-(2-bencilcarbamoil-4-{2-[5-metil-2-(4-fenoxifenil) oxazol-4-il]etoxi}fenil) propiónico
26		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-morfolin-4-ilfenil)oxazol-4-il]etoxi}fenil) propiónico

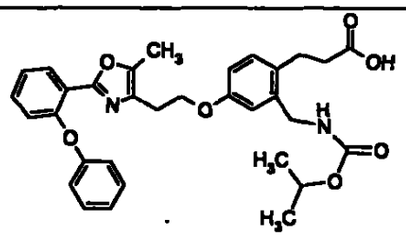
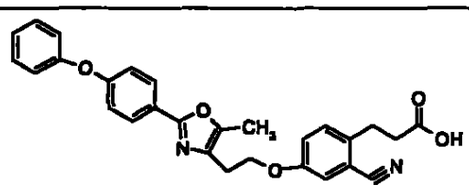
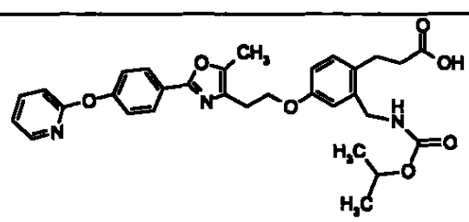
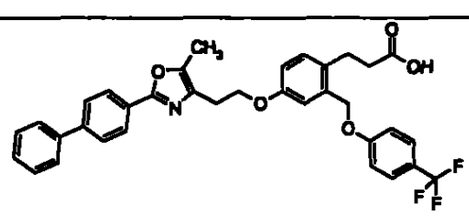
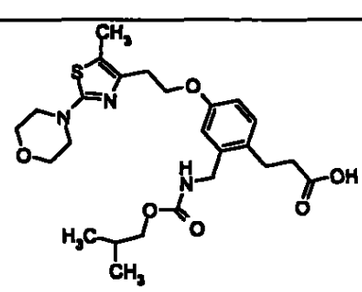
No.	Compuesto	nombre
27		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-piperidin-1-ilfenil)oxazol-4-il]etoxi}fenil) propiónico
28		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-pirimidin-2-ilfenil)oxazol-4-il]etoxi}fenil) propiónico
29		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-pirazin-2-ilfenil)oxazol-4-il]etoxi}fenil) propiónico
30		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(6-fenoxipiridin-3-il)tiazol-4-il]etoxi}fenil) propiónico
31		Ácido 3-{2-ciclohexilcarbamoil-oximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico

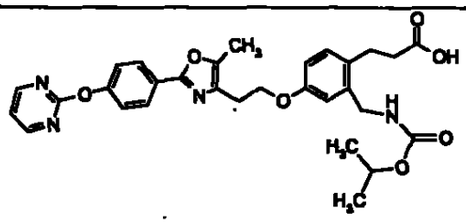
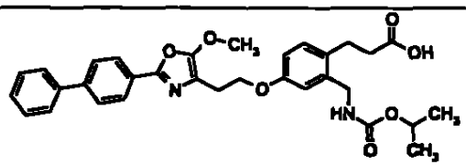
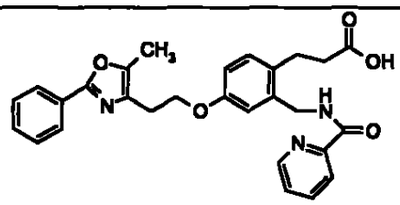
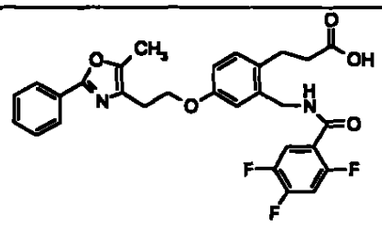
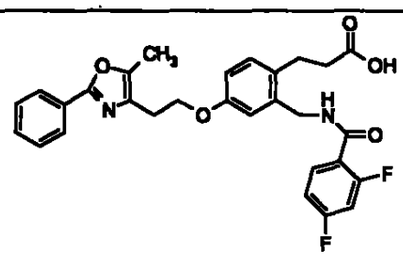
No.	Compuesto	nombre
32		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-fenilaminofenil)oxazol-4-il]etoxi}fenil) propiónico
33		Sal HCl del ácido 3-(4-{2-[5-metil-2-(6-fenilpiridin-3-il)tiazol-4-il]etoxi}-2-{[(piridina-2-carbonil)amino]metil}fenil) propiónico
34		Ácido 3-(4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-[(3-metilbutirilamino) metil]fenil} propiónico
35		Ácido 3-{2-(isopropoxicarbonil-aminometil)-4-[2-(5-metoxi-2-feniloxazol-4-il)etoxi] fenil} propiónico

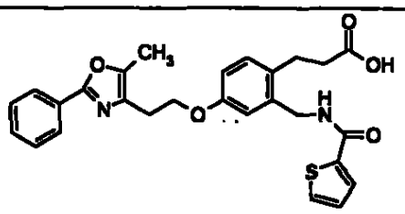
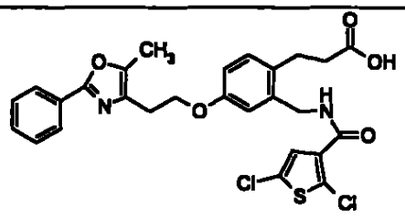
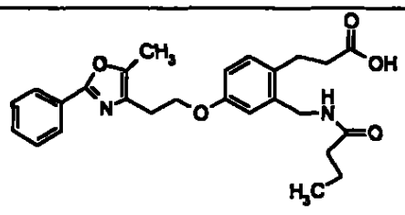
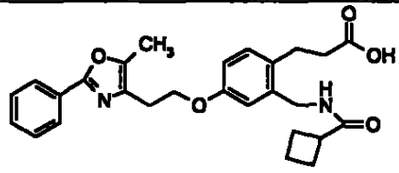
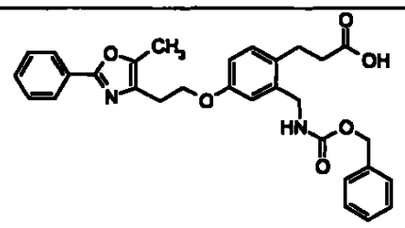
No.	Compuesto	nombre
36		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(6-fenoxipiridin-3-il)oxazol-4-il]etoxi}fenil) propiónico
37		Ácido 3-(4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-ciclohexilcarbamoiloxi-metilfenil} propiónico
38		Ácido 3-{2-ciclohexilcarbamoil-oximetil-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil} propiónico
39		Ácido 3-(2-ciclohexilcarbamoil-oximetil-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico
40		Ácido 3-(2-ciclohexilcarbamoil-oximetil-4-{2-[5-metil-2-(4-morfolin-4-ilfenil)oxazol-4-il]etoxi}fenil) propiónico

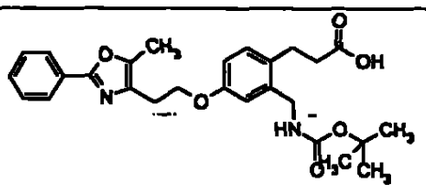
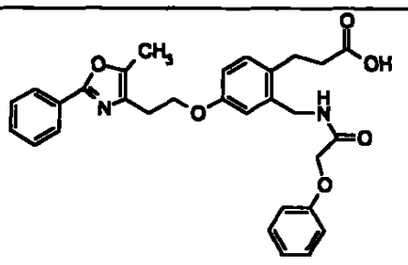
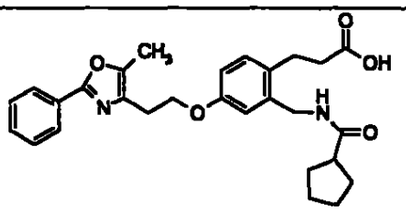
No.	Compuesto	nombre
41		Ácido 3-[2-(isopropoxicarbonil-aminometil)-4-(2-{5-metil-2-[3-(tetrahidropiran-4-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico
42		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(ciclopropilmetoxicarbonilamino metil)fenil] propiónico
43		Sal HCl del ácido 3-{2-(ciclopropilmetoxi-carbonilaminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil} propiónico
44		Sal HCl del ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(ciclobutoxicarbonil-aminometil)fenil]propiónico
45		Sal HCl del ácido 3-{2-(ciclobutoxicarbonil-aminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il) etoxi]fenil} propiónico

No.	Compuesto	nombre
46		Ácido 3-[4-[2-[2-(4-butirilaminofenil)-5-metiloxazol-4-il]etoxi]-2-(isopropoxicarbonilaminometil)-fenil] propiónico
47		Ácido 3-[2-(isopropoxicarbonil-amino-metil)-4-[2-(5-metil-2-{4-[(piridina-2-carbonil)-amino]-fenil}-oxazol-4-il)-etoxi]-fenil}-propiónico
48		Ácido 3-(4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-{[(pirazina-2-carbonil) amino]metil}fenil) propiónico
49		Ácido 3-[4-[2-[2-(3-ciclohexilcarbamoilfenil)-5-metiloxazol-4-il]etoxi]-2-(isopropoxicarbonilaminometil)-fenil] propiónico

No.	Compuesto	nombre
50		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(2-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico
51		Ácido 3-(2-ciano-4-{2-[5-metil-2-(4-fenoxi-fenil)-oxazol-4-il]-etoxi}-fenil) propiónico
52		Ácido 3-[2-(isopropoxicarbonil-aminometil)-4-(2-{5-metil-2-[4-(piridin-2-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico
53		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(4-trifluorometilfenoximetil) fenil] propiónico
54		Ácido 3-{2-(isobutoxicarbonil-aminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil} propiónico

No.	Compuesto	nombre
55		Ácido 3-[2-(isopropoxicarbonil-aminometil)-4-(2-{5-metil-2-[4-(pirimidin-2-iloxi) fenil] oxazol-4-il}etoxi)fenil] propiónico
56		Ácido 3-[4-[2-(2-bifenil-4-il-5-metoxioxazol-4-il)etoxi]-2-(isopropoxicarbonilaminometil)-fenil] propiónico
57		Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico
58		Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(2,4,5-trifluoro-benzoilamino)-metil]-fenil}-propiónico
59		Ácido 3-[2-[(2,4-difluoro-benzoilamino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

No.	Compuesto	nombre
60		ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{[(tiofeno-2-carbonil)-amino]-metil}-fenil)-propiónico
61		Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{[(tiofeno-2-carbonil)-amino]-metil}-fenil)-propiónico
62		Ácido 3-{2-(butirilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico
63		Ácido 3-{2-[(ciclobutanocarbonil-amino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico
64		Ácido 3-{2-(benciloxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

No.	Compuesto	nombre
65		Ácido 3-{2-(terc-butoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico
66		Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(2-fenoxi-acetilamino)-metil]-fenil}-propiónico
67		Ácido 3-{2-[(ciclopentanocarbonil-amino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

La presente invención también engloba un procedimiento para modular un receptor activado por el proliferador de peroxisomas (PPAR), que comprende la etapa de poner en contacto el receptor con al menos un compuesto de la presente invención o una sal, solvato o hidrato farmacéuticamente aceptable del mismo. El receptor activado por el proliferador de peroxisomas es un receptor alfa o un receptor gamma.

La presente invención también engloba un procedimiento para tratar o prevenir una enfermedad o afección mediada por el receptor gamma activado por el proliferador de peroxisomas, que comprende la etapa de administrar un

compuesto de Fórmula I o de Fórmula Ia.

La presente invención también engloba un procedimiento para disminuir la glucosa en sangre que comprende la etapa de administrar una cantidad eficaz de un compuesto de fórmula I o de fórmula Ia.

La presente invención también engloba una procedimiento para tratar o prevenir una enfermedad o afección seleccionada entre el grupo compuesto por hiperglucemia, dislipidemia, diabetes de tipo II, diabetes de tipo I, hipertrigliceridemia, síndrome X, resistencia a la insulina, insuficiencia cardíaca, dislipidemia diabética, hiperlipidemia, hipercolesterolemia, hipertensión, obesidad, bulimia, anorexia nerviosa, enfermedad cardiovascular y otras enfermedades donde la resistencia a la insulina es un componente, que comprende la etapa de administrar una cantidad eficaz de un compuesto de fórmula I o de fórmula Ia.

La presente invención también engloba un procedimiento para tratar o prevenir la diabetes mellitus en un mamífero, que comprende la etapa de administrar a un mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de fórmula I o de fórmula Ia.

La presente invención también engloba un procedimiento para tratar o prevenir una enfermedad cardiovascular en un mamífero, que comprende la etapa de administrar a un mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de fórmula I o de fórmula Ia, o una sal, solvato hidrato o estereoisómero farmacéuticamente aceptable del mismo.

La presente invención también engloba un procedimiento para tratar o prevenir el síndrome X en un mamífero, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de al menos un compuesto

de fórmula I o de fórmula Ia, o una sal, solvato, hidrato o estereoisómero farmacéuticamente aceptable del mismo.

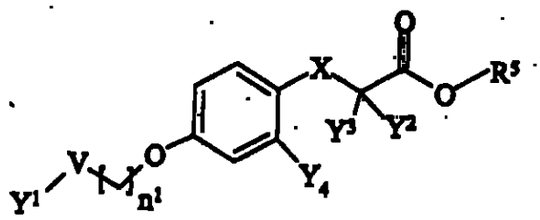
La presente invención también engloba un procedimiento para tratar o prevenir una enfermedad o afección seleccionada entre el grupo compuesto por hiperglucemia, dislipidemia, diabetes de tipo II, diabetes de tipo I, hipertrigliceridemia, síndrome X, resistencia a insulina, insuficiencia cardíaca, dislipidemia diabética, hiperlipidemia, hipercolesterolemia, hipertensión, obesidad, bulimia, anorexia nerviosa, enfermedad cardiovascular y otras enfermedades donde la resistencia a la insulina es un componente, que comprende la etapa de administrar una cantidad eficaz de un compuesto de fórmula I o Ia y una cantidad eficaz de un segundo agente terapéutico seleccionado entre el grupo compuesto por sensibilizadores de insulina, sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de α-glucosidasa, secretagogos de insulina, insulina, agentes antihiperlipidémicos, agentes que aumentan el HDL en plasma, inhibidores de la HMG-CoA reductasa, estatinas, inhibidores de acril CoA:colesterol aciltransferasa, compuestos antiobesidad, agentes antihipercolesterolémicos, fibratos, vitaminas y aspirina.

La presente invención también engloba el uso de un compuesto de fórmula I o de fórmula Ia y una sal, solvato, hidrato o estereoisómero farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para el tratamiento de una afección modulada por un PPAR.

Una realización de la presente invención también incluye los compuestos que tienen una fórmula estructural II a IX como se muestra más adelante. Estos compuestos están dentro del alcance del compuesto representado por una Fórmula estructural Ia. El sustituyente Y^1 de estos compuestos incluye

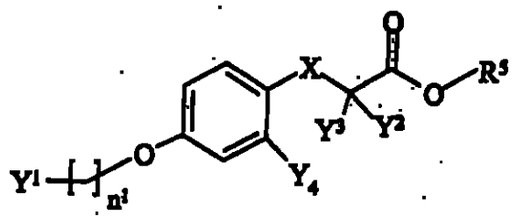


, donde Y^{1a} y  se definen anteriormente en la fórmula I, y los grupos sustituidos incluyen sustituyentes mencionados anteriormente y definidos en la realización en este documento.



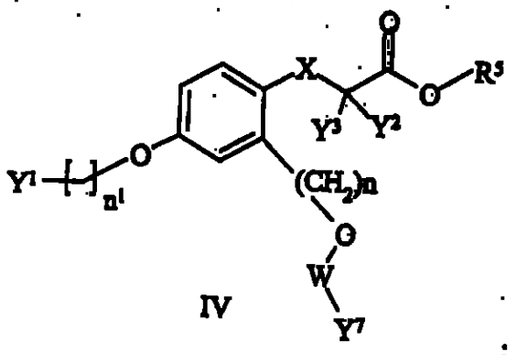
II

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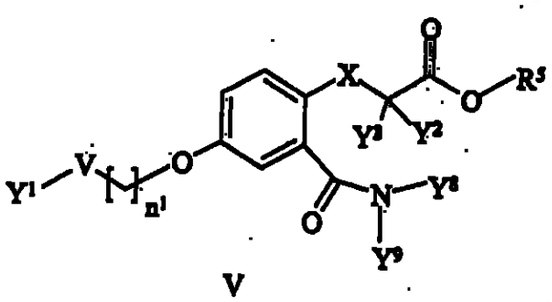
III

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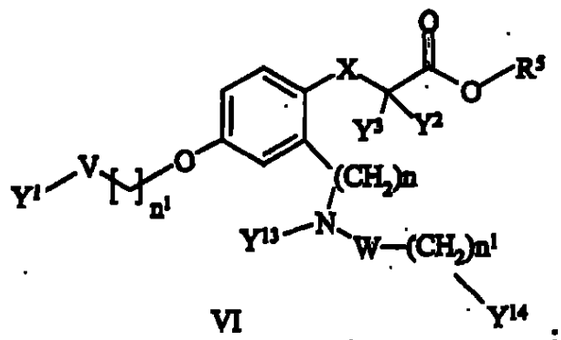
IV

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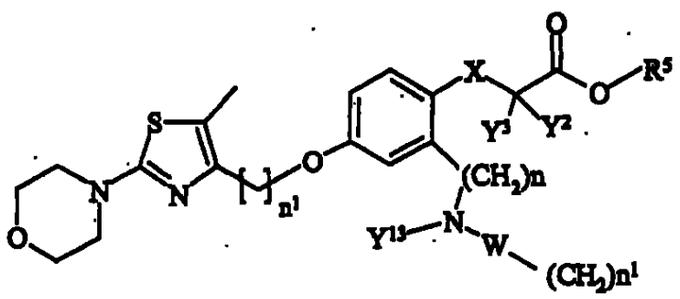


V

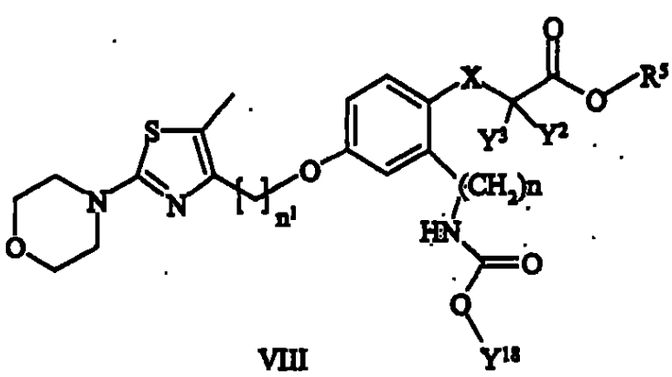
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VI ;

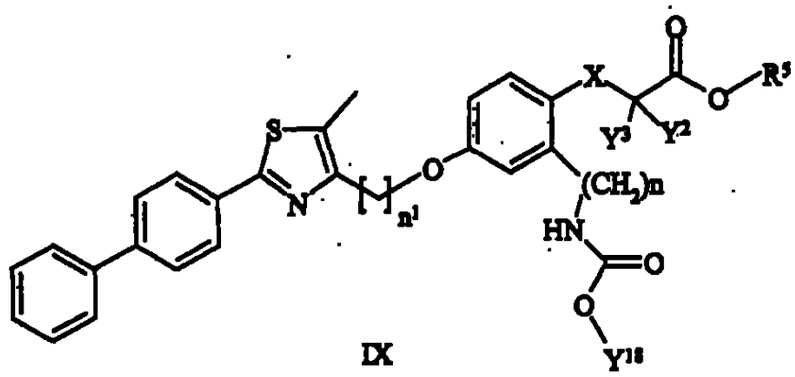


VII ;



VIII

donde Y^{18} es alquilo (C_1-C_8) de cadena lineal o ramificada; y



IX

donde Y^{18} es alquilo (C_1-C_6) de cadena lineal o ramificada.

Los términos usados para describir la presente invención tienen los siguientes significados.

Como se usa en este documento, el término "alifático" o "grupo alifático" es un grupo no aromático, que está compuesto únicamente por carbono e hidrógeno y puede contener opcionalmente una o más unidades de saturación, por ejemplo, dobles y/o triples enlaces (en este documento también denominado "alquenilo" y "alquinilo"). Un alifático o grupo alifático puede ser de cadena lineal, ramificado (en este documento, también denominado "alquilo") o cíclico (en este documento también denominado "cicloalquilo"). Cuando es de cadena lineal o ramificado, el grupo alifático contiene típicamente entre aproximadamente 1 y aproximadamente 10 átomos de carbono, más típicamente entre aproximadamente 1 y aproximadamente 6 átomos de carbono. Cuando es cíclico, un alifático contiene típicamente entre aproximadamente 3 y aproximadamente 10 átomos de carbono, más típicamente entre aproximadamente 3 y aproximadamente 7 átomos de carbono. Los alifáticos son preferiblemente grupos alquilo C_1-C_{10} de cadena lineal o ramificada (es decir, grupos alifáticos completamente saturados), más

preferiblemente, grupos alquilo C_1-C_8 de cadena lineal o ramificados. Los ejemplos incluyen, pero sin limitación, metilo, etilo, propilo, n-propilo, iso-propilo, n-butilo, sec-butilo y terc-butilo. Otros ejemplos adicionales incluyen, pero sin limitación, ciclopropilo, ciclopentilo, ciclohexilo, ciclopentilo, ciclohexililo y similares.

El término "alquilo", a menos que se indique otra cosa, se refiere a los grupos alquilo de un número designado de átomos de carbono de una configuración saturada lineal o ramificada. Los ejemplos de "alquilo" incluyen, pero sin limitación, metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo y terc-butilo, pentilo, hexilo, isopentilo y similares. Alquilo, como se ha definido anteriormente, puede estar opcionalmente sustituido con un número designado de sustituyentes como se indica en la realización indicada anteriormente.

El término "alquenilo" significa una cadena de hidrocarburo de un número específico de átomos de carbonos de configuración lineal o ramificada y que tiene al menos un doble enlace carbono-carbono, que puede estar en cualquier punto de la cadena, tal como etenilo, propenilo, butenilo, pentenilo, vinilo, alquilo, 2-butenilo y similares. Alquenilo, como se ha definido anteriormente puede estar opcionalmente sustituido con un número designado de sustituyentes según se establece en la realización indicada anteriormente.

El término "alquinilo" significa una cadena de hidrocarburo de un número específico de átomos de carbono de configuración lineal o ramificada y que tiene al menos un triple enlace carbono-carbono, que puede estar en cualquier punto de la cadena. Es un ejemplo de alquinilo acetileno. Alquinilo, como se ha definido anteriormente, puede estar opcionalmente sustituido con un número

designado de sustituyentes como se establece en la realización indicada anteriormente.

El término "cicloalquilo" se refiere a un carbociclo saturado o parcialmente saturado que contiene uno o más anillos de 3 a 12 átomos de carbono. Los ejemplos de cicloalquilo incluyen, pero sin limitación, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo, y similares. Cicloalquilo, como se ha definido anteriormente, también incluye un triciclo, tal como adamantilo. Cicloalquilo, como se ha definido anteriormente, puede estar sustituido opcionalmente con un número designado de sustituyentes como se establece en la realización indicada anteriormente.

El término "halo" se refiere a flúor, cloro, bromo y yodo.

El término "haloalquilo" es un grupo alquilo C_1-C_6, que está sustituido con uno o más átomos halo seleccionados entre F, Br, Cl y I. Un ejemplo de un grupo haloalquilo es trifluorometilo.

El término "alcoxi" representa un grupo alquilo de un número indicado de átomos de carbono unidos mediante un puente de oxígeno, tal como metoxi, etoxi, propoxi, isopropoxi, butoxi, terc-butoxi, pentoxi y similares. Alcoxi, como se ha definido anteriormente, puede estar opcionalmente sustituido con un número designado de sustituyentes como se establece en la realización indicada anteriormente.

El término "haloalquiloxi" representa un grupo haloalquilo C_1-C_6 unido mediante un puente de oxígeno, tal como OCF_3. El "haloalquiloxi", como se ha definido anteriormente, puede estar opcionalmente sustituido con un número designado de sustituyentes, como se establece en la realización indicada anteriormente.

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El término "arilo" incluye sistemas de anillos aromáticos carbocíclicos (por ejemplo, fenilo), sistemas de anillos aromáticos policíclicos condensados (por ejemplo, naftilo y antracenilo) y sistemas de anillos aromáticos condensados a sistemas de anillos no aromáticos carbocíclicos (por ejemplo, 1,2,3,4-tetrahidronaftilo). "Arilo", como se ha definido anteriormente, puede estar opcionalmente sustituido con un número designado de sustituyentes como se establece en la realización indicada anteriormente.

El término grupo "heteroarilo", como se usa en este documento, es un sistema de anillo aromático que tiene al menos un heteroátomo tal como nitrógeno, azufre u oxígeno, e incluye anillos aromáticos monocíclicos, bicíclicos o tricíclicos de 5 a 14 átomos de carbono que contienen uno o más heteroátomos seleccionados entre O, N o S. El "heteroarilo", como se ha definido anteriormente, puede estar opcionalmente sustituido con un número designado de sustituyentes como se establece en la realización indicada anteriormente. Son ejemplos de heteroarilo, pero sin limitación, furanilo, tienilo (en este documento también denominado "tiofenilo"), tiazolilo, imidazolilo, isoxazolilo, isoxazoílo, oxazoílo, pirazoílo, pirrolilo, pirazinilo, piridilo, pirimidilo, pirimidinilo y purinilo, cinolinilo, benzofuranilo, benzotienilo, benzotriazolilo, benzoxazolilo, quinolina, isoxazolilo, isoquinolina y similares.

El término "heterocicloalquilo" se refiere a un anillo no aromático que contiene uno o más átomos de oxígeno, nitrógeno o azufre e incluye un anillo no aromático monocíclico, bicíclico o tricíclico de 5 a 14 átomos de carbono que contiene uno o más heteroátomos seleccionados entre O, N o S. El "heterocicloalquilo", como se ha definido anteriormente, puede estar opcionalmente sustituido con un número designado de sustituyentes, según se

establece en la realización indicada anteriormente. Los ejemplos de heterocicloalquilo incluyen, pero sin limitación, morfolina, piperidina, piperazina, pirrolidina y tiomorfolina. El grupo heterocicloalquilo preferido es morfolina.

Un grupo aril-alquilo C_1-C_4, como se usa en este documento, es un sustituyente arilo que está unido a un compuesto mediante un grupo alquilo que tiene de uno a cuatro átomos de carbono.

Un grupo heteroaril-alquilo C_1-C_4, como se usa en este documento, es un sustituyente heteroarilo que está unido a un compuesto mediante un grupo alquilo que tiene de uno a cuatro átomos de carbono.

Un grupo cicloalquil-alquilo C_1-C_4, como se usa en este documento, es un sustituyente cicloalquilo que está unido a un compuesto mediante un grupo alquilo que tiene de uno a cuatro átomos de carbono.

Un grupo aminoalquilo es un grupo alquilo que tiene de uno a seis átomos de carbono, que está sustituido con al menos una amina representada por $NR^{12}R^{12}$, donde cada R^{12} es independientemente un alquilo C_1-C_6 o los dos R^{12} tomados conjuntamente con el nitrógeno al que están unidos forman un heterocicloalquilo de cinco o seis miembros.

A menos que se indique otra cosa, los sustituyentes para alquilo, alquenilo, cicloalquilo, arilo, heteroarilo y heterocicloalquilo también incluyen halo, carboxilo, alquilo C_1-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, nitro, ciano, CHO, hidroxilo, ácido C_1-C_6 alcanoico y $-C(O)NR^{13}R^{13}$ donde cada R^{13} es independientemente hidrógeno o un alquilo C_1-C_6.

Los sustituyentes para tiofen-2,5-diilo y fenileno incluyen H, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_4 y haloalcoxi C_1-C_4.

La expresión "ingrediente activo" significa los compuestos descritos

genéricamente por la fórmula I así como las sales, solvatos y profármacos de tales compuestos.

La expresión "farmacéuticamente aceptable" significa que el vehículo, diluyentes, excipientes y sal deben ser compatibles con los demás ingredientes de la composición, y no perjudiciales para el receptor de los mismos. Las composiciones farmacéuticas de la presente invención se preparan por procedimientos conocidos en la técnica usando ingredientes bien conocidos y fácilmente adquiribles.

"Prevenir" se refiere a reducir la probabilidad de que el receptor incurra o desarrolle cualquiera de las afecciones patológicas descritas en este documento.

"Tratar" se refiere a mediar una enfermedad o afección, y a prevenir o mitigar su progresión adicional o reducir los síntomas asociados con la enfermedad o afección.

"Cantidad farmacéuticamente eficaz" se refiere a la cantidad de un compuesto de la presente invención, o de su sal, hidrato o profármaco del mismo que producirá la respuesta biológica o médica de un tejido, sistema o mamífero. Tal cantidad puede administrarse profilácticamente a un paciente que se cree que es susceptible de desarrollar una enfermedad o afección. Tal cantidad, cuando se administra profilácticamente a un paciente, también puede ser eficaz para prevenir o aliviar la gravedad de la afección mediada. Se pretende que tal cantidad incluya una cantidad, que es suficiente para modular un receptor PPAR tal como un receptor PPARα o PPARγ para mediar una enfermedad o afección. Las afecciones mediadas por receptores PPARα o PPARγ incluyen, por ejemplo, diabetes mellitus, enfermedad cardiovascular,

Síndrome X, obesidad y enfermedad gastrointestinal. Otras afecciones asociadas con la modulación de un receptor PPAR incluyen afecciones relacionadas con la inflamación que incluyen, por ejemplo, IBD (enfermedad inflamatoria del intestino), artritis reumatoide, psoriasis, enfermedad de Alzheimer, enfermedad de Crohn y lesión por isquemia-reperfusión (apoplejía e infarto de miocardio).

Un "mamífero" es un animal individual que es un miembro de la clase taxonómica Mammalia. La clase Mammalia incluye seres humanos, monos, chimpancés, gorilas, vacas, cerdos, caballos, ovejas, perros, gatos, ratones, ratas y similares.

Se prefiere más la administración a un ser humano. Un ser humano al que se le administran los compuestos y composiciones de la presente invención tiene una enfermedad o afección en la que los niveles de glucosa en sangre no se controlan de forma adecuada sin intervención médica, pero en la que está presente insulina endógena en la sangre del ser humano. La diabetes mellitus no dependiente de insulina (NIDDM) es una enfermedad o afección crónica caracterizada por la presencia de insulina en la sangre, incluso en niveles por encima de lo normal, pero con resistencia o falta de sensibilidad a la acción de la insulina en los tejidos.

Los especialistas en la técnica reconocerán que en los compuestos de Fórmula I y de Fórmula Ia existen estereocentros. Por consiguiente, la presente invención incluye todos los estereoisómeros posibles e isómeros geométricos de fórmula I incluyendo compuestos racémicos y los isómeros ópticamente activos.

Los compuestos de Fórmula I y de Fórmula Ia contienen uno o más

centros quirales y existen en diferentes formas ópticamente activas. Cuando los compuestos de fórmula I contiene un centro quiral, los compuestos existen en dos formas enantioméricas y la presente invención incluye tanto los enantiómeros como mezclas de enantiómeros, tales como mezclas racémicas. La resolución del producto final, un intermedio o un material de partida puede efectuarse mediante cualquier procedimiento conocido en la técnica, por ejemplo, mediante la formación de sales diastereoisoméricas que pueden separarse por cristalización; la formación de derivados o complejos diastereoisoméricos que pueden separarse por cristalización y cromatografía de gas líquido o líquida; la reacción selectiva de un enantiómero con un reactivo específico de enantiómero tal como esterificación enzimática; y cromatografía de gas líquido o líquida en un medio quiral tal como un soporte quiral, por ejemplo sílice con un ligando quiral unido o en presencia de un disolvente quiral. Véase también *Sterochemistry of Carbon Compounds* de E.L. (Mcgraw Hill, 1962) y *Tables of Resolving Agents* de S. H. Wilen. Se apreciará que cuando el enantiómero deseado se convierte en otra entidad química mediante uno de los procedimientos de separación descritos anteriormente, se requiere una etapa adicional para liberar la forma enantiomérica deseada. Como alternativa, pueden sintetizarse enantiómeros específicos por síntesis asimétrica usando reactivos, sustratos, catalizadores o disolventes ópticamente activos, o convirtiendo un enantiómero en el otro por transformación asimétrica. En una realización más preferida, los compuestos de la presente invención son enantiómeros S.

Cuando un compuesto de Fórmula I o de Fórmula Ia tiene más de un sustituyente quiral, puede existir en formas diastereoisoméricas. Los pares

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diastereoisoméricos pueden separarse por métodos conocidos para los especialistas en la técnica, por ejemplo cromatografía o cristalización, y los enantiómeros individuales de cada par pueden separarse como se ha descrito anteriormente. La presente invención incluye cada diastereoisómero de los compuestos de fórmula I y mezclas de los mismos.

Ciertos compuestos de fórmula I o Ia pueden existir en diferentes formas conformacionales estables que pueden separarse. La asimetría torsional debida a la rotación restringida alrededor de un enlace sencillo asimétrico, por ejemplo debido al impedimento estérico o a la tensión del anillo, puede permitir la separación de diferentes confórmeros. La presente invención incluye cada isómero conformacional de compuestos de fórmula I y Ia y mezclas de los mismos.

Ciertos compuestos de fórmula I o Ia pueden existir en forma bipolar, y la presente invención incluye cada forma bipolar de compuestos de fórmula I o Ia y mezclas de los mismos.

Ciertos compuestos de fórmula I o Ia y sus sales pueden existir en más de una forma de cristal. Los polimorfos de compuestos de fórmula I forman parte de la presente invención y pueden prepararse por cristalización de un compuesto de fórmula I o Ia en diferentes condiciones, tales como usando diferentes disolventes o diferentes mezclas de disolventes para la recristalización; cristalización a diferentes temperaturas; y diversos modos de refrigeración que varían de refrigeración muy rápida a muy lenta durante la cristalización. Los polimorfos también pueden obtenerse calentando o fundiendo un compuesto de Fórmula I o de Fórmula Ia seguido de una refrigeración gradual o rápida. La presencia de polimorfos puede determinarse

por espectroscopía de RMN de sonda sólida, espectroscopía IR, calorimetría de exploración diferencial, difracción de rayos X en polvo u otras técnicas disponibles.

Ciertos compuestos de fórmula I o Ia y sus sales pueden existir en más de una forma de cristal, y la presente invención incluye cada forma de cristal y mezclas de las mismas.

Ciertos compuestos de fórmula I o Ia y sus sales también pueden existir en forma de solvatos, por ejemplo hidratos, y la presente invención incluye cada solvato y mezclas de los mismos.

"Sal farmacéuticamente aceptable" se refiere a sales de los compuestos de fórmula I o Ia que son sustancialmente no tóxicas para mamíferos. Las sales farmacéuticamente aceptables típicas incluyen las sales preparadas por la reacción de los compuestos de la presente invención con un ácido mineral, orgánico, una base orgánica o una base inorgánica. Tales sales se conocen como sales de adición de bases, respectivamente. Debe reconocerse que el contraión particular que forma parte de cualquier sal de la presente invención no es de naturaleza crítica mientras que la sal en su conjunto sea farmacéuticamente aceptable y el contraión no contribuya a cualidades indeseadas de la sal en su conjunto.

En virtud de su resto ácido, un compuesto de fórmula I o Ia forma sales con bases farmacéuticamente aceptables. Algunos ejemplos de sales de adición de bases incluyen sales metálicas tales como aluminio; sales de metales alcalinos tales como litio, sodio o potasio; y sales de metales alcalinotérreos tales como calcio, magnesio, amonio, o sales de amonio sustituido. Los ejemplos de sales de amonio sustituido incluyen, por ejemplo,

las formadas con alquilaminas inferiores tales como trimetilamina y trietilamina; hidroxialquilaminas tales como 2-hidroxietilamina, bis-(2-hidroxietil)-amina o tri-(2-hidroxietil)-amina; cicloalquilaminas tales como bicicloheXilamina o dibencilpiperidina, N-bencil-β-fenetilamina, deshidroabietilamina, N,N'-bisdeshidro-abietilamina, glicamina, N-piperazina metilglucamina; bases de tipo piridina tales como piridina, colidina, quinina o quinolina; y sales de aminoácidos básicos tales como lisina y arginina.

Los ejemplos de bases inorgánicas incluyen, sin limitación, hidróxido sódico, hidróxido potásico, carbonato potásico, carbonato sódico, bicarbonato sódico, bicarbonato potásico, hidróxido cálcico, carbonato cálcico, y similares.

Los compuestos de fórmula I o Ia, que están sustituidos con un grupo básico, pueden existir como sales con ácidos farmacéuticamente aceptables. La presente invención incluye tales sales. Los ejemplos de tales sales incluyen clorhidratos, bromhidratos, sulfatos, metanosulfonatos, nitratos, maleatos, acetatos, citratos, fumaratos, tartratos [por ejemplo, (+)-tartratos, (-)-tartratos o mezclas de los mismos, incluyendo mezclas racémicas], succinatos, benzoatos y sales con aminoácidos tales como ácido glutámico. Estas sales pueden prepararse por procedimientos conocidos para los especialistas en la técnica.

Ciertos compuestos de fórmula I o Ia y sus sales también pueden existir en forma de solvatos, por ejemplo hidratos, y la presente invención incluye cada solvato y mezclas de los mismos.

Los compuestos de la presente invención, que se unen y activan los PPAR, reducen los niveles de uno o más de los siguientes: glucosa, insulina, triglicéridos, ácidos grasos y/o colesterol y, por lo tanto, son útiles para el tratamiento y/o la prevención de hiperglucemia, dislipidemia y, en particular, de

la diabetes de tipo II, así como de otras enfermedades que incluyen el síndrome X, diabetes de tipo I, hipertrigliceridemia, resistencia a la insulina, dislipidemia diabética, hiperlipidemia, hipercolesterolemia, insuficiencia cardíaca, coagulopatía, hipertensión y enfermedades cardiovasculares, especialmente arteriosclerosis. Además, se indica que estos compuestos son útiles para la regulación del apetito y de la ingesta alimentaria en sujetos que padecen trastornos tales como obesidad, bulimia y anorexia nerviosa.

Los compuestos y composiciones de la presente invención también son útiles para tratar trastornos agudos o transitorios en la sensibilidad a la insulina, que a veces tiene lugar tras una intervención quirúrgica, traumatismo, infarto de miocardio y similares. Los compuestos y composiciones de la presente invención también son útiles para disminuir los niveles de triglicéridos en suero. Un nivel elevado de triglicéridos, ya sea por predisposición genética o por una dieta alta en grasas, es un factor de riesgo para el desarrollo de una enfermedad cardíaca, apoplejía y trastornos o enfermedades del sistema circulatorio. El médico especialista en la técnica sabrá como identificar a seres humanos que puedan beneficiarse de la administración de los compuestos y composiciones de la presente invención.

Además la presente invención proporciona un procedimiento para el tratamiento y/o profilaxis de la hiperglucemia en un ser humano o mamífero no humano, que comprende administrar una cantidad eficaz no tóxica de un compuesto de fórmula I o una forma tautomérica del mismo y/o una sal farmacéuticamente aceptable del mismo y/o un solvato farmacéuticamente aceptable del mismo, a un ser humano o mamífero no humano hiperglucémico que lo necesita.

Los compuestos de la presente invención son útiles como sustancias terapéuticas en la prevención o tratamiento del síndrome X, diabetes mellitus y trastornos y enfermedades endocrinos y cardiovasculares relacionados en seres humanos o animales no humanos.

La presente invención también se refiere al uso de un compuesto de fórmula I como se ha descrito anteriormente para la fabricación de un medicamento para tratar una afección mediada por PPARα o PPARγ, por separado o en combinación.

Puede usarse una cantidad terapéuticamente eficaz de un compuesto de fórmula I para la preparación de un medicamento útil para tratar el síndrome X, la diabetes, para tratar la obesidad, disminuir los niveles de triglicéridos, aumentar el nivel en plasma de lipoproteínas de alta densidad, y para tratar, prevenir o reducir el riesgo de desarrollar arteriosclerosis, y para prevenir o reducir el riesgo de tener una primera o posterior enfermedad aterosclerótica en mamíferos, particularmente en seres humanos. En general, una cantidad terapéuticamente eficaz de un compuesto de fórmula I de la presente invención reduce típicamente los niveles de glucosa en suero, más específicamente la HbA1c, de un paciente en aproximadamente un 0,7% o más; reduce típicamente los niveles de triglicéridos en suero de un paciente en aproximadamente un 20% o más; y aumenta los niveles de HDL en suero en un paciente. Preferiblemente, los niveles de HDL pueden aumentarse en aproximadamente un 30% o más.

Adicionalmente, pueden usarse conjuntamente una cantidad eficaz de un compuesto de fórmula I y una cantidad terapéuticamente eficaz de uno o más agentes activos seleccionados entre agentes antihiperlipidémicos, agentes

que aumentan el HDL en plasma, agentes antihipercolesterolémicos, fibratos, vitaminas, aspirina, secretagogos de insulina, insulina y similares, para la preparación de un medicamento útil para los tratamientos descritos anteriormente.

Ventajosamente, las composiciones que contienen el compuesto de fórmula I o las sales del mismo pueden proporcionarse en forma de dosificación unitaria, conteniendo preferiblemente cada unidad de dosificación de aproximadamente 1 a aproximadamente 500 mg. Se entiende que el médico que considera todas las circunstancias relevantes es el que determina la cantidad del compuesto o compuestos de fórmula I que se administrará.

El síndrome X incluye el síndrome de resistencia a la insulina pre-diabético y las complicaciones resultantes del mismo, resistencia a la insulina, diabetes no dependiente de insulina, dislipidemia, obesidad hiperglucémica, coagulopatía, hipertensión y otras complicaciones asociadas con la diabetes. Los procedimientos y tratamientos mencionados en este documento incluyen los anteriores y engloban el tratamiento y/o profilaxis de cualquiera o de cualquier combinación de los siguientes: síndrome de resistencia a la insulina prediabético, las complicaciones resultantes del mismo, diabetes de tipo II o no dependiente de insulina, dislipidemia, hiperglucemia, obesidad y las complicaciones asociadas con la diabetes, incluyendo enfermedad cardiovascular, especialmente arteriosclerosis.

Las composiciones se formulan y se administran de la misma forma general que se ha detallado en este documento. Los compuestos de la presente invención pueden usarse eficazmente solos o en combinación con uno o más agentes adicionales activos dependiendo de la terapia diana

deseada. La terapia de combinación incluye la administración de una sola composición de dosificación farmacéutica, que contiene un compuesto de fórmula I y uno o más agentes activos adicionales, así como administración de un compuesto de fórmula I y cada agente activo en su propia formulación de dosificación farmacéutica separada. Por ejemplo, a un paciente se le puede administrar un compuesto de fórmula I o una sal del mismo y un secretagogo de insulina tal como biguanidas, tiazolidinodionas, sulfonilureas, insulina o inhibidores de α-glucosidasa, conjuntamente en una sola composición de dosificación oral tal como un comprimido o cápsula, o cada agente puede administrarse por separado en formulaciones de dosificación oral separadas. Cuando se usan formulaciones de dosificación separadas, puede administrarse un compuesto de fórmula I y uno o más agentes activos adicionales esencialmente al mismo tiempo, es decir, conjuntamente, o en momentos escalonados separados, es decir, secuencialmente; se entiende que la terapia de combinación incluye todos estos regímenes.

Un ejemplo de combinación para el tratamiento o prevención de la arteriosclerosis puede implicar la administración de un compuesto de fórmula I o sus sales en combinación con uno o más de los segundos agentes terapéuticos activos: agentes antihiperlipidémicos; agentes que aumentan el HDL en plasma; agentes antihipercolesterolémicos, fibratos, vitaminas, aspirina y similares. Como se ha indicado anteriormente, los compuestos de fórmula I pueden administrarse en combinación con más de un agente activo adicional.

Puede observarse otro ejemplo de terapia de combinación en el tratamiento de la diabetes y de trastornos relacionados donde los compuestos de fórmula I y sus sales pueden usarse eficazmente en combinación con un

segundo agente terapéutico activo, tal como sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de α-glucosidasa, otros secretagogos de insulina, insulina así como los agentes activos descritos anteriormente, para tratar la arteriosclerosis.

Son ejemplos de segundos agentes terapéuticos sensibilizadores de insulina, agonistas de PPARγ, glitazonas, troglitazona, pioglitazona, englitazona, MCC-555, BRL 49653, biguanidas, metformin, fenformin, insulina, miméticos de insulina, sufonilureas, tolbutamida, glipizida, inhibidores de alfa-glucosidasa, acarbosa, agente que disminuye el colesterol, inhibidores de HMG-CoA reductasa, lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina, rivastatina, otras estatinas, complejantes, colestiramina, colestipol, derivados de dialquilaminoalquilo de dextrano reticulado, alcohol nicotinílico, ácido nicotínico, una sal de ácido nicotínico, agonistas de PPARα, derivados del ácido fenofíbrico, gemfibrozil, clofibrato, fenofibrato, benzafibrato, inhibidores de la absorción del colesterol, beta-sitosterol, inhibidores de acril CoA:colesterol aciltransferasa, melinamida, probucol, agonistas de PPARδ, compuestos antiobesidad, fenfluramina, dexfenfluramina, fentiraminba, sulbitramina, orlistat, inhibidores del neuropéptido Y5, agonistas de receptores β_3 adrenérgicos e inhibidores del transportador de ácidos biliares en el íleon.

Los compuestos de la presente invención y las sales, solvatos e hidratos farmacéuticamente aceptables de los mismos tienen propiedades farmacológicas valiosas y pueden usarse en composiciones farmacéuticas que contienen una cantidad terapéuticamente eficaz de un compuesto de la presente invención, o sales, ésteres o profármacos farmacéuticamente aceptables del mismo, en combinación con uno o más excipientes

farmacéuticamente aceptables. Los excipientes son sustancias inertes tales como, sin limitación, vehículos, diluyentes, cargas, agentes aromatizantes, edulcorantes, lubricantes, solubilizantes, agentes de suspensión, agentes humectantes, aglutinantes, agentes disgregantes, material de encapsulación y otros adyuvantes convencionales. La formulación apropiada depende de la vía de administración elegida. Las composiciones farmacéuticas contienen típicamente de aproximadamente un 1 a aproximadamente un 99 por ciento en peso del ingrediente activo, que es un compuesto de la presente invención.

Preferiblemente, la formulación farmacéutica está en una forma de dosificación unitaria. Una "forma de dosificación unitaria" es una unidad físicamente discreta que contiene una dosis unitaria adecuada para administración en seres humanos u otros mamíferos. Por ejemplo, una forma de dosificación unitaria puede ser una cápsula o comprimido o varias cápsulas o comprimidos. Una "dosis unitaria" es una cantidad predeterminada del compuesto activo de la presente invención, calculada para producir el efecto terapéutico deseado, en asociación con uno o más excipientes farmacéuticamente aceptables. La cantidad de ingrediente activo en una dosis unitaria puede variarse o ajustarse de aproximadamente 0,1 a aproximadamente 1000 miligramos o más de acuerdo con el tratamiento particular implicado.

El régimen de dosificación que utiliza los compuestos de la presente invención se selecciona por un especialista habitual en la medicina o en veterinaria teniendo en cuenta diversos factores, tales como, sin limitación, la especie, la edad, el peso, el sexo, el estado médico del receptor, la gravedad de la afección a tratar, la vía de administración, el nivel de función metabólica o

excretora del receptor, la forma de dosificación empleada, el compuesto particular y la sal de mismo empleada, y similares.

Preferiblemente, los compuestos de la presente invención se administran en una sola dosis diaria, o la dosis diaria total puede administrarse en dosis divididas de dos, tres o más veces al día. Cuando el suministro es a través de formas transdérmicas, la administración es continua.

Las vías adecuadas de administración de las composiciones farmacéuticas de la presente invención incluyen, por ejemplo, la administración oral, por gotas oftálmicas, rectal, transmucosa, tópica o intestinal; suministro parenteral (inyección en embolada o infusión), incluyendo inyecciones intramusculares, subcutáneas, intramedulares, así como inyecciones intratecales, intraventriculares directas, intravenosas, intraperitoneales, intranasales o intraoculares. Los compuestos de la presente invención también pueden administrarse en un sistema de suministro de fármaco dirigido, tal como en un liposoma recubierto con anticuerpo específico de células endoteliales.

Para la administración oral, los compuestos de la presente invención pueden formularse fácilmente combinando los compuestos activos con vehículos farmacéuticamente aceptables bien conocidos en la técnica. Tales vehículos permiten que los compuestos de la presente invención se formulen como comprimidos, píldoras, polvos, sellos, gránulos, grageas, cápsulas, líquidos, elixires, tinturas, geles, emulsiones, jarabes, pastas, suspensiones y similares, para ingestión oral por parte de un paciente a tratar. Las preparaciones farmacéuticas para uso oral pueden obtenerse combinando el compuesto activo con un excipiente sólido, triturando opcionalmente la mezcla

resultante y procesando la mezcla de gránulos, después de añadir auxiliares adecuados, si se desea, para obtener comprimidos o núcleos de grageas.

Para administración oral en forma de un comprimido o cápsula, el ingrediente activo puede combinarse con un vehículo farmacéuticamente aceptable no tóxico oral, tal como, sin limitación, lactosa, almidón, sacarosa, glucosa, metilcelulosa, carbonato cálcico, fosfato cálcico, sulfato cálcico, carbonato sódico, manitol, sorbitol y similares; opcionalmente, junto con agentes disgregantes, tales como, sin limitación, polivinil pirrolidona reticulada, maíz, almidón, metilcelulosa, agar, bentonita, goma xantana, ácido algínico o una sal del mismo tal como alginato sódico, y similares; y, opcionalmente, aglutinantes, por ejemplo, sin limitación, gelatina, goma arábiga, azúcares naturales, beta-lactosa, edulcorantes de maíz, gomas naturales y sintéticas, goma arábiga, tragacanto, alginato sódico, carboximetil-celulosa, polietilenglicol, ceras y similares; y, opcionalmente, agentes lubricantes, por ejemplo, sin limitación, estearato de magnesio, estearato sódico, y ácido esteárico, oleato sódico, benzoato sódico, acetato sódico, cloruro sódico, talco, y similares. Cuando una forma de unidad de dosificación es una cápsula, ésta puede contener, además de los materiales del tipo descrito anteriormente, un vehículo líquido tal como un aceite graso.

Las formulaciones en forma sólida incluyen polvos, comprimidos y cápsulas. Un vehículo sólido puede ser una o más sustancias que además pueden actuar como agentes aromatizantes, lubricantes, solubilizantes, agentes de suspensión, aglutinantes, agentes disgregantes de comprimidos y material de encapsulación.

En polvos, el vehículo es un sólido dividido finamente que se mezcla con

el ingrediente activo dividido finamente. En comprimidos, el ingrediente activo se mezcla con un vehículo que tiene las propiedades aglutinantes necesarias en proporciones adecuadas y se compacta en la forma y tamaño deseados.

Pueden estar presentes otros diversos materiales como recubrimientos o para modificar la forma física de la unidad de dosificación. Por ejemplo, los comprimidos pueden recubrirse con goma laca, azúcar o ambos. Un jarabe o elixir puede contener, además del ingrediente activo, sacarosa como agente edulcorante, metil y propilparabenos como conservantes, un colorante y un aromatizante tal como sabor de cereza o de naranja.

Las formulaciones líquidas estériles incluyen suspensiones, emulsiones, jarabes y elixires. El ingrediente activo puede disolverse o suspenderse en un vehículo farmacéuticamente aceptable, tal como agua estéril, disolvente orgánico estéril, o una mezcla tanto de agua estéril como de disolvente orgánico estéril.

El ingrediente activo también puede disolverse en un disolvente orgánico adecuado, por ejemplo, propilenglicol acuoso. Pueden realizarse otras composiciones dispersando el ingrediente activo dividido finamente en una solución de almidón acuoso o carboximetil celulosa sódica o en un aceite adecuado.

Los núcleos de grageas se proporcionan con recubrimientos adecuados. Para este propósito, pueden usarse soluciones de azúcar concentradas, que puede contener opcionalmente goma arábiga, talco, polivinil pirrolidona, gel de carbopol, polietilenglicol, y/o dióxido de titanio, soluciones de laca, y disolventes orgánicos adecuados o mezclas de disolventes. Pueden añadirse colorantes o pigmentos a los comprimidos o recubrimientos de grageas para la identificación

o para caracterizar diferentes combinaciones de dosis de compuesto activo.

Las preparaciones farmacéuticas que pueden usarse por vía oral incluyen cápsulas de ajuste por presión hechas de gelatina, así como cápsulas selladas herméticamente blandas hechas de gelatina y un plastificante tal como glicerol o sorbitol. Las cápsulas de ajuste por presión pueden contener los ingredientes activos en mezcla con una carga tal como lactosa, aglutinantes tales como almidones, y/o lubricantes, tales como talco o estearato de magnesio, y/o opcionalmente, estabilizadores. En las cápsulas blandas, los compuestos activos pueden disolverse o suspenderse en líquidos adecuados, tales como aceites grasos, parafina líquida, o polietilenglicoles líquidos. Además, pueden añadirse estabilizadores.

Todas las formulaciones para administración oral deben estar en dosificaciones adecuadas para tal administración. Las composiciones particularmente adecuadas para administración oral son formas de dosificación unitaria tales como comprimidos y cápsulas.

Para administración parenteral, los compuestos de la presente invención o sus sales pueden combinarse con medios acuosos u orgánicos estériles para formar soluciones o suspensiones inyectables. Las formulaciones para inyección pueden presentarse en forma de dosificación unitaria, tal como en ampollas o en recipientes de múltiples dosis, con un conservante añadido. Las composiciones pueden tomar formas tales como suspensiones, soluciones o emulsiones en vehículos oleosos o acuosos, y pueden contener agentes de formulación tales como agentes de suspensión, estabilizadores y/o dispersantes. Las formas farmacéuticas adecuadas para uso inyectable incluyen soluciones o dispersiones acuosas estériles y polvos estériles para la

preparación extemporánea de soluciones o dispersiones inyectables estériles. En todos los casos, la forma debe ser estéril y debe ser líquida para que pueda inyectarse. Debe ser estable en las condiciones de fabricación y almacenamiento y debe conservarse frente a cualquier contaminación. El vehículo puede ser un disolvente o un medio de dispersión que contiene, por ejemplo, agua, preferiblemente en tampones fisiológicamente compatibles tales como solución de Hank, solución de Ringer o tampón fisiológico salino, etanol, poliol (por ejemplo, glicerol, propilenglicol y polietilenglicol líquido, propilenglicol y polietilenglicol líquido), mezclas adecuadas de los mismos, y aceites vegetales. En las condiciones habituales de almacenamiento y uso, estas preparaciones contienen un conservante para prevenir el crecimiento de microorganismos.

Después, las soluciones inyectables preparadas de esta forma pueden administrarse por vía intravenosa, intraperitoneal, subcutánea o intramuscular, prefiriéndose la administración intramuscular en seres humanos.

Para administración transmucosa, en la formulación se usan penetrantes apropiados para la barrera a penetrar. Tales penetrantes generalmente se conocen en la técnica. Los compuestos activos también pueden administrarse por vía intranasal, por ejemplo, en gotas líquidas o como una pulverización.

Para administración bucal, las composiciones pueden tomar la forma de comprimidos o grageas formuladas de una forma convencional.

Para administración por inhalación, los compuestos para uso de acuerdo con la presente invención se suministran convenientemente en forma de un inhalador de polvo seco, o en una presentación de pulverización de aerosol desde envases presurizados o un nebulizador, con el uso de un propelente

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adecuado, por ejemplo, diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, dióxido de carbono u otro gas adecuado. En el caso del aerosol presurizado, la unidad de dosificación puede determinarse proporcionando una válvula para suministrar una cantidad medida. Pueden formularse cápsulas y cartuchos de gelatina para uso en un inhalador o insuflador que contienen una mezcla en polvo del compuesto y una base de polvo adecuada tal como lactosa o almidón.

Las composiciones farmacéuticas de la presente invención pueden fabricarse de una forma que sea conocida, por ejemplo, mediante procesos de mezcla, disolución, granulación, fabricación de grageas, levigación, emulsión, encapsulación, inclusión o liofilización convencionales.

En la fabricación de las composiciones de la presente invención, el ingrediente activo normalmente se mezclará con un vehículo, o se diluirá por un vehículo, o se encerrará dentro de un vehículo que puede estar en forma de una cápsula, sello, papel u otro recipiente. Cuando el vehículo sirve como diluyente, éste puede ser un sólido, un sólido liofilizado o una pasta, un semisólido o un material líquido que actúa como vehículo, o puede estar en forma de comprimidos, píldoras, polvos, grageas, elixires, suspensiones, emulsiones, soluciones, jarabes, aerosoles (como un sólido o en un medio líquido), o pomadas, que contienen, por ejemplo, hasta un 10% en peso del compuesto activo. Los compuestos de la presente invención se formulan preferiblemente antes de la administración.

Las siguientes formulaciones farmacéuticas 1 a 8 son únicamente ilustrativas y no pretenden limitar el alcance de la invención de forma alguna. "Ingrediente Activo" se refiere a un compuesto de la presente invención de

acuerdo con la fórmula I y/o la o sales del mismo.

Formulación 1

Se preparan cápsulas de gelatina dura usando los siguientes ingredientes:

	Cantidad (mg/cápsula)
Ingrediente Activo	250
Almidón, seco	200
Estearato de Magnesio	10
Total	460 mg

Formulación 2

Se prepara un comprimido usando los ingredientes que se muestran a continuación:

	Cantidad (mg/comprimido)
Ingrediente Activo	250
Celulosa, microcristalina	400
Dióxido de silicio, sin volátiles	10
Ácido esteárico	5
Total	665 mg

Los componentes se mezclan y se comprimen para formar comprimidos que pesan cada uno 665 mg.

Formulación 3

Se prepara una solución de aerosol que contiene los siguientes componentes:

	Peso
Ingrediente Activo	0,25
Etanol	25,75
Propelente 22 (clorodifluorometano)	74,00
Total	100.000

El Ingrediente Activo se mezcla con etanol y la mezcla se añade a una porción del propelente 22, se enfría a 30°C y se transfiere a un aparato de rellenado. Después, la cantidad requerida se introduce en un recipiente de acero inoxidable y se diluye con lo que sobra del propelente. Después se fijan unidades de válvula al recipiente.

Formulación 4

Se fabrican comprimidos, conteniendo cada uno 60 mg de Ingrediente activo, como sigue:

Ingrediente Activo	60 mg
Almidón	45 mg
Celulosa microcristalina	35 mg
Polivinilpirrolidona (como solución al 10% en agua)	4 mg

Carboximetil almidón sódico	4,5 mg
Estearato de *magnesio*	0,5 mg
Talco	1 mg
Total	150 mg

El ingrediente activo, el almidón y la celulosa se pasan a través de un tamiz U.S. de malla Nº 45 y se mezclan minuciosamente. La solución acuosa que contienen polivinilpirrolidona se mezcla con el polvo resultante, y después, la mezcla se pasa a través de un tamiz U.S. de malla Nº 14. Los gránulos producidos de esta forman se secan a 50ºC y se pasan a través de un tamiz U.S. de malla Nº 18. Después, el carboximetil almidón sódico, el estearato de magnesio y el talco, pasados previamente por un tamiz U.S. de malla Nº 60, se añaden a los gránulos que, después de mezclarse, se comprimen en una máquina de comprimidos para producir comprimidos que pesan cada uno 150 mg.

Formulación 5

Se fabrican cápsulas, que contienen cada una 80 mg de Ingrediente Activo, como sigue:

Ingrediente Activo	80 mg
Almidón	59 mg
Celulosa microcristalina	59 mg
Estearato de Magnesio	2 mg

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Total	200 mg

El Ingrediente activo, la celulosa, el almidón y el estearato de magnesio se mezclan, se pasan a través de un tamiz U.S. de malla Nº 45 y se introducen en cápsulas de gelatina dura en cantidades de 200 mg.

Formulación 6

Se fabrican supositorios, que contienen cada uno 225 mg de Ingrediente Activo, como sigue:

Ingrediente activo	225 mg
Glicéridos de ácidos grasos saturados	2.000 mg
Total	2.225 mg

El Ingrediente Activo se pasa a través de un tamiz U.S. de malla Nº 60 y se suspende en los glicéridos de ácidos grasos saturados previamente fundidos usando el calor mínimo necesario. Después, la mezcla se vierte en un molde de supositorios de capacidad nominal de 2 g y se deja enfriar.

Formulación 7

Se fabrican suspensiones que contienen cada una 50 mg de Ingrediente Activo por dosis de 5 ml como sigue:

Ingrediente Activo	50 mg
Carboximetil celulosa sódica	50 mg
Jarabe	1,25 ml
Solución de ácido benzoico	0,10 ml

Aroma	c.v.
Color	c.v.
Agua purificada hasta el total	5 ml

El Ingrediente Activo se pasa a través de un tamiz U.S. de malla Nº 45 y se mezcla con la carboximetil celulosa sódica y el jarabe para formar una pasta sin grumos. La solución de ácido benzoico, el aroma y el color se diluyen con una porción de agua y se añaden, con agitación. Después se añade suficiente agua para producir el volumen requerido.

Formulación 8

Puede prepararse una formulación intravenosa como sigue:

Ingrediente Activo	100 mg
Solución salina isotónica	1.000 ml

La solución de los materiales anteriores generalmente se administra por vía intravenosa a un sujeto a una velocidad de 1 ml por minuto.

En otra realización de la presente invención, el compuesto se radiomarca, tal como con carbono-14 o tritio. Dichos compuestos radiomarcados o tritiados son útiles como patrones de referencia para ensayos *in vitro* para identificar nuevos agonistas de PPARα y PPARγ.

Estudios de Unión y Cotransfección

La potencia *in vitro* de compuestos en la modulación de los receptores PPARγ , PPARα y PPARδ se determina por los procedimientos que se detallan más adelante. Se realiza una unión dependiente de ADN (unión-ABCD) usando

la tecnología de Ensayo de Centello por Proximidad (SPA) con receptores PPAR. Se usan agonistas de PPARα y PPARγ marcados con tritio como radioligandos para generar curvas de desplazamiento y valores de CI_{50} con compuestos de la presente invención. Los ensayos de contransfección se realizan en células CV-1. El plásmido indicador contiene un promotor PPRE y TK de la acilCoA oxidasa (AOX) cadena arriba del ADNc indicador de luciferasa. Los PPAR y RXRα apropiados se expresan constitutivamente usando plásmidos que contienen el promotor de CMV. Como ocurre con PPARα y PPARβ, la interferencia por el PPARγ endógeno en las células CV-1 supone un problema; para eliminar tal interferencia, se usa un sistema quimérico GAL4 en el que el dominio de unión al ADN del PPAR transfectado se reemplaza por el de GAL4, y se utiliza el elemento de respuesta GAL4 en lugar del AOX PPRE. La eficacia de contransfección se determina con respecto a las moléculas de referencia del agonista de PPARα y del agonista de PPARγ. Las eficacias se determinan por medio de un ajuste informático a una curva de concentración-respuesta, o en algunos casos a una sola concentración alta de agonista (10 μM). Un intervalo típico para la determinación de la concentración (CI_{50}) es de 1 nM a 10 μM. Para los estudios de unión o contransfección con receptores distintos de PPAR, se realizan ensayos similares usando ligandos, receptores o construcciones indicadoras, etc., apropiadas para ese receptor particular.

Estos estudios se realizan para evaluar la capacidad de los compuestos de la presente invención para unirse a y/o activar diversos factores de transcripción nuclear, particularmente huPPARa ("hu" indica "humano"), huPPARγ y huPPARδ. Estos estudios proporcionan datos *in vitro* en relación

con la eficacia y selectividad de los compuestos de la presente invención. Además, los datos de unión y cotransfección para los compuestos de la presente invención se comparan con los datos correspondientes de compuestos de referencia que actúan sobre huPPARα o huPPARγ. El intervalo típico de concentraciones para la unión es de 1 nM a 10 μM. Se determina la concentración de compuesto de ensayo requerida para conseguir un 50% de la activación máxima del PPARα ($CI_{50}\alpha$) y PPARγ ($CI_{50}\gamma$).

Evaluación de los Niveles de Triglicéridos y Colesterol en Ratones Transgénicos HuapoAI

Se encerraron cinco ratones macho de cinco a seis semanas de edad, transgénicos para apoAI humana, [C57B1/6-tgn(apoa1)1rub, Jackson Laboratory, Bar Harbor, ME] por jaula (10"x20"x8" con un lecho de virutas de álamo) con alimento (Purina 5001) y agua disponible en todo momento. Después de un periodo de aclimatación de 2 semanas, los animales se identificaron individualmente por incisiones en la oreja, se pesaron y se asignaron a grupos en función del peso corporal. Empezando la mañana siguiente, los ratones recibieron dosificaciones diarias por medio de una sonda oral durante 7 días usando una aguja de alimentación desechable curvada de 1,5" de calibre 20. Los tratamientos son compuestos de ensayo (30 mg/kg), un control positivo (fenofibrato, 100 mg/kg) o vehículo [carboximetilcelulosa al 1% (p/v)/Tween 80 al 0,25% (p/v); 0,2 ml/ratón]. Antes de terminar el día 7, los ratones se pesaron y recibieron la dosificación. Tres horas después de la dosificación, los animales se anestesiaron por inhalación de isoflurano (2-4%) y se obtuvo sangre mediante una punción cardíaca (0,7-1,0 ml). La sangre entera se transfirió a tubos separadores de suero (Vacutainer SST), se enfrió en hielo

y se dejó coagular. El suero se obtuvo después de una centrifugación a 4°C y se congeló hasta el análisis de los triglicéridos, el colesterol total, los niveles de compuesto y el perfil de lipoproteínas en suero mediante cromatografía líquida de proteína rápida (FPLC) acoplada a un sistema de detección en serie. Después de sacrificio por dislocación cervical, se escindieron y se pesaron el hígado, el corazón y las capas de grasa del epidídimo.

Los animales que recibieron vehículo tuvieron valores medios de triglicéridos de aproximadamente 60 a 80 mg/dl, que se redujeron por el fenofibrato del control positivo (33-58 mg/dl con una reducción media del 37%). Los animales que recibieron vehículo tuvieron valores de colesterol total medios en suero de aproximadamente 140 a 180 mg/dl, que aumentaron por el fenofibrato (de aproximadamente 190 a 280 mg/dl con una elevación media del 41%). Cuando se sometió al análisis de FPLC, el suero reunido de ratones transgénicos con huApoAI tratados con vehículo tenía un área del pico de colesterol asociado a lipoproteínas de alta densidad (HDLc) que variaba de 47v-seg a 62v-seg. El fenofibrato aumentó la cantidad de HDLc (68-96v-seg con un aumento medio en porcentaje del 48%). Los compuestos de ensayo se evaluaron en términos del aumento en del área bajo la curva. Los compuestos representativos de la presente invención se ensayaron usando los procedimientos anteriores o procedimientos sustancialmente similares.

Evaluación de los Niveles de Glucosa en Ratones db/db

Se encerraron ratones diabéticos macho de cinco semanas de edad (db/db) [C57BlKs/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor, ME] o compañeros de camada sin diabetes (db+) en grupos de 6 por jaula (10"x20"x8" con un lecho de virutas de álamo) con alimento (Purina 5015) y

agua disponible en todo momento. Después de un periodo de aclimatación de dos semanas, los animales se identificaron individualmente por incisiones en la oreja, se pesaron y se sometieron a extracción de muestras de sangre a través de la vena de la cola para determinar los niveles de glucosa iniciales. Se extrajo sangre (100 µl) de animales que no habían permanecido en ayunas enrollando cada ratón en una toalla, cortando la punta de la cola con un escalpelo y dejando caer la sangre desde la cola en un tubo capilar heparinizado equilibrado en el borde de la mesa. La muestra se descargó en un microtainer heparinizado con un separador de gel (VWR) y se retuvo en hielo. Se obtuvo plasma después de una centrifugación a 4°C y la glucosa se midió inmediatamente. El plasma restante se congeló hasta el final del experimento, y la glucosa y los triglicéridos se ensayaron en todas las muestras. Los animales se agruparon en función de los niveles de glucosa iniciales y de los pesos corporales. Empezando la mañana siguiente, los ratones recibieron una dosificación diaria durante 7 días por medio de una sonda oral, usando una aguja de alimentación desechable curvada de 1,5" de calibre 20. Los tratamientos son compuestos de ensayo (30 mg/kg), un agente de control positivo (30 mg/kg) o vehículo [carboximetilcelulosa al 1% (p/v)/Tween 80 al 0,25% (p/v); 0,3 ml/ratón]. El día 7, los ratones se pesaron y se sometieron a extracción de sangre (de la vena de la cola) durante aproximadamente 3 horas después de la dosificación. Veinticuatro horas después de la de la 7ª dosis (es decir, el día 8), se volvió a extraer sangre de los animales (vena de la cola). Las muestras obtenidas a partir de animales conscientes los días 0, 7 y 8 se ensayaron para determinar la glucosa. 24 horas después de la extracción de sangre, los animales se pesaron y recibieron la última dosis. Tres horas

después de la dosificación del día 8, los animales se anestesiaron por inhalación de isoflurano, y se obtuvo sangre por punción cardíaca (0,5-0,7 ml). La sangre entera se transfirió a tubos separadores de suero, se enfrió en hielo y se dejó coagular. El suero se obtuvo después de una centrifugación a 4°C y se congeló hasta que se analizaron los niveles de compuestos. Después del sacrificio por dislocación cervical, se escindieron y se pesaron el hígado, el corazón y las capas de grasa del epidídimo.

Los animales que recibieron vehículo tuvieron valores de triglicéridos medios de aproximadamente 170 a 230 mg/dl, que se redujeron mediante el control positivo de PPARγ (de aproximadamente 70 a 120 mg/dl con una reducción media del 50%). Los ratones macho db/db son hiperglucémicos (glucosa media de aproximadamente 680 a 730 mg/dl en 7° día del tratamiento), mientras que los animales no diabéticos tenían niveles de glucosa medios entre aproximadamente 190 y 230 mg/dl. El tratamiento con el agente de control positivo redujo significativamente la glucosa (de aproximadamente 350 a 550 mg/dl con una disminución media hacia la normalización del 56%).

La glucosa se mide colorimétricamente usando reactivos adquiridos en el mercado (Sigma N° 315-500). De acuerdo con los fabricantes, los procedimientos se modifican a partir de trabajos publicados (McGowan et al., *Clin. Chem*, 20:470-5 (1974) y Keston A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129ª Meeting ACS, 31C (1956); y en función de la liberación de un mol de peróxido de hidrógeno para cada mol de analito acoplado con una reacción de color descrita primero por Trinder (Trinder, P. *Ann. Clin Biochem*, 6:24 (1969)). La absorbancia del colorante producido está relacionada linealmente con el analito en la muestra.

Los ensayos se modifican adicionalmente para uso en un formato de 96 pocillos. Los patrones (Sigma Nº 339-11, Sigma Nº 16-11 y Sigma Nº CC0534 para glucosa, triglicéridos y colesterol total, respectivamente), el plasma de control de calidad (Sigma Nº A2034) y las muestras (2 ó 5 µl/pocillo) se miden por duplicado usando 200 µl de reactivo. Una alícuota adicional de muestra, introducida en un tercer pocillo con una pipeta y diluida en 200 µl de agua, proporcionó un blanco para cada espécimen. Las placas se incuban a temperatura ambiente (18, 15 y 10 minutos para la glucosa, triglicéridos y colesterol total, respectivamente) en un agitador de placas y se lee la absorbancia a 500 nm (glucosa y colesterol total) o 540 nm (triglicéridos) en un lector de placas. La absorbancia de la muestra se compara con una curva patrón (100-800, 10-500 y 100-400 mg/dl para glucosa, triglicéridos y colesterol total, respectivamente). Los valores para la muestra de control de calidad están consistentemente en el intervalo esperado y el coeficiente de variación para las muestras está por debajo del 10%. Todas las muestras de un experimento se ensayan al mismo tiempo para minimizar la variabilidad entre ensayos.

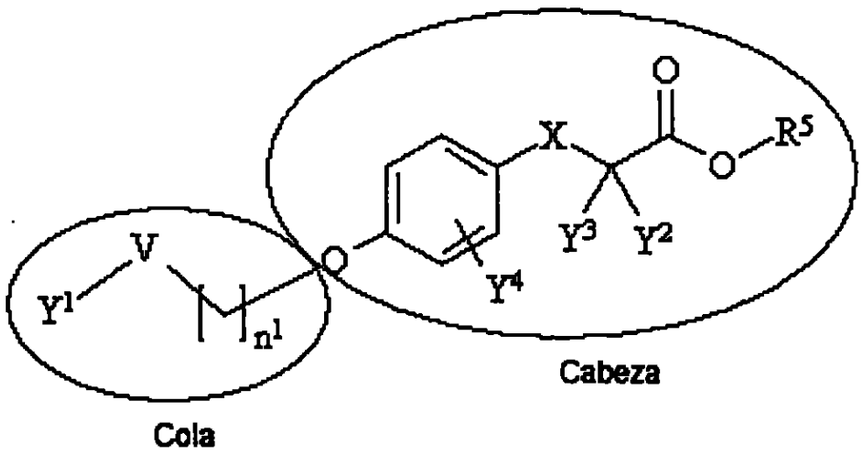
Se separan las lipoproteínas del suero y el colesterol se cuantifica con un sistema de detección en línea. La muestra se aplica a una columna de exclusión molecular 10/30 Superose® 6 HR (Amersham Pharmacia Biotech) y se eluye con solución salina tamponada con fosfato-EDTA a 0,5 ml/minuto. El reactivo de colesterol (Roche Diagnostics Chol/HP 704036) a 0,16 ml/min se mezcla con el efluente de la columna mediante una conexión en T y la mezcla se pasa a través de un reactor de tubos soldados de 15 m x 0,5 mm sumergido en un baño de agua a 37°C. El producto coloreado producido en presencia de colesterol se controla en la corriente de flujo a 505 nm y el voltaje análogo del

control se convierte en una señal digital para la recogida y el análisis. El cambio en el voltaje que corresponde al cambio en la concentración de colesterol se representa frente al tiempo, y se calcula el área bajo la curva correspondiente a la elución de VLDL, LDL y HDL (Perkin Elmer Turbochrome software).

Los compuestos de la presente invención pueden prepararse de acuerdo con los procedimientos de los siguientes esquemas y ejemplos, que pueden ilustrar además detalles para la preparación de los compuestos de la presente invención. Los compuestos ilustrados en los esquemas y ejemplos, sin embargo no se han construido como formadores del único género que se considera como la presente invención.

Esquema de Reacción General:

Los compuestos de la presente invención, en general, pueden prepararse de acuerdo con los Esquemas de Reacción descritos a continuación. Cuando se describen varios aspectos de los presentes compuestos, los términos "Cola" y "Cabeza" se usan como se ilustra el concepto a continuación.



Esquema de Reacción 1:

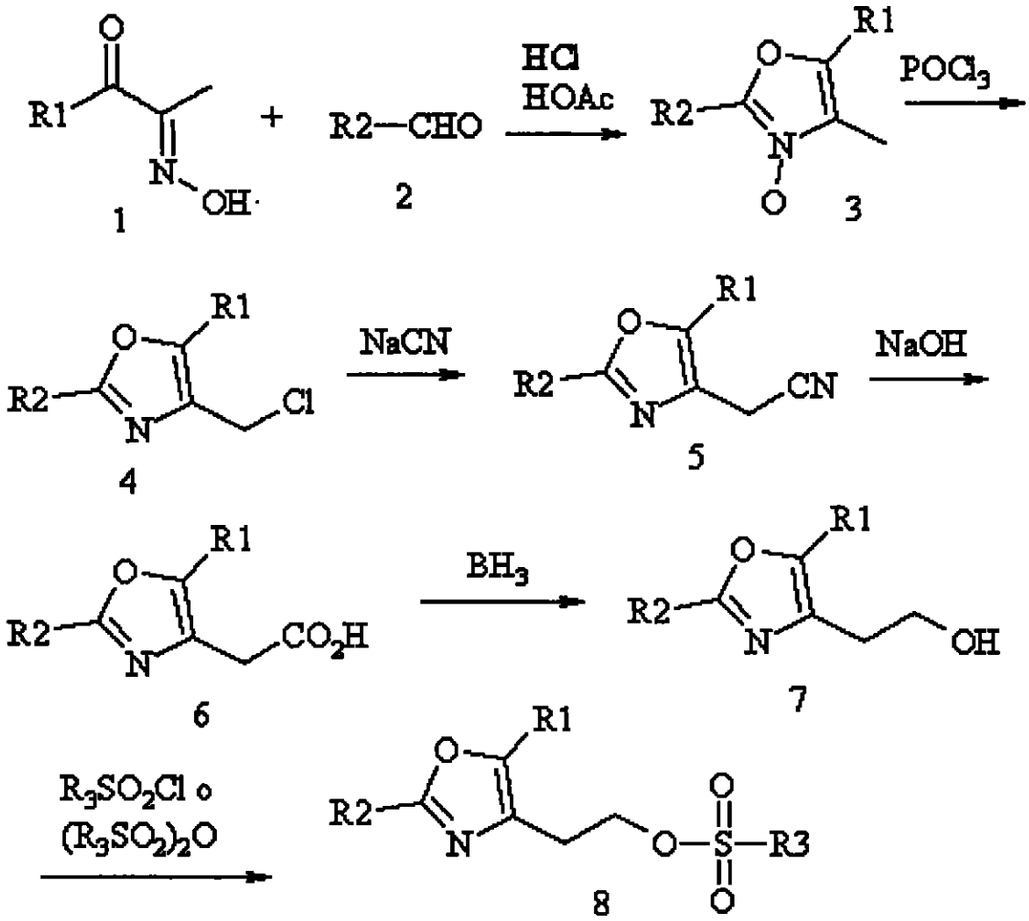


Z_1 = grupo saliente

Cabeza'=pieza de cabeza modificada como muestra la sustitución OH

Como se muestra en el esquema de reacción 1, los compuestos de la presente invención, en general, pueden dividirse en regiones de Cola y Cabeza en las que una pieza de cabeza nucleófila se acopla con una pieza de cola electrófila. Estas regiones además pueden modificarse como se muestra en los siguientes esquemas de reacción.

Esquema de Reacción 2: Pieza de cola de oxazol



R1 es H, alquilo C_1-C_6, alcoxi C_1-C_6, halo, haloalquilo o haloalcoxi;

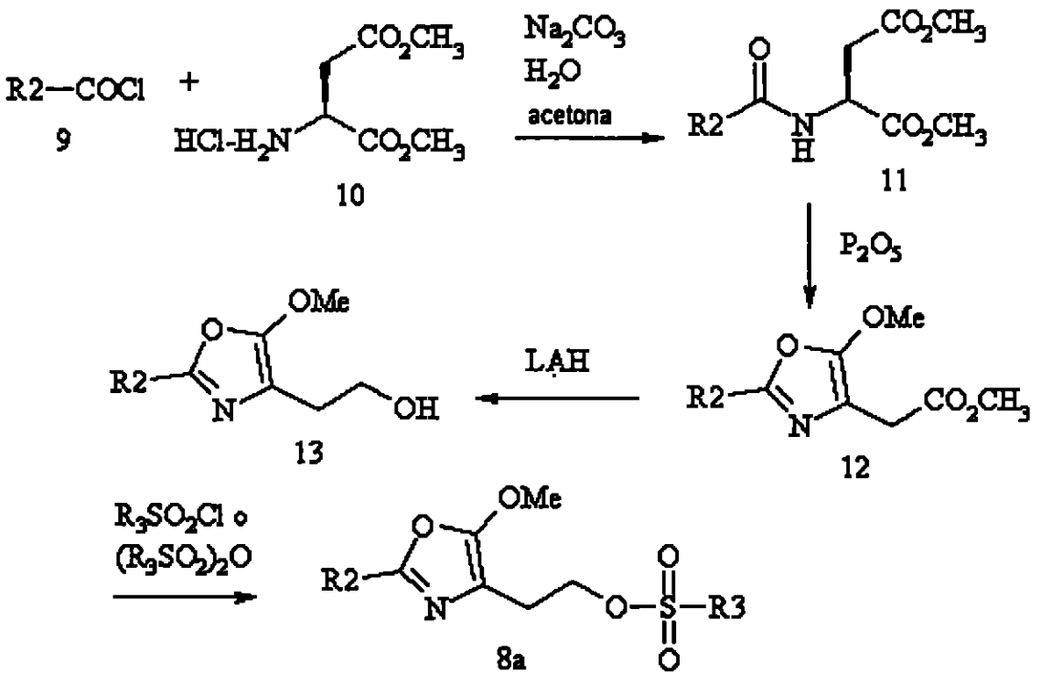
R2 es Y^{1a};

R3 es alquilo (metilo) o tolilo.

Como se muestra en el Esquema de Reacción 2, una pieza de cola de oxazol intermedio puede prepararse por una condensación de dionamonoxima (1) con aldehído (2) tal como bromobenzaldehído en presencia de un ácido tal como ácido clorhídrico o ácido acético para dar un compuesto N-óxido de oxazol (3). El n-óxido de oxazol después se trata con oxicloruro de fósforo en

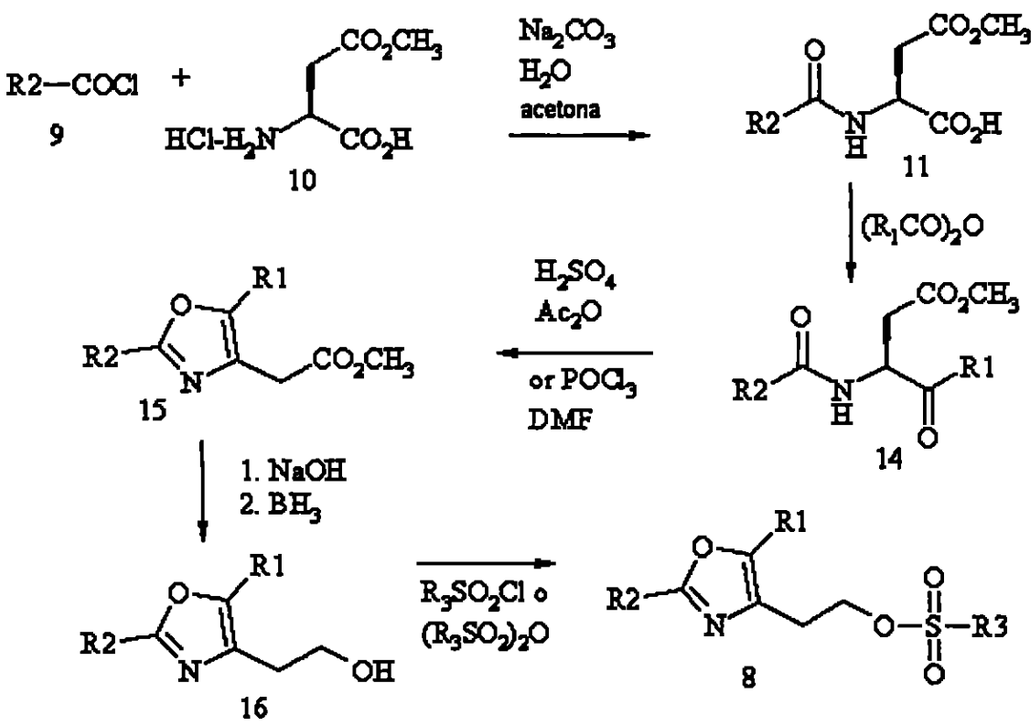
un disolvente orgánico para formar oxazol sustituido con clorometilo (4). El compuesto (4) se trata adicionalmente con un cianuro para formar un compuesto de cianometil oxazol (5). El grupo ciano del compuesto (5) se convierte en un grupo de ácido carboxílico por tratamiento con un hidróxido de metal alcalino tal como NaOH para formar un oxazol sustituido con carboximetilo (6), que se trata adicionalmente con un agente reductor de ácido carboxílico, tal como borano o hidruro de litio y aluminio (LAH) para formar el compuesto (7). El compuesto (7) puede convertirse en un oxazolil sulfonil éster (8) en presencia de una base por tratamiento con haluro de sulfonilo o un anhídrido de sulfonilo (R_3SO_2Cl o $(R_3SO_2)_2O$), tal como anhídrido de tosilo, anhídrido de mesilo, cloruro de tosilo o cloruro de mesilo.

Esquema de Reacción 3: Piezas de cola de oxazol



Como alternativa, puede prepararse un intermedio de pieza de cola de oxazol como se muestra en el Esquema de Reacción 3. Se hace reaccionar cloruro de ácido (9) con éster dimetílico del ácido L-aspártico (10) para dar el compuesto de amida (11), que experimenta ciclación para formar un anillo de oxazol (12) por tratamiento con un agente deshidratante tal como P_2O_5. El compuesto de éster (12) se reduce por tratamiento con LAH para dar el alcohol (13), que después se convierte en el oxazolil sufonil éster (8a) como se ha descrito en el Esquema de Reacción 2.

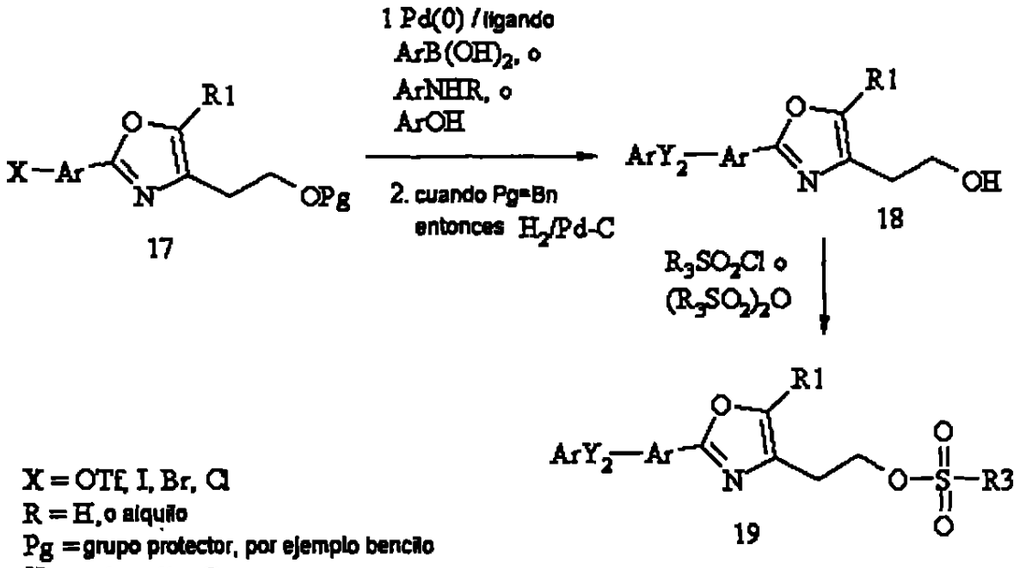
Esquema de Reacción 4: Piezas de cola de oxazol



En el Esquema de Reacción 4 se muestra otra ruta para un intermedio de pieza de cola de oxazol. Se hace reaccionar cloruro de ácido (9) y monometil éster del ácido L-aspártico (10) para dar el compuesto de amida (11), que se hace reaccionar adicionalmente para dar la cetona (14). El

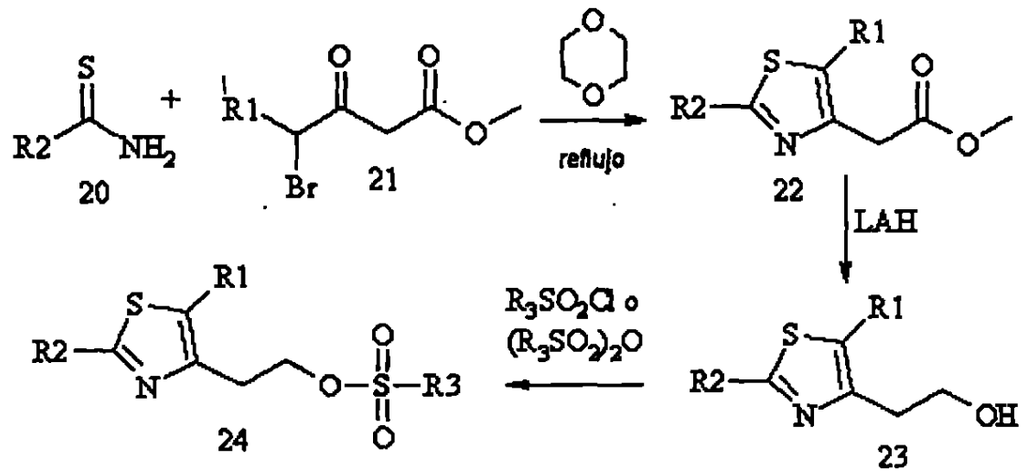
compuesto de cetona experimenta una ciclación en presencia de un agente deshidratante tal como $POCl_3$ o H_2SO_4/anhídrido acético para formar el anillo de oxazol (15). El compuesto (15) experimenta reducción para dar el alcohol (16), que después se convierte en el oxazol sulfonil éster (8) descrito anteriormente en el Esquema de Reacción 2.

Esquema de Reacción 5: Pieza de cola de oxazol



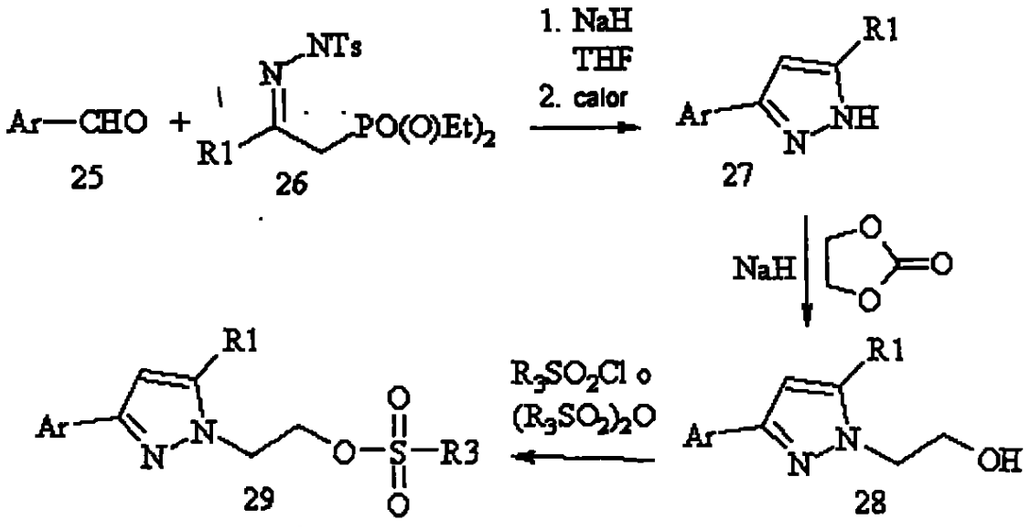
En el Esquema de Reacción 5 se muestra otra ruta para un intermedio de pieza de cola de oxazol. El compuesto de oxazol (17) puede experimentar una reacción de acoplamiento en presencia de un catalizador de paladio con un ácido arilborónico, alcohol arílico o aril amina seguido de desprotección para producir el compuesto correspondiente (18). El compuesto (18) después se convierte en el oxazolil sulfonil éster (19) como se ha descrito anteriormente en el Esquema de Reacción 2.

Esquema de Reacción 6: Pieza de cola de tiazol



Como se muestra en el esquema de reacción 6, un intermedio de pieza de cola de tiazol pueden prepararse por condensación del compuesto (20) con bromo alquil éster (21) en presencia de 1,4-dioxano seguido de ciclación para dar el compuesto de tiazol (22). El tiazol (22) después se experimenta una reducción de éster para dar el alcohol (13), que se convierte adicionalmente en el tiazol sulfonil éster (8) como se ha descrito anteriormente en el Esquema de Reacción 2.

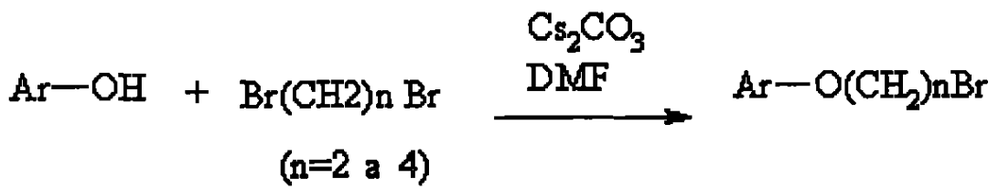
Esquema de Reacción 7: Pieza de cola de pirazol



Ar = Y[1a]

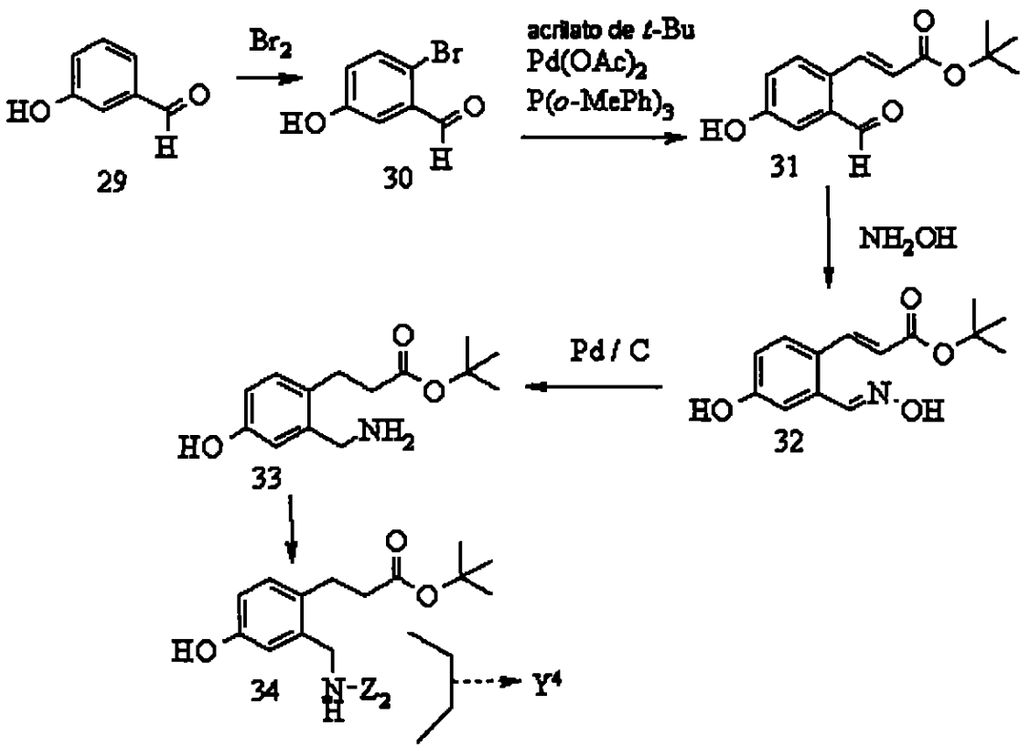
Como se muestra en el Esquema de Reacción 7, un intermedio de pieza de cola de pirazol puede prepararse por condensación de un arilaldehído (25) con el compuesto (26) en presencia de una base seguido de ciclación para dar el compuesto de pirazol (27). El compuesto (27) se trata con carbonato de etileno en presencia de una base tal como NaH para dar el compuesto alquilado (28), que después se convierte en el pirazol sulfonilo éster (29) como ha descrito anteriormente en el esquema de reacción 2.

Esquema de Reacción 8: Preparación de bromuro de aril éter



El Esquema de Reacción 8 muestra la preparación de bromuro de aril éter por una reacción de sustitución nucleófila de un alcohol arílico con un dibromuro en presencia de una base.

Esquema de Reacción 9: Preparación de dihidrocinamato de aminometilo

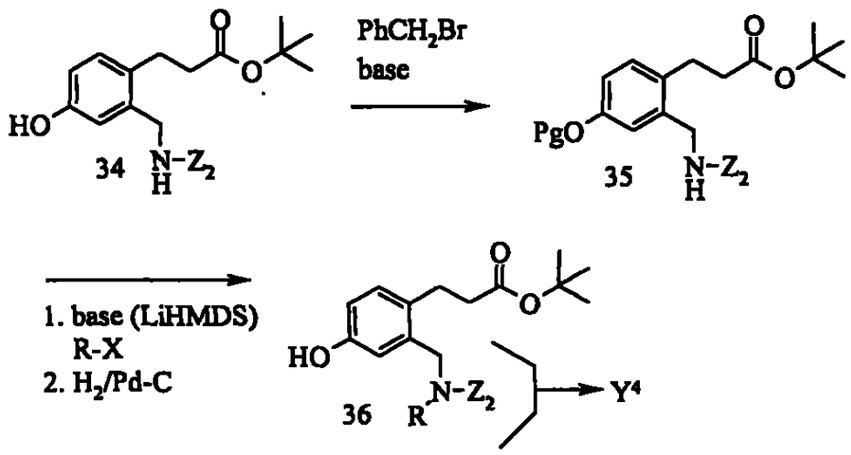


Z_2 = COR, CONHR, CSNHR, COOR, SO_2R;
donde R se selecciona entre Y^7

El Esquema de Reacción 9 muestra la ruta de síntesis para preparar piezas de cabeza de dihidrocinamato de aminometilo. Se hace reaccionar 3-hidroxibenzaldehído (29) con bromuro para dar 2-bromo-5-hidroxibenzaldehído (30), que después se acopla para dar acrilato de t-butilo para dar el compuesto (31). El compuesto (31) se trata con NH_2OH para dar la oxima (32), que experimenta hidrogenación para dar el dihidrocinamato de aminometilo (33).

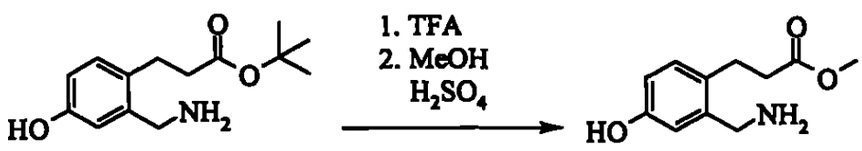
Pueden introducirse diversos grupos funcionales (Z_2) en la porción aminometilo del compuesto (33) para producir el compuesto (34).

Esquema de Reacción 10: Pieza de cabeza de N-alquilo



Como se muestra en el Esquema de Reacción 10, la porción aminometilo del compuesto de pieza de cabeza (34) puede modificarse adicionalmente. El fenol (34) se protege con un grupo protector tal como un grupo bencilo para dar el compuesto (35). El compuesto (35) experimenta una reacción de sustitución nucleófila con un haluro de alquilo (RX) en condiciones básicas seguido de una desprotección para dar el compuesto de fenol (36).

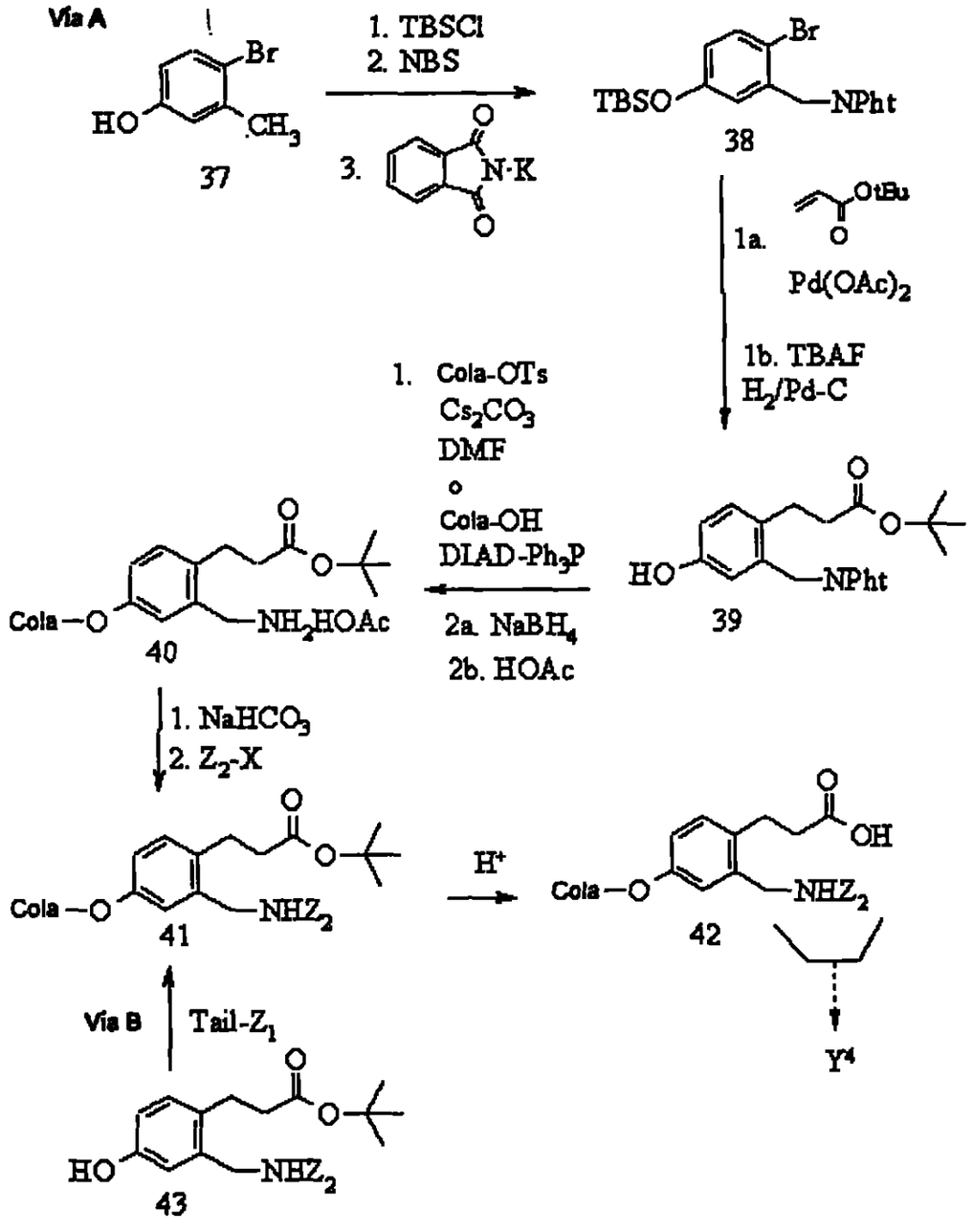
Esquema de Reacción 11: Transesterificación



El Esquema de Reacción 11 ilustra una reacción de transesterificación del compuesto como se ha mostrado anteriormente. El éster *terc*-butílico puede

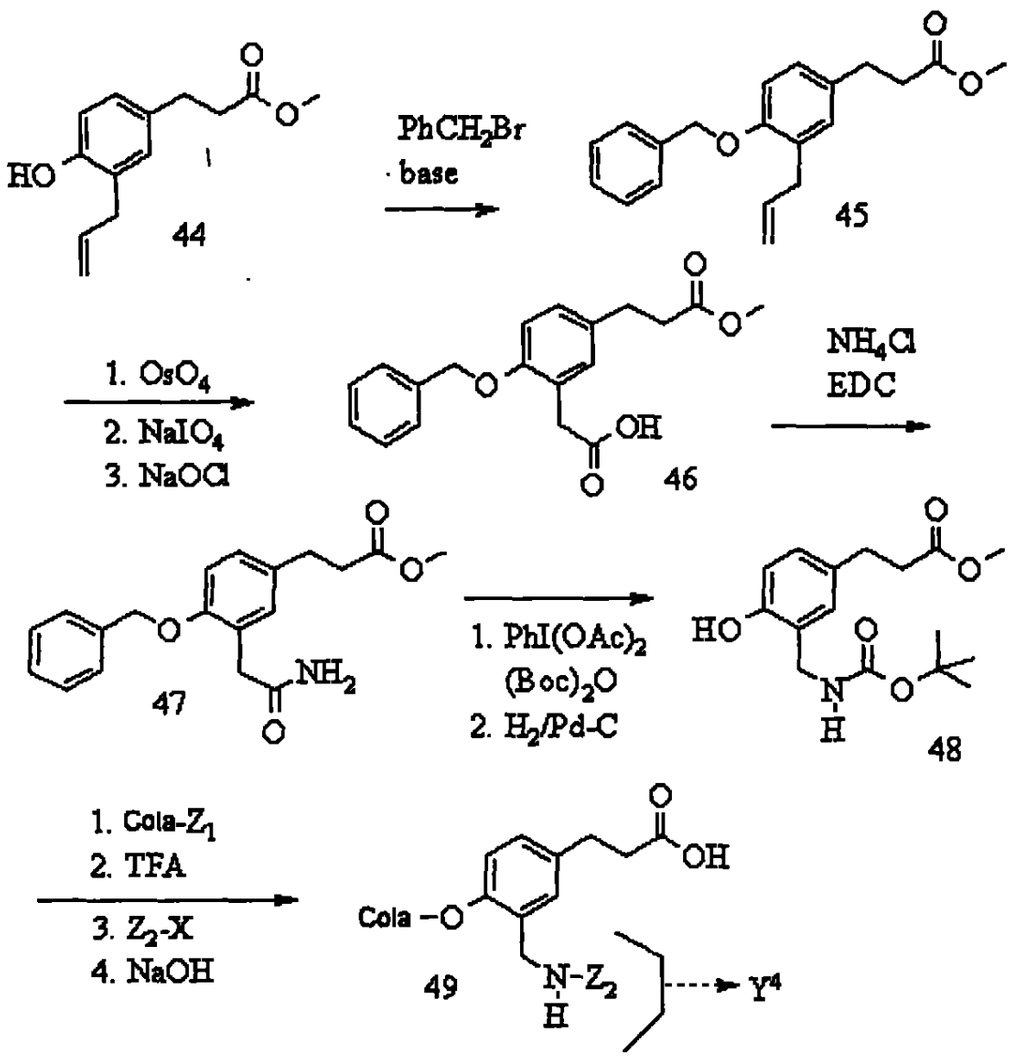
escindirse en condiciones ácidas tal como en TFA. El grupo de ácido carboxílico correspondiente puede re-esterificarse con un alcohol apropiado tal como metanol en presencia de un ácido tal como H_2SO_4.

Esquema de Reacción 12: Acoplamiento de pieza de cabeza con dihidrocinamatos de aminometilo



Como se muestra en el Esquema de Reacción 12, pueden modificarse piezas de cabeza y piezas de cola para introducir diversos grupos funcionales. En la vía A, El grupo protector (TBS) primero se une al fenol de compuesto (37) y después seguido de la bromación del radical y seguido de la alquilación con ftalimida potásica produce el compuesto (38). El compuesto (38) experimenta una reacción de acoplamiento de Heck con acrilato de *terc*-butilo en presencia de un catalizador de paladio y después la desprotección del grupo sililo seguido de hidrogenación para dar el compuesto (39). El compuesto (39) se acopla con una pieza de cola y la retirada del grupo ftaloílo produce el compuesto (40). Después de la neutralización, la función amino de (40) puede modificarse para dar (41). La hidrólisis facilitada en condiciones ácidas da (42). Como alternativa, como se muestra en la vía B, el compuesto (42) puede obtenerse por acoplamiento de piezas de cabeza (43) con una pieza de cola para dar el compuesto (41) seguido de hidrólisis de éster.

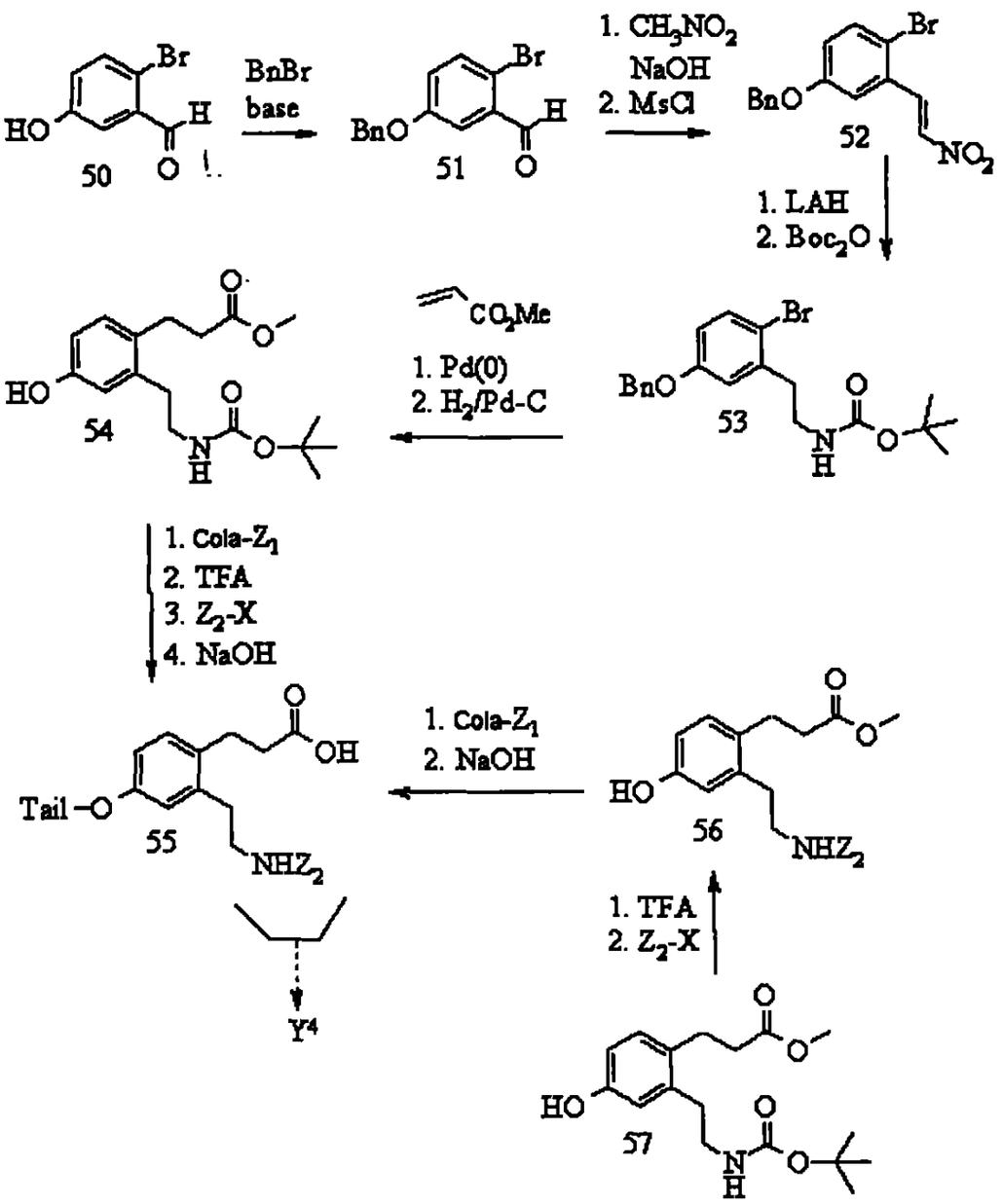
Esquema de Reacción 13: Síntesis de dihidrocinamato de meta-aminometilo



El Esquema de Reacción 13 muestra una síntesis para dihidrocinamatos de aminometilo meta-sustituidos. Un grupo protector tal como bencilo se une al fenol del compuesto (44) para dar el compuesto protegido (45). El compuesto (45) experimenta formación de glicol seguido de reacciones de escisión y oxidación para dar el compuesto de ácido carboxílico (46), que después se convierte en el compuesto de amida (47). El compuesto (47) experimenta una

redisposición y posterior protección de amina con anhídrido de Boc seguido de desprotección de éter bencílico para producir el fenol (48). El compuesto (48) se acopla con una pieza de cola seguido de desprotección para dar el intermedio, que después se experimenta una modificación adicional en la porción aminometilo del compuesto, seguido de hidrólisis para dar el compuesto (49).

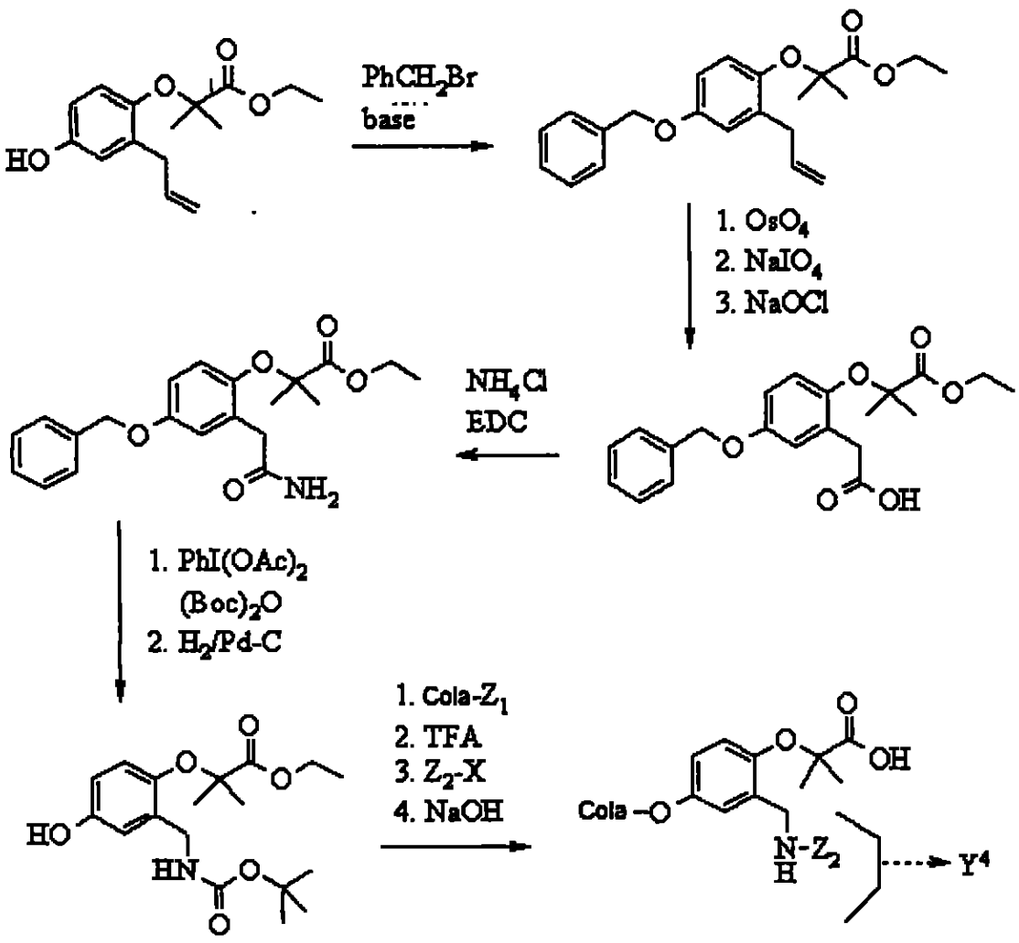
Esquema de Reacción 14: Síntesis de dihidrocinamatos de aminoetilo



El Esquema de Reacción 14 muestra la ruta de síntesis para preparar piezas de cabeza de dihidrocinamato de aminoetilo. Un grupo protector tal como bencilo se une al alcohol arílico del compuesto (50) para dar el compuesto protegido (51), que después se convierte en un compuesto de nitro-

olefina (52). El compuesto (52) experimenta reducción de la nitro-olefina por tratamiento con LAH seguido de introducción de un grupo protector de amina tal como Boc para dar el compuesto (53). El compuesto (53) experimenta una reacción de acoplamiento con acrilato de metilo en presencia de un catalizador de paladio seguido de desprotección del grupo fenol para dar el compuesto de fenol (54). El compuesto (54) después se acopla con una pieza de cola seguido de desprotección del grupo Boc para dar el compuesto intermedio, que después puede experimentar una modificación adicional en la porción de aminoetilo de compuestos seguido de hidrólisis para dar el compuesto (55). Como alternativa, el compuesto (57) se desprotege seguido de modificación en la porción de aminoetilo del compuesto para dar el compuesto (56). El compuesto (56) puede acoplarse con una pieza de cola seguido de hidrólisis de éster para producir el compuesto (55).

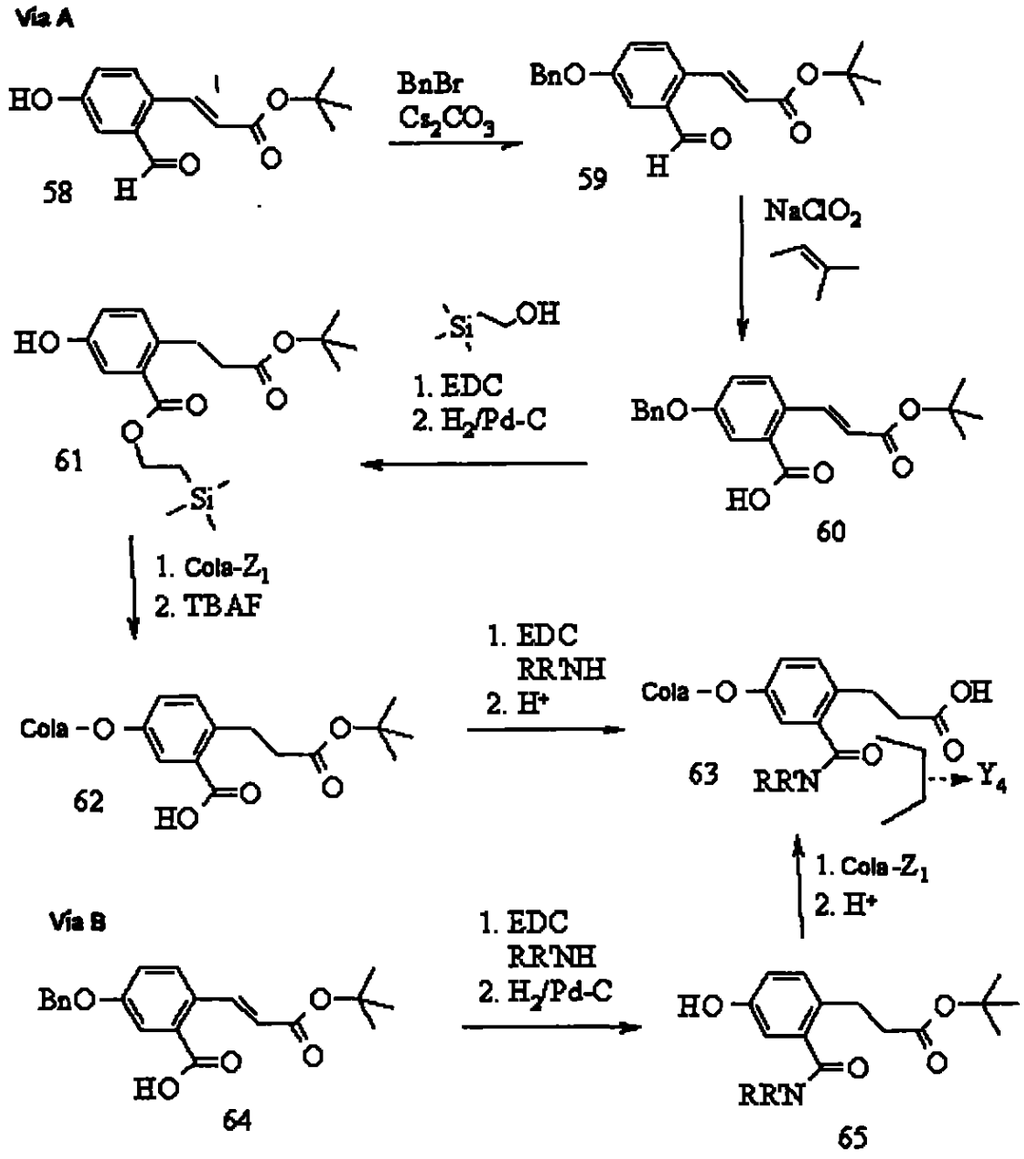
Esquema de Reacción 15: Síntesis de fibratos de aminometilo



El Esquema de Reacción 15 muestra una ruta sintética para preparar compuestos de fibrato de aminometilo. La reacción se realiza siguiendo una ruta sintética sustancialmente similar a la descrita en el Esquema de Reacción 13.

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Esquema de Reacción 16: Síntesis de hidrocinamatos de carboxamida

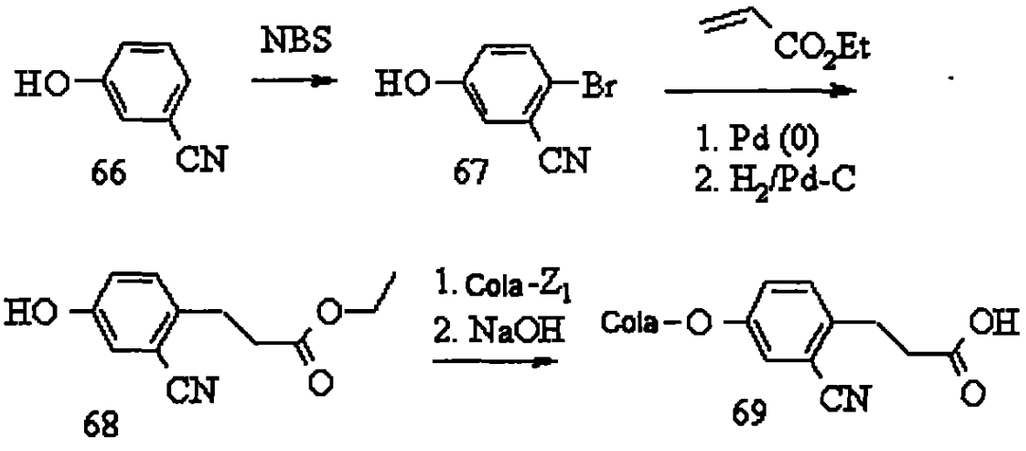


$Y^4 = (C_0\text{-}C_3)C(O)NR^5(C_0\text{-}C_5)\text{-}Y^7$

El Esquema de Reacción 16 muestra la ruta de síntesis para hidrocinamatos de carboxamido por la vía A a la vía B. En la vía A, el grupo protector tal como bencilo se une al fenol del compuesto (58) para dar el

compuesto protegido (59). El compuesto (59) se oxida para dar el compuesto de ácido carboxílico (60), que después experimenta esterificación seguido de desprotección del fenol para dar el compuesto (61). El compuesto (61) se acopla con una pieza de cola seguido de desprotección del grupo ácido carboxílico para dar el compuesto (62), que después experimente formación de amida seguido de hidrólisis de éster para producir el compuesto (63). Como alternativa, como se muestra en la vía B, el compuesto (64) puede experimentar una formación de amida seguido de reducción y desprotección del grupo fenol para dar el compuesto (65). El compuesto (65) después puede acoplarse con una pieza de cola seguido de hidrólisis de éster para producir el compuesto (63).

Esquema de Reacción 17: Síntesis de dihidrocinamatos de ciano

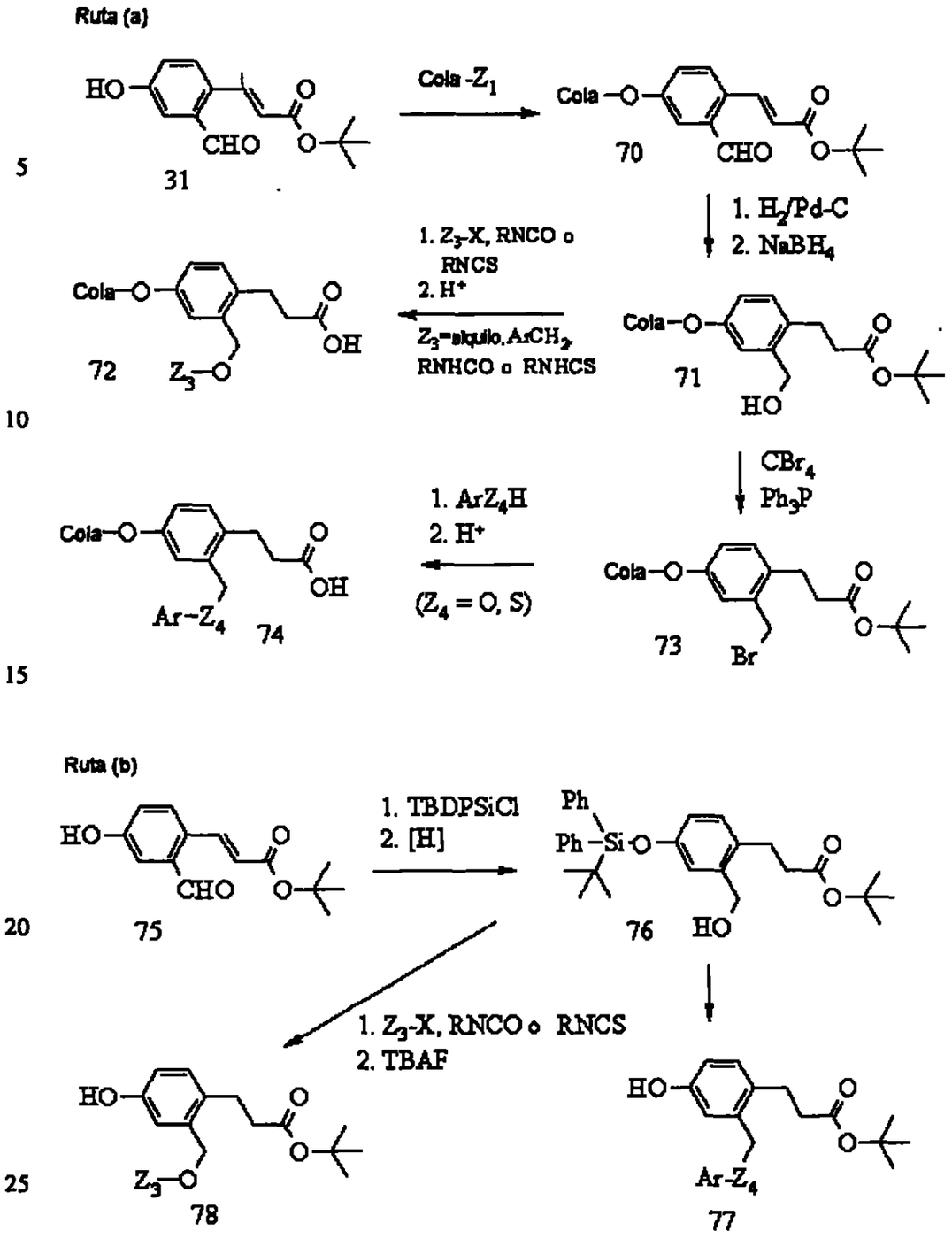


Pueden prepararse dihidrocinamatos de ciano como se muestra en el Esquema de Reacción 17. El compuesto (66) se broma con un agente de bromación tal como NBS para dar el compuesto (67), que después experimenta una reacción de acoplamiento de Heck con acrilato de etilo en presencia de un catalizador de paladio seguido de hidrogenación para dar el compuesto (68).

El compuesto (68) se acopla con una pieza de cola seguido de hidrólisis de éster para producir el compuesto ácido carboxílico (69).

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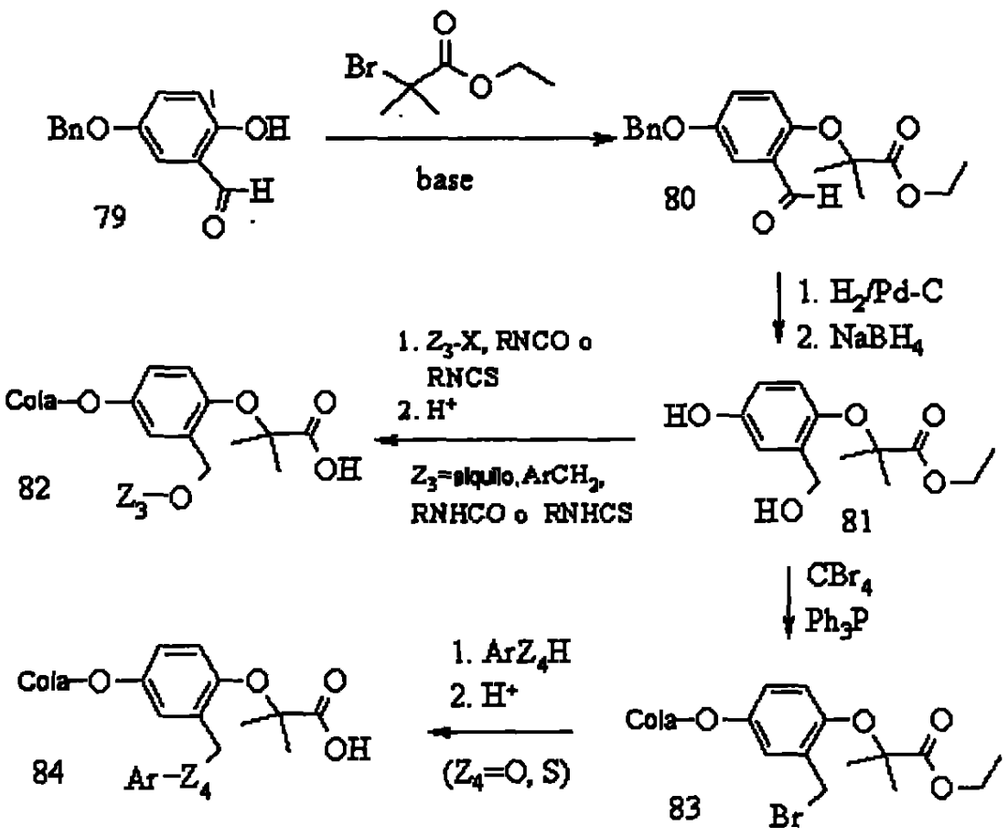
Esquema de Reacción 18: Síntesis de dihidrocinamatos de alcoxi



Pueden prepararse dihidrocinamatos de alcoxi como se muestra en el Esquema de Reacción 18. En la ruta (a), el compuesto (31) se acopla con una pieza de cola para dar el compuesto (70), que después experimenta reducción secuencial del doble enlace y aldehído para dar el compuesto del alcohol (71). El compuesto (71) experimenta la reacción de condensación con un isocianato o tioisocianato, haluro de alquilo o haluro arílico seguido de hidrólisis de éster para dar el compuesto (72). Como alternativa, el compuesto (71) puede convertirse en el correspondiente haluro (73) usando un tetrahaluro de carbono y trifenilfosfina. Una reacción de sustitución nucleófila seguido de hidrólisis de éster produce el compuesto (74).

En la ruta (b), un grupo protector tal comoTBDPSi se une al alcohol arílico del compuesto (75) para dar el compuesto (76), que después experimenta una secuencia de reacción similar a la descrita en la ruta (a) para dar el fenol (77). Como alternativa, el compuesto (76) puede experimentar la reacción de condensación con Z_3-X seguido de desprotección para producir el fenol (78). Los compuestos de fenol (77) y (78) pueden tomarse separadamente para dar los compuesto finales por reacción por piezas de cola seguido de hidrólisis de ácido.

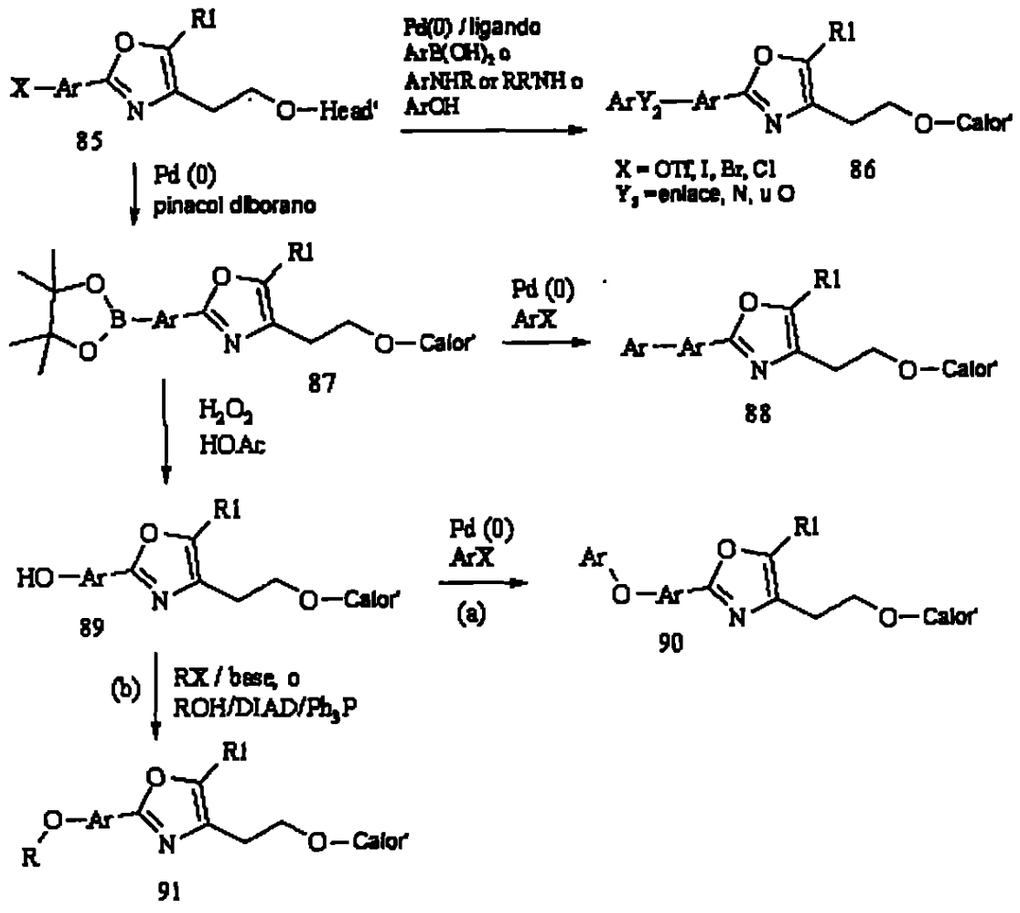
Esquema de Reacción 19: Síntesis de fibratos de alcoxialquilo



El Esquema de Reacción 19 ilustra una ruta sintética para preparar compuestos de fibrato de alcoxialquilo. El compuesto (79) se hace reaccionar con 2-bromoisobutirato de etilo en presencia de una base para dar el compuesto (80). El fenol del compuesto (80) se desprotege seguido de reducción de aldehído en presencia de un agente reductor tal como $NaBH_4$ para dar el compuesto (81). El fenol (81) después experimenta una reacción con Z_3-X seguido de hidrólisis para dar el compuesto de fibrato de alcoxialquilo (82). Como alternativa, el compuesto de fenol (81) puede convertirse en el correspondiente haluro (83) usando un tetrahaluro de carbono y trifenilfosfina.

El tratamiento del compuesto (83) con ArZ_4H seguido de hidrólisis de éster produce el compuesto (84).

Esquema de Reacción 20: Modificación de la pieza de cabeza



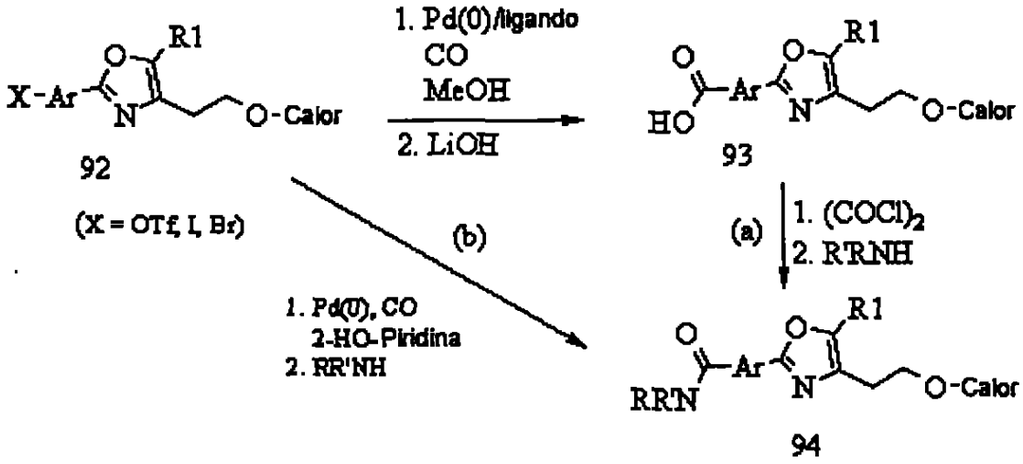
Ar-Y^7-Ar; Ar-Ar; Ar-O-Ar = Y^{1a}

R = H, o alquilo

El Esquema de Reacción 20 ilustra rutas sintéticas para los compuestos con piezas de cabeza modificados. El compuesto de oxazol (85) puede experimentar una reacción de acoplamiento con un alcohol arilborónico, arílico, amina o amina secundaria en presencia de un catalizador de paladio para dar

un compuesto de pieza de cabeza modificado (86). Como alternativa, el compuesto (85) experimenta una reacción de acoplamiento con pinacol de borano en presencia de un catalizador de paladio para dar el compuesto (87), que después se acopla con haluro de arilo para dar un compuesto de diarilo (88). Como alternativa, el compuesto (87) puede oxidarse para dar el fenol (89), que después se acopla con un haluro de arilo en presencia de un catalizador de paladio para dar el compuesto de aril-ariloxi (90) as como se muestra en la ruta (a). Como alternativa, el compuesto (89) puede experimentar una reacción nucleófila con un haluro o alcohol alquílico como se muestra en la ruta (b) para formar el compuesto de éter (91).

Esquema de Reacción 21: Modificación de la pieza de cola



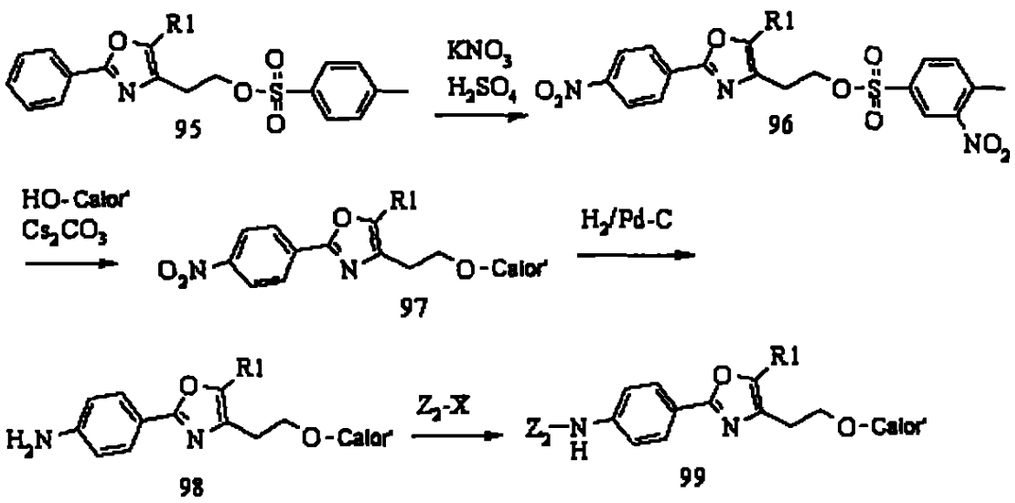
Ar-C(O)NRR' = Y^{1a}

NR'R = sustituyentes definidos en Y^{1a}

El Esquema de Reacción 21 muestra una ruta sintética para modificar la pieza de cola de los presente compuestos. En la ruta (a), el compuesto de pieza de cola de oxazol (92) experimenta carbonilación para dar el compuesto de ácido carboxílico (93), que se convierte en el cloruro de ácido seguido de

reacción con una amina para formar un compuesto de amida (94). Análogamente, en la ruta (b), el compuesto modificado (94) se realiza por carbonilación catalizada con paladio para formar un éster de hidroxipiridina intermedio seguido por una reacción con amina para formar el compuesto de amida.

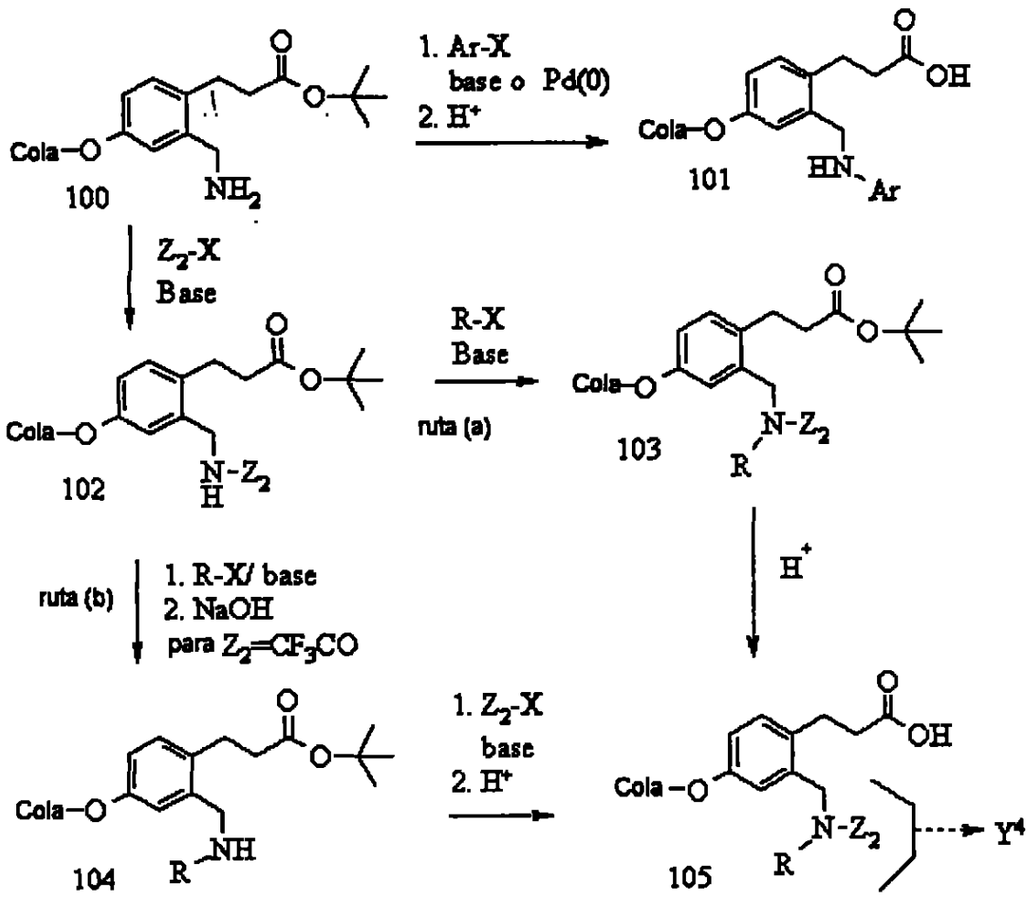
Esquema de Reacción 22: Modificación en la pieza de cola



$NH\text{-}Z^2$ = sustituyentes definidos Y^{1a}

El Esquema de Reacción 22 muestra una ruta sintética para modificar la pieza de cola de los presentes compuestos. El compuesto de oxazolil sufonil éster (95) se nitra para dar el compuesto (96), que después experimenta una reacción de acoplamiento con una pieza de cabeza para dar el compuesto (97). El grupo nitro del anillo de fenilo se reduce para dar el compuesto de anilina, que se modifica para dar el compuesto (99).

Esquema de Reacción 23: Modificación en la pieza de cabeza N

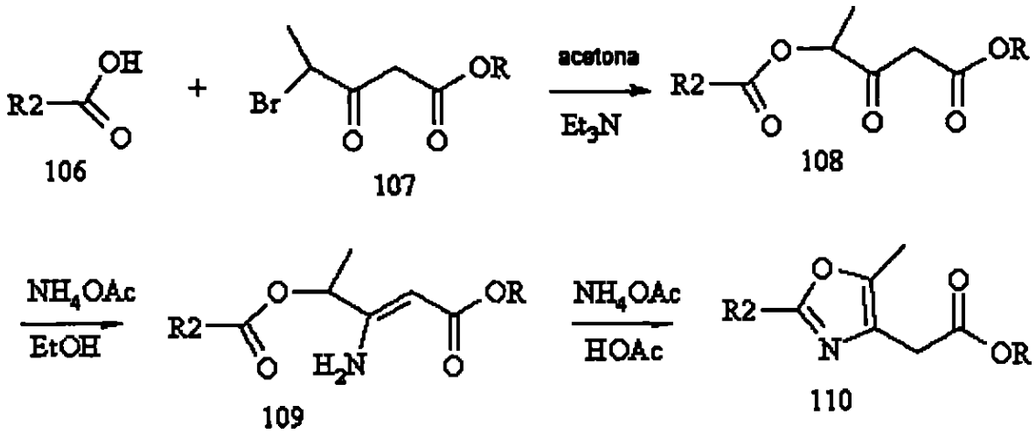


El Esquema de Reacción 23 muestra una ruta sintética para modificar la pieza de cabeza de los presentes compuesto. El compuesto de pieza de cabeza (100) puede modificarse por acoplamiento con haluro de arilo (Ar-X) en presencia de un catalizador de paladio seguido de hidrólisis de éster para dar el compuesto (101). Como alternativa, el compuesto (100) puede hacerse reaccionar con Z_2-X en presencia de una base para dar el compuesto de aminometilo modificado (102). En la ruta (a), el compuesto (102) puede experimentar sustitución nucleófila en la amina seguido de hidrólisis de éster

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para dar el compuesto de ácido (105). Como alternativa, por la ruta (b) con Z_2 como un grupo trifluro-acetilo, la alquilación en condiciones básicas seguido de hidrólisis básica acuosa da el compuesto de amina secundaria (104). La posterior funcionalización de la amina con Z_2-X seguido de hidrólisis de ácida produce el compuesto (105).

Esquema de Reacción 24: Pieza de cola de oxazol



R2 = Y^{1a} tales como arilo, aril-Z-aril o heteroaril-Z-arilo, o alquilo

R = alquilo

En el Esquema de Reacción 24 se muestra una ruta de sintética alternativa para piezas de cabeza de oxazol. El ácido carboxílico (106) se condensa con 2-bromo-3-oxopentanoato (preferiblemente éster metílico) (107) para dar el cetoéster (108). Este último se convierte en un intermedio de intermedia (109) por tratamiento con acetato amónico anhidro. La posterior ciclación del compuesto (109) ácido acético en presencia de acetato amónico anhidro da el compuesto (110). El uso de acetato amónico anhidro obtenido por evaporación azeotrópica con etanol elimina el agua en la reacción, lo que provoca la descarboxilación del compuesto (110). Además, algo del agua

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liberada en la reacción se retira en la etapa de enamina. Estas modificaciones junto con un procedimiento de aislamiento simplificado conduce a la formación de mayores rendimientos del oxazol (110).

En los Esquemas, Preparaciones y Ejemplos mostrados a continuación, diversos reactivos, símbolos y abreviaturas tienen los siguientes significados:

BINAP	2,2'-Bis(difenilfosfino)-1,1'-binaftilo
Boc	t-butoxicarbonilo
CBZ	benciloxicarbonilo
DCM	diclorometano
DEAD	azodicarboxilato de dietilo
DI	desionizado/a
DIAD	azodicarboxilato de diisopropilo
DIPEA	diisopropiletilamina
DMAP	4-dimetilamino piridina
DMF	N,N-dimetilformamida
DMSO	dimetilsulfóxido
eq. (equiv)	equivalente (s)
EDC	1-(3-dimetilaminopropil)-3-etilcarbodiimida HCl
ESI-MS	termonebulización iónica-espectroscopía de masas
Et	etilo
EtOAc	acetato de etilo
FMOC	carbamato de 9-flurorenilmetilo
HATU	hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio
HOAc	ácido acético

HOAT:	1-hidroxi-7-azabenzotriazol
HOBT	1-hidroxibenzotriazol hidrato
HPLC	cromatografía líquida de alta resolución
HRMS	espectro de masas de alta resolución
h	hora(s)
LRMS	espectro de masas de baja resolución
LAH	hidruro de litio y aluminio
Me	metilo
Ms	metanosulfonilo
NBS	N-bromosuccinimida
$Pd_2(dba)_3$	tris(dibencilidenoacetona) dipaladio(0)
F	fenilo
Fe	fenilalanina
Pr	propilo
t.a.	temperatura ambiente
TBAF	fluoruro de tetrabutilamonio
TBS	tercbutildimetilsililo
TFA	ácido trifluoroacético
TEA	trietilamina
THF	tetrahidrofurano
TLC	cromatografía de capa fina

Procedimiento Convencional

Los siguientes procedimientos convencionales (A) a € se usan para preparar los compuestos de la presente invención como se ilustra en los Ejemplos mostrados a continuación.

Procedimiento Convencional (A): Acoplamiento de Mitsunobu de Piezas de Cabeza de Alcohol Arílico con Piezas de Cola de Alcohol

Una mezcla de 2-(5-metil-2-naftalen-2-il-oxazol-4-il)-etanol (112 mg, 0,442 mmol, 1 equiv), éster terc-butílico del ácido 3-[4-hidroxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (150 mg, 0,445 mmol, 1,00 equiv), y trifenilfosfina (116 mg, 0,442 mmol, 1,00 equiv) en tolueno (10 ml) a temperatura ambiente se trató con azodicarboxilato de dietilo (90 µL, 92 mg, 0,46 mmol, 1,0 equiv) durante un periodo de aproximadamente 3 minutos. La mezcla se agitó durante aproximadamente 23 horas y se concentró. El material bruto se purificó por cromatografía en gel de sílice.

Procedimiento Convencional (B): Hidrólisis de Éster en Condiciones Ácidas

Una solución del compuesto del título que contenía éster terc-butílico (0,5 mmol) en CH_2Cl_2 (6 ml) se trató con 90 % ácido trifluoroacético/agua (3 ml) y se agitó a temperatura ambiente durante aproximadamente 3 horas y después se concentró para dar el correspondiente compuesto de ácido carboxílico. El material bruto se purificó por cromatografía en gel de sílice cuando fue necesario.

Procedimiento Convencional (C): Hidrólisis de Éster en Condiciones Ácidas

Una mezcla del compuesto del título que contenía éster terc-butílico (0,2 mmol) en 4 M HCl en 1,4-dioxano (5 ml) se agitó a temperatura ambiente durante aproximadamente 16 horas y se concentró para dar el correspondiente compuesto de ácido carboxílico. El material bruto se purificó por cromatografía en gel de sílice cuando fue necesario.

Procedimiento Convencional (D): Hidrólisis de Éster en Condiciones Básicas:

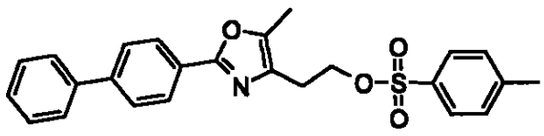
Una solución de éster (0,25 mmol) en MeOH (3 ml) y THF (1,5 ml) se trató con NaOH 2 N (1 ml) y se calentó a 55°C durante aproximadamente 2 horas. La mezcla se enfrió y se concentró. El residuo se repartió entre CH_2Cl_2 (10 ml), salmuera (5 ml) y 5N HCl (1 ml). La capa orgánica se secó (Na_2SO_4) y se concentró. El material bruto se purificó por cromatografía en gel de sílice cuando fue necesario.

PREPARACIÓN DE INTERMEDIOS

Preparación de Piezas de cola - Oxazoles

Preparación 1

2-(2-Bifenil-4-il-5-metil-oxazol-4-il)etil éster del ácido tolueno-4-sulfónico



Etapa A: Óxido de 4,5-dimetil-2-(4-bromofenil)-oxazol

Una solución de monooxima de 2,3-butanodiona (50 g, 0,49 mol) y 4-bromo-benzaldehído (101 g, 0,54 mol) en ácido acético (500 ml) se enfrió a 0°C y después se burbujeó HCl gaseoso a través de la solución durante 35 min mientras que la reacción se agitaba en un baño de hielo. Se añadió éter dietílico (500 ml) a la reacción para precipitar el producto, y la suspensión resultante se agitó 45 min a 0°C antes de filtrarse. Los sólidos se aclararon con Et_2O (50 ml), se recogieron en agua (1 l), y a la suspensión se le añadió NH_4OH conc. (60 ml). Esta mezcla se extrajo con $CHCl_3$. La capa orgánica se secó ($MgSO_4$) y se concentró para dar 97,4 g (74%) de óxido de 4,5-dimetil-2-(4-bromofenil)-oxazol en forma de un sólido blanco. El compuesto debe usarse

directamente en las siguientes 24–48 h. ^{1}H RMN (500 MHz, $CDCl_3$) 8,34 (d, J = 9,0 Hz, 2H), 7,61 (d, J = 9,0 Hz, 2H), 2,35 (s, 3H), 2,20 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) 142,1, 131,9, 129,5, 126,3, 124,1, 122,2, 11,1, 6,2; IR (KBr) 1685, 1529, 1418, 1377, 1233, 1165 cm^{-1}; UV (EtOH) $_{max}$ 307 nm (24371); HRMS (TOF) m/z calculado para $C_{11}H_{11}{}^{79}BrNO_2$: 267,997. Encontrado 267,9951.

Etapa B: 2-(4-Bromofenil–4-(clorometil)–5-metiloxazol

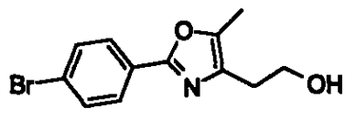
Una solución de óxido de 4,5-dimetil-2-(4-bromofenil)-oxazol óxido (96,6 g, 0,36 mol) en $CHCl_3$ (0,90 l) se trató gota a gota con oxicloruro de fósforo (61,1 g, 0,40 mol) produciendo una exotermia en la reacción y después se agitó a reflujo durante 30 min. La reacción se enfrió a temperatura ambiente y se lavó con agua (2 x 1 l). Los lavados acuosos combinados se extrajeron de nuevo con CH_2Cl_2 (2 x 400 ml). Las capas orgánicas se secaron ($MgSO_4$) y se concentraron para dar el producto bruto que se recristalizó en hexanos calientes (300 ml), decantando el sobrenadante caliente decantando el sobrenadante caliente de un material oleoso oscuro. El aceite oscuro restante se agitó en más hexanos calientes (200 ml), y los sobrenadantes combinados se enfriaron a 0°C. El producto se aisló por filtración en forma de un polvo de color verde-lima (74,2 g, 72%): Rf = 0,39 en 20% acetato de etilo/hexanos. ^{1}H RMN (500 MHz, $CDCl_3$) 7,88–7,86 (m, 2H), 7,59–7,56 (m, 2H), 4,54 (s, 2H), 2,42 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) 159,2, 146,9, 133,2, 132,0, 127,6, 126,1, 124,7, 37,1, 11,5; IR (KBr) 2970, 1633, 1599, 1481, 1401, 1258, 1117, 1008 cm^{-1}; UV (EtOH) $_{max}$ 281 nm (21349); HRMS (FAB) m/z calculado para $C_{11}H_{10}{}^{79}BrClNO$: 285,9634. Encontrado 285,9641; Anal. Calculado para $C_{11}H_9ClBrNO$: C, 46,11; H, 3,17; N, 4,89; Cl, 12,37; Br, 27,88. Encontrado C, 46,28; H 3,07; N, 4,81; Cl, 12,36; Br, 27,88.

Etapa C: Ácido 2-(4-bromofenil)-5-metil-4-oxazol acético

A una solución de 2-(4-bromofenil–4-(clorometil)–5-metiloxazol (64,8 g, 0,23 mol) en DMF (400 ml) se le añadió cianuro potásico en polvo (22,1 g, 0,34 mol) y yoduro potásico (28,6 g, 0,17 mol), y la mezcla resultante se calentó a 85°C durante 3,5 h. La mezcla de reacción se enfrió a temperatura ambiente. Se disolvió carbonato potásico (5 g) en agua (800 ml) y se añadió gota a gota a la reacción para precipitar 2-(4-bromofenil–4-(cianometil)–5-metiloxazol (agitar vigorosamente durante 15 min después de la adición) que se aisló por filtración y se lavó con agua (2 x 400 ml). El 2-(4-bromofenil–4-(cianometil)–5-metiloxazol bruto se usó en la siguiente etapa sin purificación. ^{1}H RMN (300 MHz, $CDCl_3$) 7,85 (m, 2H), 7,58 (m, 2H), 3,64 (s, 3H), 2,43 (s, 3H).

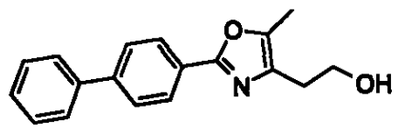
El 2-(4-bromofenil–4-(cianometil)–5-metiloxazol bruto (asumido 0,22 mol) se combinó con 2-metoxietanol (630 ml) y a la reacción se le añadió KOH sólido al 85% (74,6 g, 1,33 mol) en agua (360 ml). La mezcla se calentó a reflujo durante 3 h, se enfrió, se inactivó con HCl 2 M (500 ml), y se extrajo con CH_2Cl_2. La capa orgánica se secó ($MgSO_4$) y se concentró, usando tolueno para retirar por destilación azeotrópica el 2-metoxietanol residual. El producto bruto (57,3 g) se recristalizó en tolueno (450 ml) para dar 39,8 g (60%) de ácido 2-(4-bromofenil)-5-metil-4-oxazol acético en forma de un polvo blanco. Rf = 0,23 en 10% MeOH/CH_2Cl_2; ^{1}H RMN (500 MHz, $CDCl_3$) 9,00 (s a, 1H), 7,85–7,83 (m, 2H), 7,58–7,56 (m, 2H), 3,62 (s, 3H), 2,36 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) 173,8, 159,0, 146,2, 132,0, 129,1, 127,6, 125,9, 124,7, 31,5, 10,2; IR ($CHCl_3$) 2923, 1699, 1641, 1481, 1428, 1306, 1234, 1010, 829, 727 cm^{-1}; UV $(EtOH)_{max}$ 288 nm (19626).

Etapa D: 2-(4-Bromofenil)-5-metil-4-oxazoletanol



Una solución de ácido 2-(4-bromofenil)-5-metil-4-oxazol acético (39,1 g, 0,13 mol) en THF seco (175 ml) se trató gota a gota con complejo de complejo de borano/THF (227 ml de una solución 1,0 M en THF, 1,3 mol) durante 2 h a aproximadamente 35°C. Después de agitar durante 2 h a temperatura ambiente en una atmósfera de N_2. La reacción se interrumpió con la adición lenta de metanol (60 ml) y se agitó durante una noche a temperatura ambiente. La reacción se diluyó con NaOH 1 N (50 ml) y se extrajo con CH_2Cl_2 (2 x 200 ml). La capa orgánica se lavó con H_2O (3 x 100 ml), se secó ($MgSO_4$), y se concentró. El producto bruto (38,7 g) se recristalizó en tolueno (200 ml, sólido lavado con hexanos fríos) para dar 26,9 g (72%) de 2-(4-bromofenil)-5-metil-4-oxazoletanol en forma de un polvo blanco. Rf = 0,37 en MeOH al 10%/CH_2Cl_2, ^{1}H RMN (500 MHz, $CDCl_3$) 7,84–7,82 (m, 2H), 7,57–7,55 (m, 2H), 3,91 (q, J = 5,5 Hz, 2H), 3,14 (t, J = 6 Hz, OH), 2,72 (t, J = 5,5 Hz, 2H), 2,33 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) 158,7, 144,5, 134,2, 131,9, 127,4, 126,4, 124,3, 61,8, 28,1, 10,1; IR (KBr) 3293, 2948, 1642, 15985, 1480, 1472, 1401, 1053, 1003, 836, 734 cm^{-1}; UV (EtOH) $_{max}$ 290 nm (20860); Anal. Calculado para $C_{12}H_{12}BrNO_2$: C, 51,09; H, 4,29; N, 4,96; Br, 28,32. Encontrado C, 51,31; H 4,06; N, 4,90; Br, 28,19,

Etapa E: 2-(Bifenil-4-il-5-metil-oxazol-4-il)etanol



Se disolvieron 2-(4-bromofenil)-5-metil-4-oxazoletanol (10,0 g, 35,0 mmol) y ácido fenilborónico (4,5 g, 38,0 mmol) en n-propanol (120 ml) antes de añadir trifenilfosfina (165,2 mg, 0,63 mmol), acetato de paladio (46 mg, 2,1 mmol), y Na_2CO_3 (4,5 g, 42 mmol disuelto en 30 ml de H_2O destilado). La solución se calentó a reflujo y se agitó durante 1,5 h. Después de enfriar a temperatura ambiente, la mezcla se concentró y después se repartió entre CH_2Cl_2 (100 ml) y NaOH 1 N (100 ml). La fase acuosa se extrajo con CH_2Cl_2 (2 x 50 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$) y se concentraron a presión reducida para proporcionar 2-(4-bifenil)-5-metil-4-oxazoletanol (9,5 g, rendimiento del 97%) en forma de un sólido blanco que se usó directamente sin purificación adicional. ^1H RMN (500 MHz, $CDCl_3$) 8,01 (d, 2H), 7,77-7,50 (m, 4H), 7,46 (m, 2H), 7,38 (m, 1H), 3,91 (q, J = 5,5 Hz, 2H), 3,18 (t, J = 6 Hz, OH), 2,72 (t, J = 5,5 Hz, 2H), 2,33 (s, 3H).

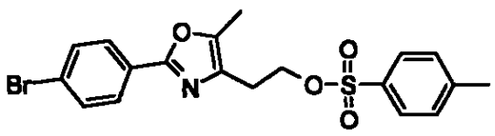
Etapa F: 2-(2-Bifenil-4-il-5-metil-oxazol-4-il)etil éster del ácido tolueno-4 sulfónico

A una solución de 2-(bifenil-4-il-5-metil-oxazol-4-il)etanol (15,8 g, 56,6 mmol) en CH_2Cl_2 (250 ml) a temperatura ambiente en una atmósfera de N_2 se le añadió en porciones piridina (14,7 g, 185 mmol, 15,0 ml), DMAP (2,03 g, 16,6 mmol), y después anhídrido de tosilo (24,57 g, 75,2 mmol). La reacción mostró una exotermia de 32°C y se agitó 30 min antes de añadirse más anhídrido de tosilo (2,3 g). La mezcla se diluyó con CH_2Cl_2 (100 ml) y se agitó vigorosamente con HCl 1 N (150 ml) durante 15 min. La fase orgánica se secó ($MgSO_4$) y se filtró a través de una capa de gel de sílice (100 ml, cargado con CH_2Cl_2). El gel de sílice se eluyó con acetato de etilo (100 ml), y la solución se concentró para dar 2-(2-bifenil-4-il-5-metil-oxazol-4-il)etil éster del ácido

toluen-4-sulfónico en forma de un sólido blanco (23,3 g, 95%). Rf = 0,51 en 60% acetato de etilo/hexanos. ^{1}H RMN (400 MHz, $CDCl_3$) 7,97 (d, 2H), 7,70 (d, 2H), 7,66 (t, 2H), 7,65 (d, 2H), 7,51 (t, 1H), 7,42 (d, 2H), 7,24 (d, 2H), 4,37 (t, 2H), 2,88 (t, 2H), 2,37 (s, 3H), 2,26 (s, 3H).

Preparación 2

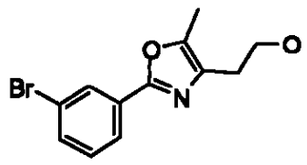
2-(4-Bromofenil-5-metil-oxazol-4-il)etil éster del ácido toluen-4-sulfónico



El compuesto del título se preparó a partir de 2-(4-bromofenil)-5-metil-4-oxazoletanol de acuerdo con el Procedimiento 1, Etapa F: MS (ESI) m/z 436,0 $(M+H)^+$.

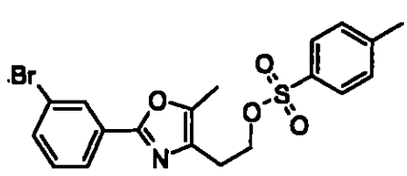
Los siguientes compuestos intermedios se prepararon sustancialmente de una forma similar a la descrita en las Preparaciones 1 y 2,

2-(3-Bromofenil)-5-metil-4-oxazoletanol:



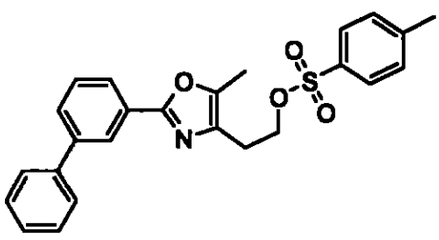
^{1}H RMN (300 MHz, d_6-DMSO) δ 7,99 (s, 1H), 7,88 (d, J = 7,7 Hz, 1H), 7,64 (d, J = 7,7 Hz, 1H), 7,44 (t, J = 7,7 Hz, 1H), 4,61 (t, J = 5,5 Hz, OH), 3,63 (q, J = 5,5 Hz, 2H), 2,60 (t, J = 6,6 Hz, 2H), 2,32 (s, 3H);

2-(3-bromofenil-5-metil-oxazol-4-il)etil éster del ácido toluen-4-sulfónico



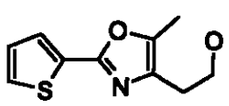
^{1}H RMN (400 MHz, $CDCl_3$) δ 8,01 (t, J = 1,6 Hz, 1H) 7,80 (dt, J = 7,6 Hz, J = 1,6 Hz, 1H), 7,66 (d, J = 8,4 Hz, 2H), 7,53 (dt, J = 7,6 Hz, J = 1,6 Hz, 1H), 7,30 (t, J = 7,6 Hz, 1H), 7,19 (d, J = 8,4 Hz, 2H), 4,30 (t, J = 6,4 Hz, 2H), 2,82 (t, J = 6,4 Hz, 2H), 2,31 (s, 3H), 2,24 (s, 3H); MS (ESI) m/z 436,0 $(M+H)^+$.

2-(2-bifenil-3-il-5-metil-oxazol-4-il)etil éster del ácido tolueno-4-sulfónico



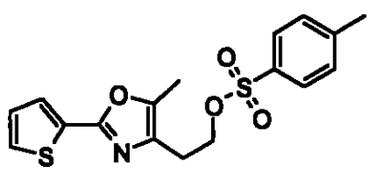
^{1}H RMN (300 MHz, $CDCl_3$) δ 7,99 (s, 1H), 7,80 (d, J = 8,0 Hz, 1H), 7,64 (d, 8,0 Hz, 1H), 7,51 (d, J = 9,0 Hz, 1H), 7,30 (t, J = 8,0 Hz, 1H), 7,20 (d, J = 9,0 Hz, 1H), 4,30 (t, J = 7,0 Hz, 2H), 2,80 (t, J = 7,0 Hz, 2H), 2,30 (s, 3H), 2,23 (s, 3H).

2-(5-Metil-2-tiofen-2-il-4-oxazoletanol



^{1}H RMN (500 MHz, $CDCl_3$): d 7,54 (m, 1H), 7,33 (m, 1H), 7,03 (m, 1H), 3,87 (t, J = 5,8 Hz, 2H), 3,5 (s, 1H), 2,67 (t, J = 5,8 Hz, 2H), 2,25 (s, 3 H)

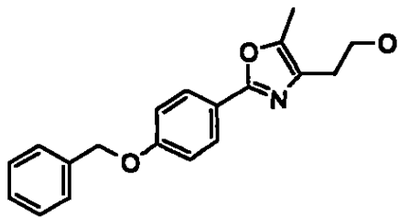
2-(5-metil-2-tiofen-2-iloxazol-4-il)etil éster del ácido tolueno-4-sulfónico



^{1}H RMN (400 MHz, $CDCl_3$): d 7,67 (d, J = 8,3 Hz, 2H), 7,51 (dd, J = 3,8, 1,4 Hz, 1H), 7,37 (dd, J = 4,9, 1,2 Hz, 1H), 7,21 (d, J = 7,9 Hz, 2H), 7,08 (dd, J =

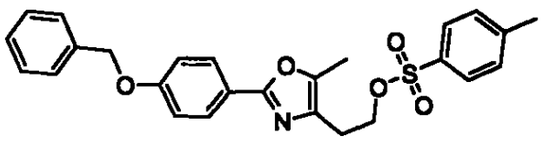
4,8, 3,5 Hz, 1H), 4,28 (t, J = 6,3 Hz, 2H) , 2,80 (t, J = 6,3 Hz, 2H), 2,28 (s, 3H), 2,26 (s, 3 H); p.f. 107-109°C.

2-[2-(4-Benciloxi-fenil)-5-metil-oxazol-4-il]-etanol



^{1}H RMN (500 MHz, $CDCl_3$) δ 7,91 (d, 2H, J = 8,60 Hz), 7,45-34 (m, 5H), 7,02 (d, 2H, J = 8,60 Hz), 5,11 (s, 2H), 3,91 (t, 2H , J = 5,7 Hz), 2,71 (t, 2H, J = 5,7 Hz), 2,31 (s, 3H); MS (ES^+) Calculado para $C_{19}H_{20}NO_3$: Encontrado m/e 310 (M + 1, 100%)

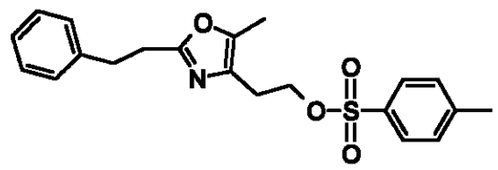
2-[2-(4-benciloxi-fenil)-5-metil-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico



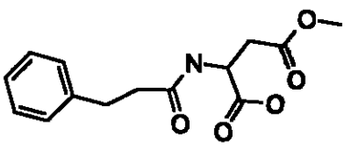
^{1}H RMN (500 MHz, $CDCl_3$) δ 7,80-7,78 (m, 2H), 7,67-7,65 (m, 2H), 7,45-7,34 (m, 5H), 7,25-7,17 (m, 2H), 7,02-6,99 (m, 2H), 5,12 (s, 2H), 4,29 (t, 2H, J = 6,45 Hz), 2,80 (t, 2H, J = 6,45 Hz), 2,27 (s, 3H), 2,22 (s, 3H); HRMS (ES^+) m/z masa exacta calculada para $C_{26}H_{26}NO_5S$ 464,1532, encontrada 464,1531; Anal. Calculado para $C_{26}H_{25}NO_5S$: C, 67,37; H, 5,44; N, 3,02. Encontrado C, 66,59; H 5,33; N, 3,06,

Preparación 3

2-(5-metil-2-fenetil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico

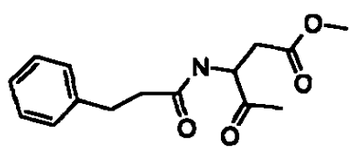


Etapa A: 4-Metil éster del ácido 2-(3-fenil-propionilamino)-succínico



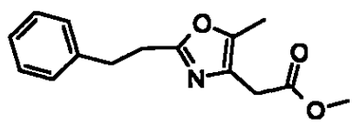
Se combinaron L-aspartato de metilo (15,0 g, 0,082 mol), agua DI (245 ml), acetona (20 ml), y Na_2CO_3 (30,8 g, 0,286 mol) y la solución se enfrió a 5°C. Al compuesto se le añadió cloruro de 3-fenil-propionilo (13,3 ml, 0,089 mol) gota a gota mediante un embudo de adición durante 10 min. La reacción se dejó calentar a temperatura ambiente y se agitó durante 2 h. A la suspensión viscosa se le añadió HCl conc. (50 ml) hasta que el p.f. fue ≤ 4,0. La mezcla de reacción se extrajo con CH_2Cl_2 (3 x 100 ml). Las capas orgánicas combinadas se lavaron con agua, se secaron ($MgSO_4$), se filtraron y se concentraron. El aceite incoloro transparente se usó sin purificación adicional. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,92 (s a, 1H), 7,28-7,17 (m, 5H), 6,57 (d, J = 7,6 Hz, 1H), 4,87 (m, 1H), 3,67 (s, 3H), 2,96 (t, J = 7,6 Hz, 2H), 2,89 (A de ABX, J_{AB} = 17,6 Hz, J_{AX} = 4,8 Hz, 1H), 2,88 (B de ABX, J_{BA} = 17,6 Hz, J_{BX} = 4,0 Hz, 1H), 2,69 (t, J = 7,6 Hz, 2H); MS (EI+) 280 (M+H), 302 (M+H+Na).

Etapa B: éster metílico del ácido 4-oxo-3-(3-fenil-propionilamino)-pentanoico



Se combinaron 4-metil éster del ácido 2-(3-fenil-propionilamino)-succínico (10 g, 36 mmol), piridina (50 ml) y anhídrido acético (45 ml) en un matraz de 500 ml. La mezcla de reacción se calentó a 90°C durante 2 h y después se enfrió a temperatura ambiente. Después de concentrar la mezcla de reacción a presión reducida, se añadió agua DI (100 ml). La mezcla de reacción se repartió entre agua y CH_2Cl_2 (200 ml). La fase orgánica se lavó con HCl 1 N (50 ml), se secó ($MgSO_4$), se filtró, y se concentró. El material se usó sin purificación adicional. ^1H RMN (400 MHz, $CDCl_3$) δ 7,31-7,20 (m, 5H), 6,79 (d a, J = 7,6 Hz, 1H), 4,72 (X de ABX, 1H), 3,65 (s, 3H), 3,01-2,93 (m, 3H), 2,71-2,62 (m, 3H), 2,11 (s, 3H); MS (EI) 278,1 (M+H).

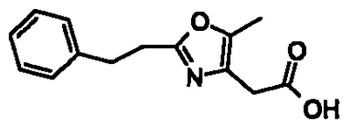
Etapa C: Éster metílico del ácido (5-Metil-2-fenetil-oxazol-4-il)-acético



En un matraz de 100 ml, se combinaron éster metílico del ácido 4-oxo-3-(3-fenil-propionilamino)-pentanoico (10 g, 36 mmol) y anhídrido acético (28 ml). Después de la adición de H_2SO_4 concentrado (1 ml), la solución se calentó a 90°C durante 30 min y se enfrió a temperatura ambiente. La reacción se diluyó lentamente con agua DI (30 ml, exotermia potencial). La mezcla de reacción se repartió entre CH_2Cl_2 (150 ml) y agua (150 ml). La fase orgánica se lavó con agua DI, 10% $NaHCO_3$ (ac.), salmuera (150 ml), y después se secó ($MgSO_4$) y se concentró hasta un aceite pardo. El residuo se purificó por cromatografía en columna (600 ml SiO_2, EtOAc al 35%/hexanos) para proporcionar el producto

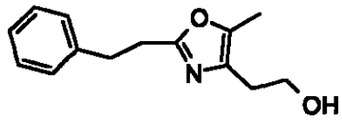
deseado (3,25 g) en forma de un aceite amarillo pálido. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,33-7,20 (m, 5H), 3,72 (s, 3H), 3,47 (s, 2H), 3,08-2,96 (m, 4H), 2,24 (s, 3H); MS (EI+) 260 (M+H).

Etapa D: Ácido (5-metil-2-fenetil-oxazol-4-il)-acético



Se trató éster metílico del ácido (5-metil-2-fenetil-oxazol-4-il)-acético (8,75 g, 33,8 mmol), en MeOH (120 ml) con 5N NaOH (40 ml), y después la solución se calentó a 40 °C. Después de 40 min, la mezcla de reacción se concentró. El residuo se suspendió en agua (75 ml) y se acidificó a pH=1 con HCl 5 N. La mezcla se extrajo con EtOAc (2x), se secó ($MgSO_4$), y se concentró para proporcionar 5,25 g (63%) del producto en forma de un sólido blanquecino. ^{1}H RMN (400 MHz, $CDCl_3$) δ ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,33-7,20 (m, 5H), 3,52 (s, 2H), 3,06-3,03 (m, 4H), 2,24 (s, 3H).

Etapa E: 2-(5-Metil-2-fenetil-oxazol-4-il)-etanol



Se añadió complejo de BH_3-THF (49 ml de una solución 1,0 M en THF) gota a gota mediante un embudo de adicción durante 50 min a una solución de ácido (5-metil-2-fenetil-oxazol-4-il)-acético (5,05 g, 20,6 mmol) en THF (35 ml). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, y después se inactivó con MeOH (12 ml). Después de calentar a 50 °C durante 2 h, la mezcla de reacción se enfrió a temperatura ambiente, y después se repartió entre CH_2Cl_2 y NaOH 1 N. La fase orgánica se lavó con salmuera (1x 50 ml),

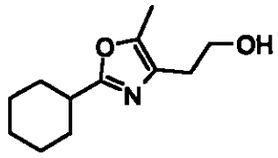
se secó sobre $MgSO_4$ y se concentró hasta obtener un residuo, que se purificó por cromatografía en columna (500 ml SiO_2, EtOAc al 35%/hexanos) para proporcionar 3,99 g (84%) del producto deseado en forma de un aceite incoloro transparente. ^1H RMN (400 MHz, $CDCl_3$) δ 7,33-7,20 (m, 5H), 3,84 (q, J = 5,6 Hz, 2H), 3,06-2,67 (m, 4H), 2,62 (t, J = 5,6 Hz, 2H), 2,22 (s, 3H); MS (EI+) 232,19 (M+H); 254,15 (M+H+Na).

Etapa F: 2-(5-metil-2-fenetil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico

Una solución de 2-(5-metil-2-fenetil-oxazol-4-il)-etanol (1,2 g, 5,19 mmol) en CH_2Cl_2 a 0°C se trató con piridina (1,64 g, 20,7 mmol, 1,68 ml), DMAP (190 mg, 1,56 mmol), y anhídrido de tosilo (2,2 g, 6,75 mmol). La reacción se calentó a temperatura ambiente y, después de 90 min, la solución se filtró a través de una capa de gel de sílice (aclarada con CH_2Cl_2). El producto se usó sin purificación adicional. ^1H RMN (400 MHz, $CDCl_3$) δ 7,73 (d, J = 8,4 Hz, 2H), 7,31-7,17 (m, 7H), 4,21 (t, J = 6,8 Hz, 2H), 3,01-2,88 (m, 4H), 2,75 (t, J = 6,8 Hz, 2H), 2,43 (s, 3H), 2,19 (s, 3H).

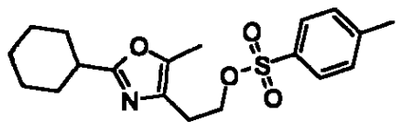
Los siguientes compuestos intermedios se prepararon sustancialmente de una forma similar a la descrita en la Preparación 3.

2-(2-Ciclohexil-5-metil-oxazol-4-il)-etanol:



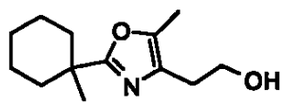
^1H RMN (400 MHz, $CDCl_3$) d3,73 (t, *J* = 6,8 Hz, 2H), 2,58 (tt, *J* = 11,6, 3,6 Hz, 1H), 2,54 (t, *J* = 6,8 Hz, 2H), 2,13 (s, 3H), 1,93-1,89 (m, 2H), 1,74 (dt, *J* = 12,8, 3,6 Hz, 2H), 1,67-1,62 (m, 1H), 1,41 (qd, *J* = 12,0, 3,2 Hz, 1H), 1,33-1,17 (m, 4H); MS (EI+) 210,1 (M+H).

2-(2-ciclohexil-5-metil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico



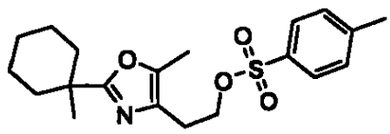
^{1}H RMN (400 MHz, $CDCl_3$) d 7,67 (d, *J* = 8,4 Hz, 2H), 7,27 (d, *J* = 8,4 Hz, 2H), 4,16 (t, *J* = 6,8 Hz, 2H), 2,70 (t, *J* = 6,8 Hz, 2H), 2,56 (tt, *J* = 11,6, 3,6 Hz, 1H), 2,39 (s, 3H), 2,13 (s, 3H), 1,93-1,89 (m, 2H), 1,74 (dt, *J* = 12,8, 3,6 Hz, 2H), 1,67-1,62 (m, 1H), 1,41 (qd, *J* = 12,0, 3,2 Hz, 1H), 1,33-1,17 (m, 4H); MS (EI+) 364,1 $(M+H)^+$.

2-[5-Metil-2-(1-metilciclohexil)oxazol-4-il]etanol



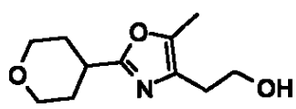
MS (EI+) 224,1 $(M+H)^+$.

2-[5-metil-2-(1-metilciclohexil)oxazol-4-il]etil éster del ácido tolueno-4-sulfónico



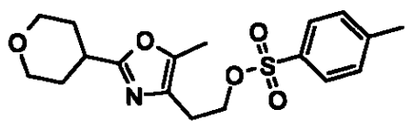
^{1}H RMN (400 MHz, $CDCl_3$) δ 7,73 (d, J = 8,4 Hz, 2H), 7,30 (t, J = 8,4 Hz, 2H), 4,12 (t, J = 6,6 Hz, 2H), 2,76 (t, J = 6,6 Hz, 2H), 2,42 (s, 3H), 2,17 (s, 3H), 2,61-2,02 (m, 2H), 1,56-1,30 (m, 8H), 1,19 (s, 3H); MS (EI) 378,2 $(M + H)^+$.

2-[5-Metil-2-(tetrahidro-piran-4-il)-oxazol-4-il]-etanol



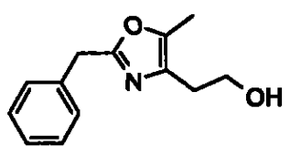
MS (EI) 212,2 $(M + H)^+$.

2-[5-metil-2-(tetrahidro-piran-4-il)-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico



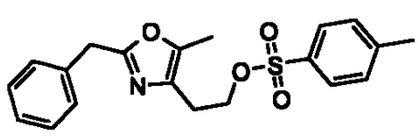
MS (EI) 366,2 $(M + H)^+$.

2-(2-Bencil-5-metil-oxazol-4-il)-etanol



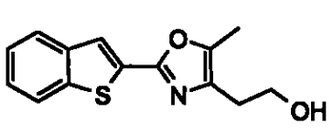
MS (EI) 218,0 $(M + H)^+$.

2-(2-bencil-5-metil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico



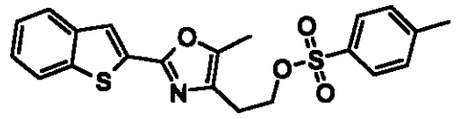
MS (EI) 372,1 $(M + H)^+$.

2-(2-Benzo[b]tiofen-2-il-5-metil-oxazol-4-il)-etanol



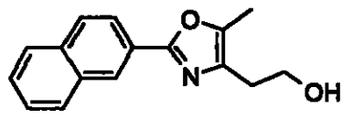
^{1}H RMN ($CDCl_3$) δ 7,81 (m, 3 H), 7,38 (m, 2 H), 3,94 (m, 2 H), 3,07 (s a, 1 H), 2,73 (t, 2 H, J = 6 Hz), 2,34 (s, 3 H); ^{13}C RMN ($CDCl_3$) δ 155,9, 145,0, 140,5, 139,8, 134,5, 129,9, 125,9, 125,1, 124,7, 123,7, 122,7, 61,9, 28,5, 10,4; MS (EI) 260,1 $(M + H)^+$.

2-(2-Benzo[b]tiofen-2-il-5-metil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico



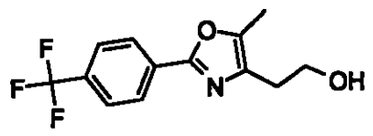
^{1}H RMN ($CDCl_3$) δ 7,85 (m, 1 H), 7,84 (m, 1 H), 7,75 (s, 1 H), 7,67 (d, 2 H, *J* = 8 Hz), 7,39 (m, 2 H), 7,21 (m, 2 H), 4,31 (t, 2 H, *J* = 2 Hz), 2,83 (t, 2 H, *J* = 6 Hz), 2,32 (s, 3 H), 2,19 (s, 3 H).

2-(5-Metil-2-naftalen-2-il-oxazol-4-il)-etanol



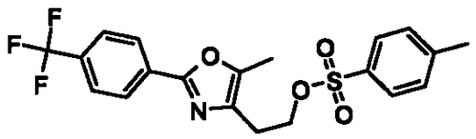
HRMS calculado para $C_{16}H_{16}NO_2$: m/z 254,1181. Encontrado: 254,1167.

2-[5-Metil-2-(4-trifluorometil-fenil)-oxazol-4-il]-etanol



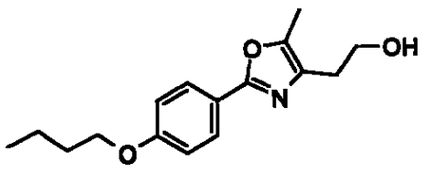
MS (EI) 272 $(M + H)^+$.

2-[5-metil-2-(4-trifluorometil-fenil)-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico



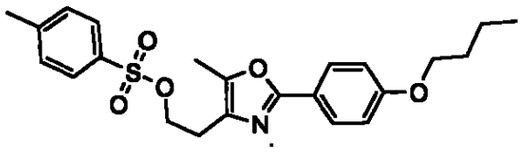
MS (EI) 426 $(M + H)^+$; p.f. 110,2°C.

2-[2-(4-Butoxi-fenil)-5-metil-oxazol-4-il]-etanol



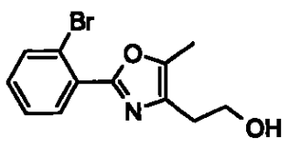
MS (EI) 276 $(M + H)^+$.

2-[2-(4-butoxi-fenil)-5-metil-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico



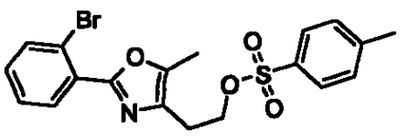
MS (EI) 430 $(M + H)^+$; p.f. 84,9°C.

2-(2-Bromofenil-5-metil-oxazol-4-il)-etanol



MS (EI) 282,1 $(M + H)^+$.

2-(2-bromofenil-5-metil-oxazol-4-il)etil éster del ácido tolueno-4-sulfónico

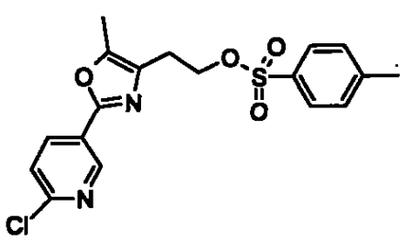


MS (EI) 438,1 $(M + H)^+$.

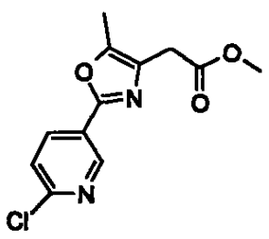
612.219

Preparación 4

2-[2-(6-cloro-piridin-3-il)-5-metil-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico

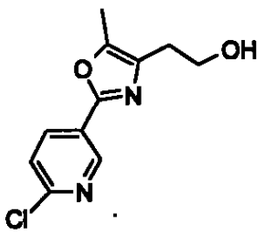


Etapa A: Éster metílico del ácido 3-[2-(6-cloro-piridin-3-il)-5-metil-oxazol-4-il]-acético



De acuerdo con la Preparación 3, Etapas A a C, se convirtió ácido 6-ácido cloronicotínico en el compuesto del título. MS (ESI) m/z 267 $(M+H)^+$.

Etapa B: 3-[2-(6-Cloro-piridin-3-il)-5-metil-oxazol-4-il]-etanol



Una solución de éster metílico del ácido 3-[2-(6-cloro-piridin-3-il)-5-metil-oxazol-4-il]-acético (500 mg, 1,88 mmol) en THF (20 ml) a 0°C se trató con LAH (90 mg, 2,3 mmol). La mezcla de reacción se agitó durante 1 h y inactivó con

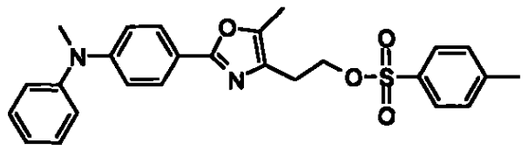
agua (0,1ml), NaOH al 15% (0,1 ml), y agua (0,3 ml). La mezcla se filtró a través de Celite y se concentró para dar el alcohol del título que se usó en la siguiente etapa sin purificación adicional. MS (ESI) m/z 239 $(M+H)^+$.

Etapa C: 2-[2-(6-Cloro-piridin-3-il)-5-metil-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico

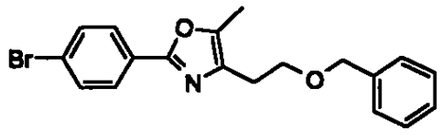
Una solución de 3-[2-(6-cloro-piridin-3-il)-5-metil-oxazol-4-il]-etanol bruto (1,88 mmol max) en CH_2Cl_2 (10 ml) se trató con cloruro de *para*-toluenosulfonilo (0,4 g, 2,3 mmol), DMAP (40 mg), y trietilamina (0,4 ml, 2,82 mmol). La mezcla de reacción se agitó a temperatura ambiente durante una noche y se diluyó con CH_2Cl_2 (20 ml). La mezcla se lavó con agua, y la capa orgánica se secó ($MgSO_4$), se filtró, y se concentró. El producto bruto se purificó por cromatografía en gel de sílice (hexanos/EtOAc 10/1 a 2/1) para producir el compuesto del título (295 mg, 40% en dos etapas). MS (ESI) m/z 393 $(M+H)^+$.

Preparación 5

2-{5-metil-2-[4-(metil-fenil-amino)-fenil]-oxazol-4-il}-etil éster del ácido tolueno-4-sulfónico

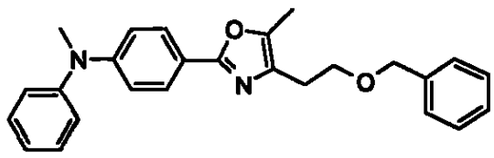


Etapa A: 4-(2-Benciloxi-etil)-2-(4-bromo-fenil)-5-metil-oxazol



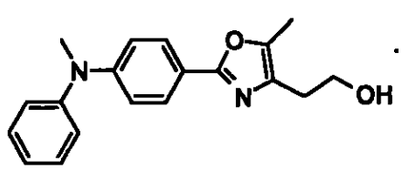
Una solución de 2-[2-(4-bromo-fenil)-5-metil-oxazol-4-il]-etanol (3,17 g, 11,2 mmol) en DMF (25 ml) se trató con NaH (0,67 g, dispersión en aceite al 60%) a 0°C y se agitó durante 5 min. Se añadió bromuro de bencilo (2,90 g, 16,9 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 3 h. La reacción se interrumpió con agua, y la mezcla se extrajo con EtOAc (2 x 150 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4), se concentraron, y se purificaron por cromatografía en una columna de gel de sílice (10% EtOAc/hexanos) para producir el compuesto del título en forma de un aceite (2,50 g, 60%).

Etapa B: {4-[4-(2-Benciloxi-etil)-5-metil-oxazol-2-il]-fenil}-metil-fenil-amina



Una solución de 4-(2-benciloxi-etil)-2-(4-bromo-fenil)-5-metil-oxazol (200 mg, 0,538 mmol) en tolueno (5,0 ml) en un tubo cerrado herméticamente en una atmósfera de gas nitrógeno se trató con $Pd(OAc)_2$ (50 mg), 2-(di-t-butilfosfino)bifenilo (20 mg), N-metil anilina (115 mg, 1,08 mmol), y t-butóxido sódico (104 mg, 1,08 mmol). El tubo se cerró herméticamente y se calentó a 105 °C durante 14 h. La mezcla se enfrió y se purificó directamente por cromatografía en columna de gel de sílice (30-50% EtOAc/hexanos) para producir el compuesto del título (195 mg, 91%). MS (ESI) m/z 399,3 $(M+H)^+$.

Etapa C: 2-{5-Metil-2-[4-(metil-fenil-amino)-fenil]-oxazol-4-il}-etanol



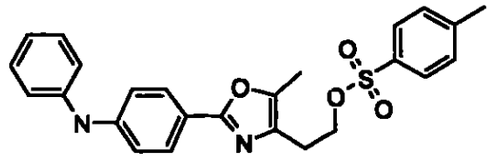
Una solución de {4-[4-(2-benciloxi-etil)-5-metil-oxazol-2-il]-fenil}-metil-fenil-amina (195 mg, 0,490 mmol) en THF (2 ml) y EtOH (10 ml) se trató con una suspensión de Pd/C (200 mg) en EtOH (2 ml). La mezcla resultante se trató con hidrógeno en una presión de globo durante 14 h y se filtró a través de una capa de celite. El filtrado se concentró, y el producto bruto se purificó por cromatografía en una columna de gel de sílice (50% EtOAc/hexanos) para producir el compuesto del título (91 mg, 60%).

Etapa D: 2-{5-metil-2-[4-(metil-fenil-amino)-fenil]-oxazol-4-il}-etil éster del ácido tolueno-4-sulfónico

Una solución de 2-{5-metil-2-[4-(metil-fenil-amino)-fenil]-oxazol-4-il}-etanol (91 mg, 0,30 mmol) en CH_2Cl_2 (4,0 ml) se trató con cloruro de *para*-toluenosulfonilo (68 mg, 0,36 mmol), trietilamina (0,20 ml) y unos pocos cristales de DMAP. La mezcla resultante se agitó a temperatura ambiente durante 14 h y se inactivó con agua (0,2 ml). La mezcla se purificó directamente por cromatografía en columna de gel de sílice (40% EtOAc/hexanos) para producir el compuesto del título (120 mg, 83%). MS (ESI) m/z 463,1 $(M+H)^+$.

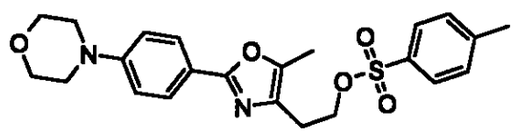
Los siguientes compuestos intermedios se prepararon de una forma sustancialmente similar a la de la Preparación 5.

2-[5-metil-2-(4-fenilamino-fenil)-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico



MS (ESI) m/z 449,1 $(M+H)^+$.

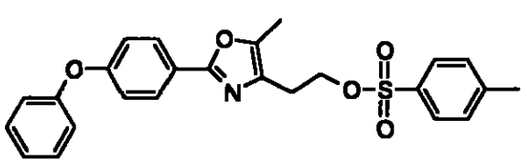
2-[5-metil-2-(4-morfolin-4-il-fenil)-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico



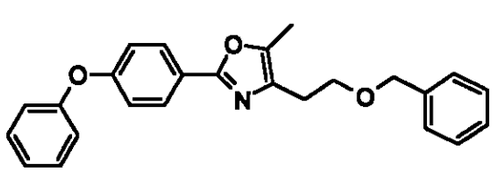
MS (ESI) m/z 443,1 $(M+H)^+$.

Preparación 6

2-[5-metil-2-(4-fenoxi-fenil)-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico



Etapa A: 4-(2-Benciloxi-etil)-5-metil-2-(4-fenoxi-fenil)-oxazol



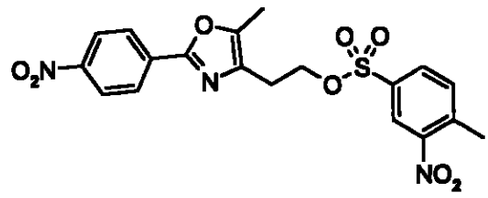
Una mezcla de 4-(2-benciloxi-etil)-2-(4-bromo-fenil)-5-metil-oxazol (0,025 mol, 9,2 g), fenol (0,03 mol, 2,8 g), K_3PO_4 (0,05 mol, 10,6 g), 2-(di-*terc*-butilfosfino)bifenilo (1,8 mmol, 0,54 g) y $Pd(OAc)_2$ (1,2 mmol, 0,28 g) en tolueno (350 ml) se desgasificó con nitrógeno y se calentó a 100°C durante 18 h. Se añadieron más $Pd(OAc)_2$ (0,5 g) y ligando de fosfina (1,0 g) y la mezcla se calentó durante 5 h a 100°C. La reacción se concentró y se purificó directamente por cromatografía en gel de sílice (4/1 hexanos/acetato de etilo) para dar el compuesto del título (7,6 g).

Etapa B: 2-[5-metil-2-(4-fenoxi-fenil)-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico

De acuerdo con la Preparación 5, Etapas C a D, se convirtió 4-(2-benciloxi-etil)-5-metil-2-(4-fenoxi-fenil)-oxazol en el compuesto del título. ^{1}HRMN (400 MHz, $CDCl_3$) δ 7,81 (d, 2H, J = 9,1 Hz), 7,67 (d, 2H, J = 8,2 Hz), 7,37 (t, 2H, J = 8,2 Hz), 7,15 (m, 3H), 7,12 (m, 4H), 4,39 (t, 2H, J = 6,4 Hz), 2,81 (t, 2H, 6,4 Hz), 2,30 (s, 3H), 2,25 (s, 3H).

Preparación 7

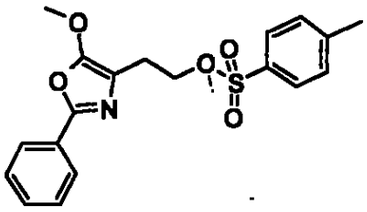
2-[5-Metil-2-(4-nitro-fenil)-oxazol-4-il]-etil éster del ácido 4-metil-3-nitro-bencenosulfónico



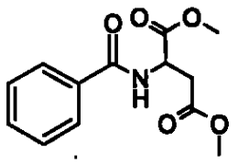
Una mezcla de nitrato potásico (3,0 g, 30 mmol, 2,7 equiv) y ácido sulfúrico (10 ml, 18 g, 94 mmol, 17 equiv) se enfrió a 0°C. Se añadió 2-(5-metil-2-fenil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (4,00 g, 11,2 mmol, 1 equiv) y el baño de hielo se retiró. La mezcla de reacción se calentó con una pistola de calor hasta que se disolvió el tosilato. Después de 30 min, la solución se vertió en H_2O (100 ml) y se extrajo con EtOAc (100 ml). La capa orgánica se secó (Na_2SO_4) y se concentró (75°C) hasta un aceite naranja (4,41 g). El producto bruto se purificó por cromatografía ultrarrápida en gel de sílice (30-50% EtOAc/hexanos) para dar el compuesto del título en forma de un sólido amarillo (3,64 g, 73%). MS (ESI) m/z 447 $(M+H)^+$.

Preparación 8

2-(5-metoxi-2-fenil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico

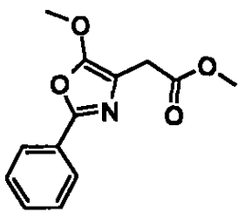


Etapa A: Dimetil éster del ácido 2-benzoilamino-succínico



Una mezcla de cloruro de benzoílo (3,20 ml, 27,7 mmol), Éster dimetílico del ácido L-aspártico (5,0 g, 25,2 mmol) y trietilamina (5,3 ml, 38 mmol) en CH_2Cl_2 (50 ml) se agitó a temperatura ambiente durante 2 h y se diluyó con agua. La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró. El residuo se purificó por cromatografía en gel de sílice (hexanos/EtOAc 1/1) para producir un sólido blanco (5,3 g, 79%). MS (ESI) m/z 266 $(M+H)^+$.

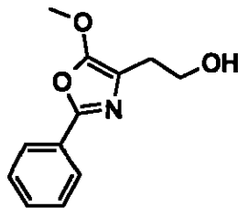
Etapa B: Éster metílico del ácido 3-(5-metoxi-2-fenil-oxazol-4-il)-acético



Una mezcla de éster dimetílico del ácido 2-benzoilamino-succínico (5,3 g, 20 mmol) en 1,2-dicloroetano (15 ml) se trató con P_2O_5 (5,3g, 30 mmol) y Celite (3,2 g) y se calentó a 85°C durante 2 h. El disolvente se decantó y se concentró. El residuo se disolvió en CH_2Cl_2 y se lavó con $NaHCO_3$ acuoso

saturado. La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró. El residuo se purificó por cromatografía en gel de sílice (hexanos/EtOAc 10/1 a 3/1) para producir el compuesto del título (2,9 g, 59%). MS (ESI) m/z 247 $(M+H)^+$.

Etapa C: 3-(5-Metoxi-2-fenil-oxazol-4-il)-etanol



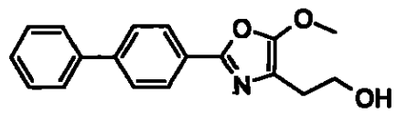
A suspension de LAH (0,56 g, 14,1 mmol) en THF (100 ml) a -78°C se trató gota a gota con una solución de éster metílico del ácido 3-(5-metoxi-2-fenil-oxazol-4-il)-acético (2,9 g, 11,7 mmol) en THF (100 ml). Después de completarse la adición, la mezcla de reacción se calentó hasta la temperatura ambiente, se enfrió a -20°C, y se inactivó con H_2O (0,8 ml), NaOH al 15% (0,8 ml), y H_2O (2,4 ml). La mezcla se filtró a través de Celite y se concentró para dar el compuesto del título en forma de un aceite. MS (ESI) m/z 220,3 $(M+H)^+$.

Etapa D: 2-(5-metoxi-2-fenil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico

Una solución de 3-(5-metoxi-2-fenil-oxazol-4-il)-etanol bruto (11,7 mmol max) en CH_2Cl_2 (100 ml) se trató con cloruro de *para*-toluenosulfonilo (2,7 g, 14,0 mmol), DMAP (100 mg), y trietilamina (2,5 ml, 17,6 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h y se lavó con agua. La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró. El residuo se purificó por cromatografía en gel de sílice (hexanos/EtOAc, 10/1 a 1/1) para producir el compuesto del título (2,0 g, 46% en dos etapas). MS (ESI) m/z 374 $(M+H)^+$.

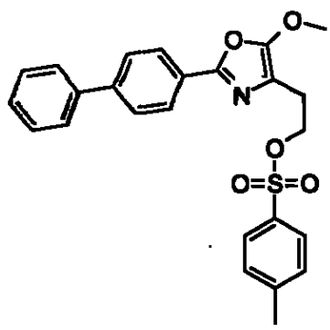
Los siguientes compuestos intermedios se prepararon de una forma sustancialmente similar a la de la Preparación 8.

2-(2-Bifenil-4-il-5-metoxi-oxazol-4-il)-etanol



MS (ESI) m/z 296,0 $(M+H)^+$.

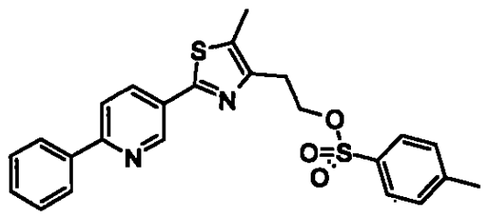
2-(2-Bifenil-4-il-5-metoxi-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico



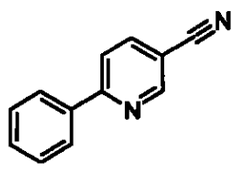
MS (ESI) m/z 450,1 $(M+H)^+$.

Preparación 9

2-[5-Metil-2-(6-fenil-piridin-3-il)tiazol-4-il]etil éster del ácido tolueno-4-sulfónico

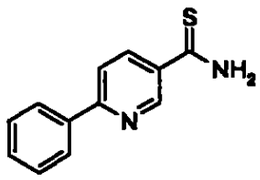


Etapa A: 2-Fenil-5-cianopiridina



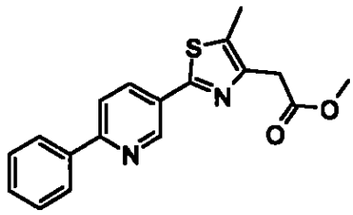
Se calentaron 5-ciano-2-cloropiridina (5,0 g, 36,1 mmol), ácido fenilborónico (6,6 g, 54 mmol), tetraquis(trifenilfosfina) paladio (0) (0,5 g), y Na_2CO_3 acuoso (7,6 g), en tolueno (100 ml) a 90°C durante 16 h. La mezcla se diluyó con EtOAc y se lavó con H_2O. La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró. El residuo se purificó por cromatografía en gel de sílice (hexanos/EtOAc 2/1) para producir el compuesto del título (6,1 g, 94%). MS (ESI) m/z 181 $(M+H)^+$.

Etapa B:



Una mezcla de 2-fenil-5-cianopiridina (6,0 g, 33 mmol) y tioacetamida (4,0 g, 53 mmol) en HCl 4 N en 1,4-dioxano (50 ml) se calentó a 98°C durante 20 h. La mezcla de reacción se enfrió y se vertió en $NaHCO_3$ acuoso saturado. El precipitado se recogió, se lavó con agua, y se secó al vacío (60°C) para producir el compuesto del título en forma de un sólido amarillo (7,0 g, 99%).

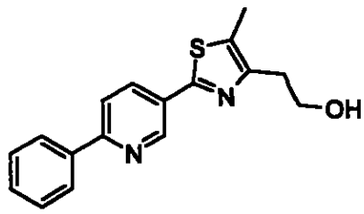
Etapa C: Éster metílico del ácido [5-metil-2-(6-fenil-piridin-3-il)-tiazol-4-il]-acético



Una mezcla de 6-fenil-tionicotinamida (7,0 g) y éster metílico del ácido 4-bromo-3-oxo-pentanoico (9,15 g, 35 mmol) en 1,4-dioxano (30 ml) se calentó a

reflujo durante 4 h. La mezcla de reacción se enfrió, se vertió en $NaHCO_3$ acuoso saturado y se extrajo con CH_2Cl_2. La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró. El residuo se purificó por cromatografía en gel de sílice (hexanos/EtOAc, 2/1) para producir el compuesto del título (6,0 g, 56%). MS (ESI) m/z 325 $(M+H)^+$.

Etapa D: [5-Metil-2-(6-fenil-piridin-3-il)-tiazol-4-il]-etanol



Una solución de éster metílico del ácido [5-metil-2-(6-fenil-piridin-3-il)-tiazol-4-il]-acético (6,0 g, 18,5 mmol) en THF (500 ml) se añadió gota a gota a una suspensión de LAH (0,90 g, 22,2 mmol) en THF (300 ml) a -78°C. Después de completarse la adición, la mezcla de reacción se dejó calentar a temperatura ambiente, se enfrió a -20 °C, y se inactivó secuencialmente con H_2O (1,1 ml), NaOH al 15% (1,1 ml), y H_2O (3,3 ml). La mezcla se filtró a través de Celite, y el filtrado se concentró para dar el compuesto del título en forma de un aceite que se usó directamente en la siguiente etapa.

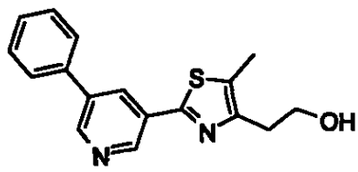
Etapa E: 2-[5-Metil-2-(6-fenil-piridin-3-il)tiazol-4-il]etil éster del ácido tolueno-4-sulfónico

Una mezcla de [5-metil-2-(6-fenil-piridin-3-il)-tiazol-4-il]-etanol (18,5 mmol max), cloruro de *para*-toluenosulfonilo (3,89 g, 20,5 mmol), DMAP (500 mg), y trietilamina (4,0 ml, 28,0 mmol) en CH_2Cl_2 (300 ml) se agitó a temperatura ambiente durante 2,5 h. La mezcla de reacción se diluyó con agua, y la capa orgánica se separó, se secó ($MgSO_4$), se filtró, y se concentró. El residuo se

purificó por cromatografía en gel de sílice (hexanos/EtOAc, 10/1 a 1/1) para producir el compuesto del título en forma de un sólido (2,0 g, 46% en dos etapas). MS (ESI) m/z 451 $(M+H)^+$.

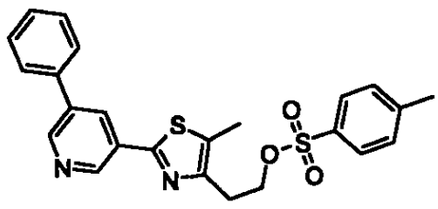
Los siguientes compuestos intermedios se prepararon de una forma sustancialmente similar a la de la Preparación 9.

2-[5-Metil-2-(5-fenil-piridin-3-il)-tiazol-4-il]-etanol



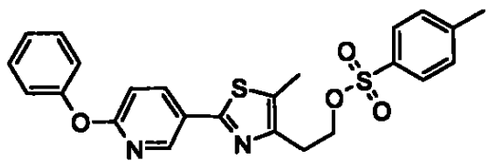
MS (ESI) m/z 297 $(M+H)^+$.

2-[5-Metil-2-(5-fenil-piridin-3-il)tiazol-4-il]etil éster del ácido tolueno-4-sulfónico



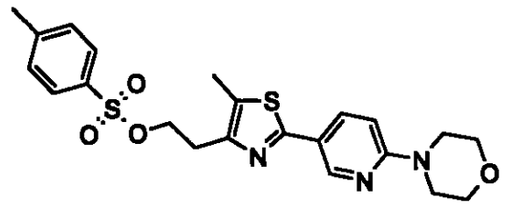
MS (ESI) m/z 451 $(M+H)^+$.

2-[5-Metil-2-(6-fenoxi-piridin-3-il)-tiazol-4-il]-etil éster del ácido tolueno-4-sulfónico



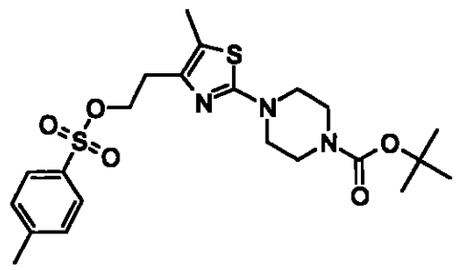
^{1}HRMN 400 MHz ($CDCl_3$) δ 8,52 (2, 1H), 8,03 (d, 1H, J = 6,9 Hz), 7,63 (d, 2H, J = 8,6 Hz), 7,42 (t, 2H, J = 7,7 Hz), 7,2 (m,5H), 6,91 (1H, d, J = 7,7 Hz), 4,37 (t, 2H, J = 6,3 Hz), 3,02 (t, 2H, J = 6,3 Hz), 2,39 (s, 3H), 2,28 (s, 3H).

2-[5-Metil-2-(6-morfolin-4-il-piridin-3-il)-tiazol-4-il]-etil éster del ácido tolueno-4-sulfónico



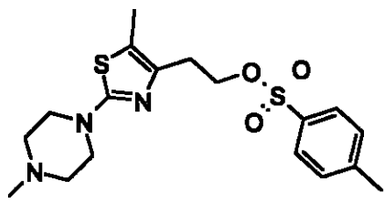
^{1}HRMN 400 MHz ($CDCl_3$) δ 8,51 (s, 1H), 7,82 (d, 1H, J = 8,5 Hz), 7,63 (d, 2H, J = 7,8 Hz), 7,19 (d, 2h, J = 7,8 Hz), 6,61 (d, 1H, J = 8,5 Hz), 4,37 (t, 2H, J = 6,5 Hz), 3,82 (t, 2H, J = 5,2 Hz), 3,58 (t, 2H, J = 5,2 Hz), 2,99 (t, 2H, J = 6,5 Hz), 2,35 (s, 3H), 2,27 (s, 3H).

Éster terc-butílico del ácido 4-{5-Metil-4-[2-(tolueno-4-sulfoniloxi)-etil]-tiazol-2-il}-piperazina-1-carboxílico



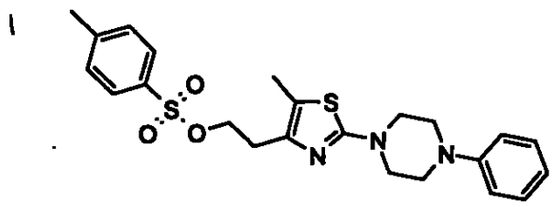
MS (ESI) m/z 482 $(M+H)^+$.

2-[5-Metil-2-(4-metil-piperazin-1-il)-tiazol-4-il]-etil éster del ácido tolueno-4-sulfónico



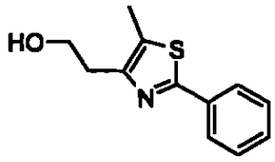
MS (ESI) m/z 396,1 $(M+H)^+$.

2-[5-Metil-2-(4-fenil-piperazin-1-il)-tiazol-4-il]-etil éster del ácido tolueno-4-sulfónico



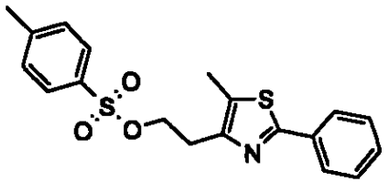
MS (ESI) m/z 458,1 $(M+H)^+$.

2-(5-Metil-2-fenil-tiazol-4-il)-etanol



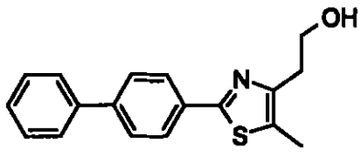
MS (ESI) m/z 220 $(M+H)^+$.

2-(5-Metil-2-fenil-tiazol-4-il)-etil éster del ácido tolueno-4-sulfónico:



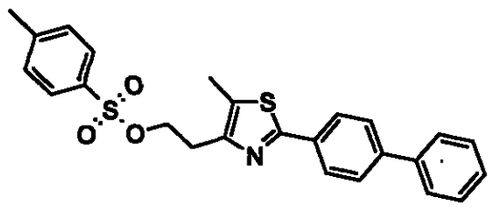
MS (ESI) m/z 374 $(M+H)^+$.

2-(2-Bifenil-4-il-5-metil-tiazol-4-il)-etanol



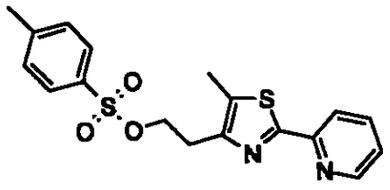
MS (ESI) m/z 296 $(M+H)^+$.

2-(2-Bifenil-4-il-5-metil-tiazol-4-il)-etil éster del ácido tolueno-4-sulfónico



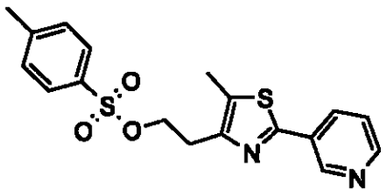
MS (ESI) m/z 450 $(M+H)^+$.

2-(5-Metil-2-piridin-2-iltiazol-4-il) etil éster del ácido tolueno-4-sulfónico



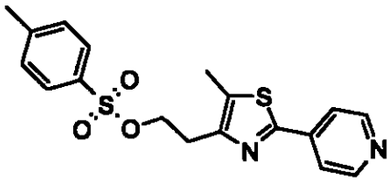
MS (ESI) m/z 375,1 $(M+H)^+$.

2-(5-Metil-2-piridin-3-iltiazol-4-il) etil éster del ácido tolueno-4-sulfónico



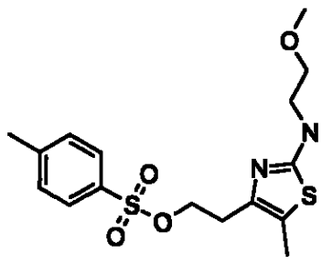
MS (ESI) m/z 375,1 $(M+H)^+$.

2-(5-Metil-2-piridin-4-iltiazol-4-il) etil éster del ácido tolueno-4-sulfónico



MS (ESI) m/z 375 $(M+H)^+$. MS (ESI) m/z 383,1 $(M+H)^+$.

2-[2-(2-Metoxietilamino)-5-metiltiazol-4-il] etil éster del ácido tolueno-4-sulfónico

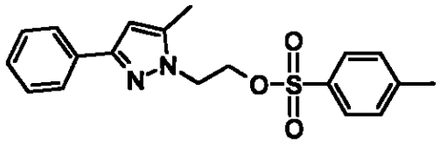


MS (ESI) m/z 371 $(M+H)^+$.

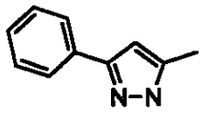
Pirazoles

Preparación 10

2-(5-Metil-3-fenil-pirazol-1-il)-etil éster del ácido tolueno-4-sulfónico

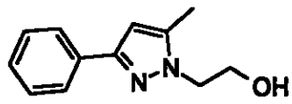


Etapa A: 5-Metil-3-fenil-1*H*-pirazol



Se añadió hidracina hidrato (9,0 ml, 99 mmol, 35% en peso en H_2O; 0,64 equiv) a una solución de benzoilacetona (25,00 g, 154,1 mmol, 1 equiv) en etanol (250 ml). Después de agitar durante 14 h, se añadió más hidracina hidrato (8,0 ml, 88 mmol, 0,57 equiv). Después de 2 h, la solución de reacción se concentró (95°C) para dar el compuesto del título en forma de un sólido blanco (24,31 g, 99,7%). HRMS Calculado para $C_{10}H_{11}N_2$: m/z 159,0922. Encontrado: 159,0917

Etapa B: 2-(5-Metil-3-fenil-pirazol-1-il)-etanol



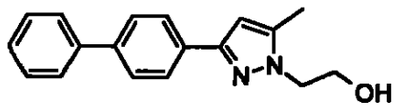
Se añadió hidruro sódico (2,5 g, 1,5 g NaH, 62 mmol, 1,1 equiv) durante un periodo de 3 min a una solución de 5-metil-3-fenil-1*H*-pirazol (9,00 g, 56,9 mmol, 1 equiv) en DMF (90 ml) y se enfrió a 0 °C en un baño de hielo. Después de agitar durante 15 min, se añadió carbonato de etileno (7,6 ml, 10 g, 110 mmol, 2,0 equiv). El baño se retiró, y la mezcla de reacción se agitó durante 15 h. La mezcla se trató con K_2CO_3 ac. 4 M (90 ml), se calentó a reflujo durante 5 h, y se diluyó con H_2O (200 ml). Después de dejar que la mezcla caliente se enfriara durante 15 min, se añadió más H_2O (100 ml) y después hexanos (100 ml). La mezcla se agitó vigorosamente y después se dejó separar. Los cristales formados se combinaron con la capa orgánica superior. La capa acuosa se separó, y los cristales se recogieron por filtración al vacío y se lavaron con hexanos (2 x 50 ml). Los cristales se disolvieron en Et_2O/EtOAc (1:1; 200 ml), y la solución se secó (Na_2SO_4), se filtró, y se concentró (75 °C) para dar el compuesto del título en forma de un sólido cristalino blanquecino (6,86 g, 59,6%). HRMS Calculado para $C_{12}H_{15}N_2O$: m/z 203,1184. Encontrado: 203,1168

Etapa C: 2-(5-Metil-3-fenil-pirazol-1-il)-etil éster del ácido tolueno-4-sulfónico

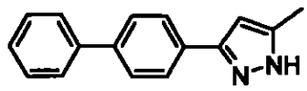
De acuerdo con la Preparación 9, Etapa E, se convirtió 2-(5-metil-3-fenil-pirazol-1-il)-etanol en el compuesto del título. MS (ESI) m/z 357 $(M+H)^+$.

Preparación 11

2-(3-Bifenil-4-il-5-metil-pirazol-1-il)-etanol



Etapa A: 5-Bifenil-4-il-3-metil-1*H*-pirazol



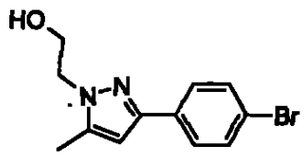
A una mezcla agitada de NaH (1,98 g, .049 mol, dispersión en aceite al 60%) en THF seco (30 ml) se le añadió gota a gota durante 15 min. una suspensión de dietoxifosforilacetona tosil hidrazona (8,97 g, .024 mol; N Almirante *Syn. Lett.* 1999, 302,) en una mezcla de THF (35 ml) y DMF (5,0 ml). La solución amarilla se agitó a 0-5°C durante 30 min y se trató con a carboxaldehído de 4-bifenilo (3,10 g, .0169 mol) en THF seco (30 ml) a 0-5°C durante 15 min. La solución naranja se calentó y se agitó a reflujo durante 4 h y se agitó a temperatura ambiente durante una noche. La mezcla se vertió en NaH_2PO_4 ac. al 5% (350 ml) y se extrajo con EtOAc (2 x 200ml). Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron, y se concentraron para dar un semi-sólido amarillo. Este material se trituró con EtOAc caliente (20 ml) y se filtró. El sólido se lavó con EtOAc (2 x 10 ml) y se secó a alto vacío para dar el compuesto del título (2,61 g, 47%): HRMS Calculado para $C_{16}H_{15}N_2$: m/z 235,1235. Encontrado: 235,1230,

Etapa B: 2-(3-Bifenil-4-il-5-metil-pirazol-1-il)-etanol

El compuesto del título se preparó a partir de 5-bifenil-4-il-3-metil-1*H*-pirazol de acuerdo con la Preparación 10, Etapa B. HRMS Calculado para $C_{18}H_{19}N_2O$: m/z 279,1497. Encontrado: 279,1496,

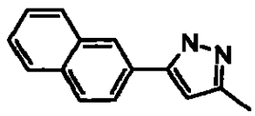
Los siguientes compuestos intermedios se prepararon sustancialmente de una forma similar a la descrita en las Preparaciones 10 y 11.

2-[3-(4-Bromo-fenil)-5-metil-pirazol-1-il]-etanol



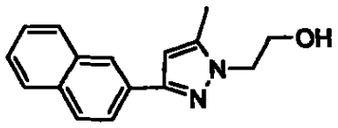
HRMS Calculado para $C_{12}H_{14}BrN_2O$: m/z 281,0289. Encontrado: 281,0288.

3-Metil-5-naftalen-2-il-1*H*-pirazol



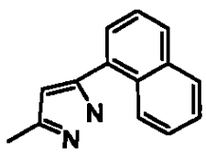
HRMS Calculado para $C_{14}H_{12}N_2$: m/z 208,1001. Encontrado: 208,0981.

2-(5-Metil-3-naftalen-2-il-pirazol-1-il)-etanol



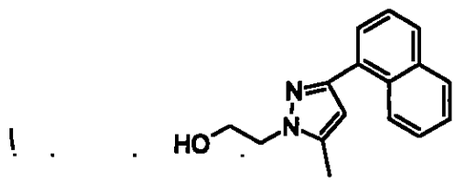
HRMS Calculado para $C_{16}H_{17}N_2O$: m/z 253,1341. Encontrado: 253,1339.

3-Metil-5-naftalen-1-il-1*H*-pirazol



Anal Calculado para $C_{14}H_{12}N_2$: C, 80,74; H, 5,81; N, 13,45. Encontrado: C, 80,93; H, 5,70; N, 13,42; p.f. 115-117°C.

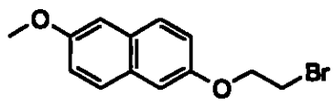
2-(5-Metil-3-naftalen-1-il-pirazol-1-il)-etanol.



Preparaciones de bromuro de éter arílico

Preparación 12

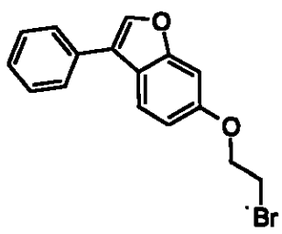
2-(2-Bromo-etoxi)-6-metoxinaftaleno



A una solución de 6-metoxinaftalen-2-ol (1,07 g, 6,14 mmol) en DMF (4 ml) se le añadieron carbonato de cesio (3,11 g, 9,55 mmol) y dibromoetano (2,5 ml, 29 mmol). La mezcla se agitó y se calentó a 55°C durante 48 h. La mezcla de reacción se enfrió, se filtró, se diluyó con EtOAc, y se lavó con salmuera (2 x 30 ml). La capa orgánica se secó (Na_2SO_4) y se concentró. El producto bruto se purificó usando cromatografía radial (2:98 a 25:75 de EtOAc:Hex) para dar el compuesto del título en forma de un sólido blanco (0,52 g, 30 %): ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,61 (t, J = 6,1 Hz, 2H), 3,82 (s, 3H), 4,30 (t, J = 6,4 Hz, 2H), 7,01-7,08 (m, 4H), 7,56 (dd, J = 12,0, 9,0 Hz, 2H).

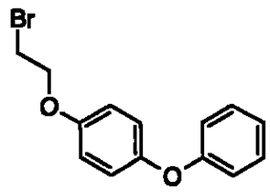
Los siguientes compuestos intermedios se prepararon de una forma sustancialmente similar a la de la Preparación 12.

6-(2-Bromoetoxi)-3-fenilbenzofurano



El compuesto anterior se prepara a partir de 3-fenilbenzofurano-6-ol (véase *Bull. Soc. Chim. Fr.*, 942 (1962)). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,60 (t, J = 6,4 Hz, 2H), 4,28 (t, J = 6,4 Hz, 2H), 6,88 (dd, J = 8,8, 2,4 Hz, 1H), 7,00 (d, J = 2,4 Hz, 1H), 7,26-7,30 (m, 1H), 7,36-7,44 (m, 2H), 7,52-7,56 (m, 2H), 7,63 (d, J = 9,8 Hz, 2H).

4-(2-Bromoetoxi)-1-fenoxibenceno



^{1}H RMN (400 MHz, $CDCl_3$) δ 3,55 (t, J = 6,4 Hz, 2H), 4,19 (t, J = 6,1 Hz, 2H), 6,80-6,90 (m, 6H), 6,96 (t, J = 7,3 Hz, 1H), 7,17-7,24 (m, 2H).

4-(3-Bromoetoxi)bifenil: MS (ESI) m/z 295 $(M+NH_3)^+$.

3-(2-Bromoetoxi)bifenil: ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,58 (t, J = 6,4 Hz, 2H), 4,27 (t, J = 6,4 Hz, 2H), 6,81 (dd, J = 8,3, 2,4 Hz, 1H), 6,90 (d, J = 8,8 Hz, 1H), 7,13 (dd, J = 7,8, 1,0 Hz, 1H), 7,26-7,33 (m, 2H), 7,34-7,37 (m, 2H), 7,43-7,50 (m, 2H).

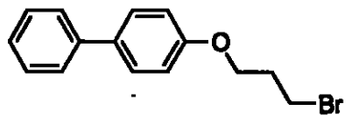
6-(4-Bromopropoxi)-3-fenilbenzofurano: ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,26-2,33 (m, 2H), 3,57 (t, J = 6,4 Hz, 2H), 4,11 (t, J = 5,9 Hz, 2H), 6,89 (dd, J = 8,6, 2,2 Hz, 1H), 7,01 (d, J = 2,0 Hz, 1H), 7,29 (t, J = 7,6 Hz, 1H), 7,40 (t, J = 7,6 Hz, 2H), 7,56 (d, J = 6,8 Hz, 2H), 7,57-7,65 (m, 2H).

2-(4-Bromopropoxi)-6-metoxinaftaleno: ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,29 (t, J = 6,1 Hz, 2H), 3,56 (t, J = 6,4 Hz, 2H), 3,81 (4,11 (t, J = 5,9 Hz, 2H), 7,01-7,14 (m, 4H), 7,52-7,57 (m, 2H).

3-(4-Bromopropoxi)bifenil: ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,27 (t, J = 6,1 Hz, 2H), 3,55 (t, J = 6,6 Hz, 2H), 4,09 (t, J = 5,9 Hz, 2H), 6,81 (dd, J = 2,9, 1,0

Hz, 1H), 7,05 (t, J = 2,0 Hz, 1H), 7,07 (t, J = 2,0 Hz, 1H), 7,22-7,24 (m, 2H), 7,26-7,37 (m, 2H), 7,43-7,52 (m, 3H).

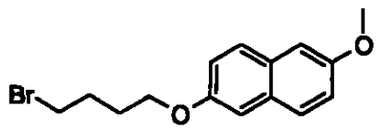
4-(3-Bromopropoxi)-bifenil:



^{1}H-RMN (200,15 MHz, $CDCl_3$): đ 7,57-7,29 (m, 7H), 6,98 (dd, 2H, J = 6,72, 1,88), 4,15 (t, 2H, J = 5,92), 3,62 (t, 2H, J = 6,44), 2,34 (qn, 2H, J = 5,92).

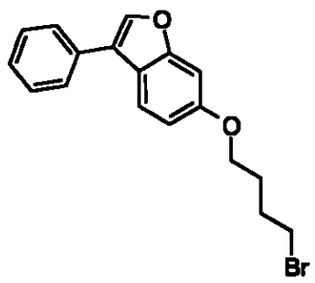
4-(3-Bromopropoxi)-1-fenoxibenceno: ^{1}H-RMN (300 MHz, $CDCl_3$): đ 7,3 (2H, m), 7,1 (2H, m), 7,0(2H, m), 6,9 (2H, m), 4,1 (2H, m); 3,6 (2H, m); 2,3 (2H, m).

2-(4-Bromobutoxi)-6-metoxinaftaleno



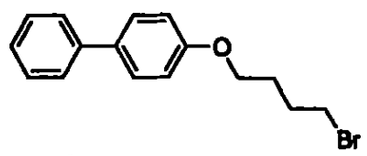
^{1}H RMN (400 MHz, $CDCl_3$) δ 1,88-1,97 (m, 2H), 1,99-2,10 (m, 2H), 3,41-3,48 (m, 2H), 3,81 (s, 3H), 4,00 (t, J = 5,9 Hz, 2H), 7,00-7,05 (m, 3H), 7,13-7,19 (m, 1H), 7,54 (t, J = 8,1 Hz, 2H).

6-(4-Bromobutoxi)-3-fenilbenzofurano



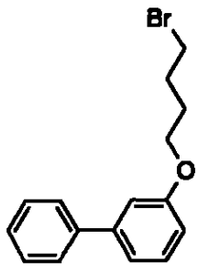
^{1}H RMN (400 MHz, $CDCl_3$) δ 1,90-1,98 (m, 2H), 2,01-2,04 (m, 2H), 3,41-3,44 (m, 2H), 3,94-3,99 (m, 2H), 6,83-6,91 (m, 1H). 6,96-6,97 (m, 1H), 7,27-7,29 (m, 1H), 7,36-7,43 (m, 2H), 7,53-7,62 (m, 4H).

4-(4-Bromobutoxi)bifenilo



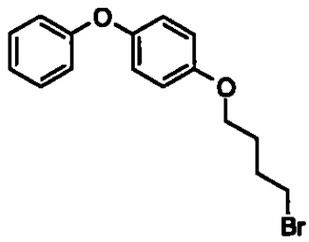
^{1}H RMN (400 MHz, $CDCl_3$) δ 2,03 (t, J = 6,8 Hz, 2H), 3,42 (t, J = 6,6 Hz, 2H), 3,96 (t, J = 6,5 Hz, 2H), 6,87 (d, J = 7,8 Hz, 2H), 7,17-7,23 (m, 3H), 7,32 (t, J = 7,6 Hz, 1H), 7,42-7,47 (m, 4H).

3-(4-Bromobutoxi)bifenilo



^{1}H RMN (400 MHz, $CDCl_3$) δ 1,86-1,95 (m, 2H), 1,96-2,05 (m, 2H), 2,42 (t, J = 6,6 Hz, 2H), 3,98 (t, J = 6,1 Hz, 2H), 6,79 (dd, J = 7,3, 2,0 Hz, 1H), 7,03-7,11 (m, 1H), 7,26 (t, J = 7,8 Hz, 2H), 7,35 (t, J = 7,8 Hz, 2H), 7,42-7,51 (m, 2H).

4-(4-Bromobutoxi)-1-fenoxibenceno

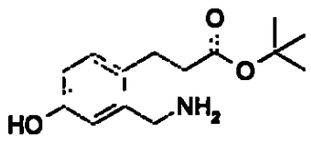


^{1}H RMN (400 MHz, $CDCl_3$) δ 1,83-2,03 (m, 2H), 1,96-2,03 (m, 2H), 3,41 (t, J = 6,6 Hz, 2H), 3,90 (t, J = 6,5 Hz, 2H), 6,76-6,78 (m, 2H), 6,79-6,90 (m, 4H), 6,94-6,97 (m, 1H), 7,19-7,23 (m, 2H).

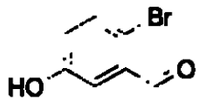
Preparaciones de Piezas de Cabeza

Preparación 13

Éster terc-butílico del ácido 3-(2-Aminometil-4-hidroxi-fenil)-propiónico

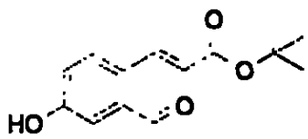


Etapa A: 2-Bromo-5-hidroxibenzaldehído



A una suspensión de 3-hidroxibenzaldehído (1 kg, 8,2 mol) en CH_2Cl_2 (10 l) se le añadió una solución de bromo (1,3 kg, 8,2 mol) en CH_2Cl_2 (620 ml) durante 1 h. Después de agitar durante aproximadamente 22 h, los sólidos se aislaron por filtración, se lavaron con CH_2Cl_2 (4 l), y se secaron al vacío para producir de 2-bromo-5-hidroxibenzaldehído en forma de un sólido castaño (1,05 kg, 63%).

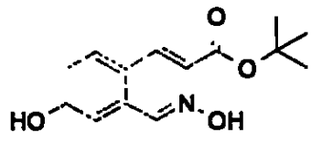
Etapa B: Éster terc-butílico del ácido 3-(2-formil-4-hidroxi-fenil)-acrílico



A una solución de 2-bromo-5-hidroxibenzaldehído (200 g, 1,0 mole) en propionitrilo (6 l) en una atmósfera de N_2 se le añadió tri-o-tolil fosfina (75,4 g, 0,25 mol) y diisopropiletilamina (350 ml, 260 g, 2,0 mol). La solución se desgasificó y se purgó con N_2 tres veces. A esta solución se le añadió acrilato de terc-butilo (440 ml, 385 g, 3,0 mol) y trímero de acetato de paladio (27,8 g, 0,12 mol). La mezcla se desgasificó tres veces y se calentó a 80°C durante 30 min. Después de 30 min, la reacción se enfrió a temperatura ambiente y se

filtró. Los sólidos se lavaron con acetonitrilo. El filtrado se transfirió a un embudo de decantación con acetonitrilo (4 l total) y se extrajo con hexanos (4 x 5 l). La capa de propionitrilo/acetonitrilo se concentró por evaporación rotatoria. El residuo se disolvió en tolueno (4 l) y se lavó sucesivamente con HCl 1 N (1 l), agua (1 l), y salmuera (1 l). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró para producir el producto bruto en forma de un sólido pardo húmedo (293 g). El producto bruto se disolvió en CH_2Cl_2 (600 ml) con agitación. A esta solución se le añadieron hexanos (1,8 l) durante ~2 h, y la suspensión resultante se agitó a temperatura ambiente durante 1 h. La suspensión se enfrió en un baño de agua enfriada con hielo y se agitó durante 1 h. El producto se aisló por filtración, se lavó con hexanos, y se secó al vacío para producir el producto en forma de un sólido castaño (199,5 g, 80,6%).

Etapa C: Éster terc-butílico del ácido 3-[4-hidroxi-2-(hidroxiimino-metil)-fenil]-acrílico



Una suspensión de clorhidrato de hidroxilamina (8,33 g, 0,12 mol), piridina (9,49 g, 0,12 mol), y etanol (100 ml) se agitó a temperatura ambiente durante 30 min. Se añadió éster terc-butílico del ácido 3-(2-formil-4-hidroxi-fenil)-acrílico (14,90 g, 0,06 mol) seguido de un aclarado de etanol (49 ml). La solución parda resultante se agitó a temperatura ambiente durante 16 h y se concentró. El residuo se suspendió en agua (150 ml) y se extrajo con acetato de etilo (3 x 100 ml). Las capas orgánicas combinadas se lavaron con una solución saturada de NaCl (2 x 100 ml), se secaron (Na_2SO_4), y se filtraron a través de un lecho de gel de sílice para retirar pequeñas cantidades de

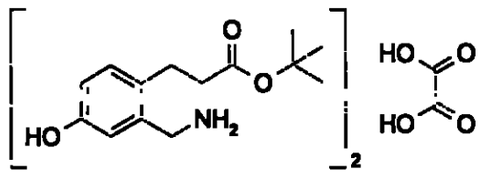
impurezas polares. El filtrado se concentró para dar el producto bruto (16,04 g). Una muestra de 13,56 g del material bruto se cristalizó en heptano (70 ml) y acetato de etilo (80 ml) para dar el compuesto del título (7,41 g, 55%), p.f. 146-149°C. ^{1}H RMN (CD_3OD): δ1,53 (s, 9H), 4,83 (s, 2H), 6,15-6,23 (d, 1H), 6,82-6,87 (dd, 1H), 7,10-7,12 (d, 1H), 7,52-7,55 (d, 1H), 7,98-8,03 (d, 1H), 8,37 (s, 1H). MS (ES^+) m/z 286,1 ($[M+Na]^+$). MS (ES^-) m/z 262,2 ($[M-H]^-$). Anal. Calculado para $C_{14}H_{17}NO_4$: C: 63,8658; H: 6,5081; N: 5,3198. Encontrado: C: 63,71; H: 6,38; N: 5,51,

Etapa D: Éster terc-butílico del ácido 3-(2-aminometil-4-hidroxi-fenil)-propiónico

Una solución de éster terc-butílico del ácido 3-[4-hidroxi-2-(hidroxiimino-metil)-fenil]-acrílico (0,50 g, 1,9 mmol) en etanol (50 ml) se trató con paladio al 10% sobre carbono (0,25 g). La suspensión resultante se trató con hidrógeno usando un aparato agitador Parr a temperatura ambiente y 50 psi (344,73 kPa) durante 16 h. La mezcla de reacción se filtró a través de Celite, se aclaró con etanol (20 ml), y se concentró. El residuo se disolvió en acetato de etilo (50 ml) y se lavó con una solución al 10% de K_2CO_3 (2 x 25 ml) y NaOH 1 N (2 x 25 ml). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró. El residuo se cristalizó en acetato de isopropilo para dar el compuesto del título (0,14 g, 40%), p.f. 154-157°C. ^{1}H RMN (CD_3OD): δ1,37 (s, 9H), 2,44-2,50 (t, 2H), 2,80-2,85 (t, 2H), 3,75 (s, 2H), 4,83 (s, 3H), 6,57-6,63 (dd, 1H), 6,75-6,77 (d, 1H), 6,95-7,00 (d, 1H). MS (ES^+) m/z 252,1 ($[M+H]^+$). MS (ES^-) m/z 250,2 ($[M-H]^-$). Anal. Calculado para $C_{14}H_{21}NO_3$: C: 66,9069; H: 8,4222; N: 5,5731. Encontrado: C: 66,57; H: 8,29; N: 5,60.

Preparación 14

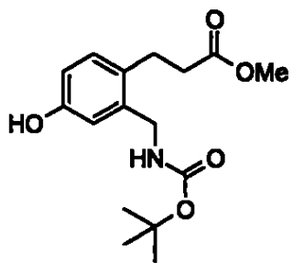
Etandioato del éster terc-butílico del ácido 3-(2-aminometil-4-hidroxi-fenil)-propiónico (2: 1)



Alternativo a la cristalización de éster terc-butílico del ácido 3-(2-aminometil-4-hidroxi-fenil)-propiónico en acetato de isopropilo. El terc-butil-3-[2-(aminometil)-4-hidroxifenil]propanoato bruto (0,50 g, 0,002 mol) se disolvió en acetato de etilo a reflujo (10 ml). Se añadió una solución de ácido oxálico (0,18 g, 0,002 mol) disuelto en acetato de etilo (5 ml) e inmediatamente se produjo un precipitado. La suspensión resultante se enfrió a 0°C y se filtró. El producto aislado se suspendió en etanol (5 ml), se enfrió a 0°C, y se filtró para dar etandioato del éster terc-butílico del ácido 3-(2-aminometil-4-hidroxi-fenil)-propiónico (2:1) (0,41 g, 69%). p.f. 188-190°C. ^{1}H RMN (DMSO-d_6): d1,36 (s, 18H), 2,39-2,45 (t, 4H), 2,47-2,52 (m, 4H), 2,70-2,76 (t, 4H), 3,83 (s, 4H), 6,61-6,65 (dd, 2H), 6,77-6,82 (d, 2H), 6,97-7,01 (d, 2H). MS (ES^+) m/z 252,1 ($[M+H]^+$). MS (ES^-) m/z 250,2 ($[M-H]^-$). Anal. Calculado para $C_{30}H_{44}N_2O_{10}$: C: 60,80; H: 7,48; N: 4,73. Encontrado: C: 60,79; H: 7,51; N: 4,81,

Preparación 15

Metil éster del ácido 3-[2-(terc-butoxicarbonilamino-metil)-4-hidroxi-fenil]-propiónico

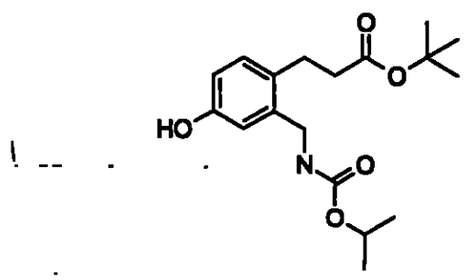


Una solución de éster terc-butílico del ácido 3-(2-aminometil-4-hidroxi-fenil)-propiónico (1,00 g, 3,98 mmol) en CH_2Cl_2 (10 ml) se trató con agua (12 gotas) y después con TFA (10 ml). La solución se agitó a temperatura ambiente durante 6,5 h y se concentró. El residuo se diluyó con 2,2-dimetoxipropano (40 ml), HCl conc. (4 ml), y después con MeOH (10 ml). La solución se agitó durante 18 h y se concentró para dar ácido 3-(2-aminometil-4-hidroxi-fenil)-propiónico: sal HCl en forma de un sólido castaño. MS (ES^-) m/z 208 [M-1].

El sólido se diluyó con THF (20 ml) y una solución acuosa saturada de $NaHCO_3$ (12 ml) y se trató con dicarbonato de di-*terc*-butilo (1,09 g, 5,00 mmol). La mezcla se agitó durante 3 h y se concentró y el residuo se repartió entre EtOAc (75 ml) y HCl 1 N (30 ml). La capa orgánica se secó (Na_2SO_4), y se concentró para dar el compuesto del título (1,16 g, 94 %). MS (ES^-) m/z 308 [M-1].

Preparación 16

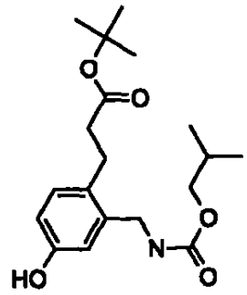
Éster terc-butílico del ácido 3-[4-hidroxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



Una suspensión de éster terc-butílico del ácido 3-(2-aminometil-4-hidroxi-fenil)-propiónico (75,4 g, 0,3 mol) en CH_2Cl_2 (900 ml) a 1°C se trató con trietilamina (60,7 g, 0,6 mol). Se añadió cloroformiato de isopropilo (300 ml, 0,3 mol, 1M en tolueno) mientras se mantenía la temperatura por debajo de 12°C. La solución resultante se agitó 16 h a temperatura ambiente. Después de 16 h, se añadió más cloroformiato de isopropilo (15 ml, 0,015 mol, 1,0M en tolueno) y la reacción se agitó durante 1 h. La mezcla de reacción se lavó con HCl 1 N (2 x 200 ml) y una solución de $NaHCO_3$ saturado (2 x 200 ml). La capa orgánica se secó (Na_2SO_4) y se concentró. El residuo se purificó por filtración a través de gel de sílice Merck 62 (750 gramos, CH_2Cl_2/MeOH 100/0 a 96/4) para dar el compuesto del título (95,48 g, 94,3%). ^1H RMN (300 MHz, $CDCl_3$): d1,20-1,24 (d, 6H), 1,40 (s, 9H), 2,46-2,52 (t, 2H), 2,81-2,86 (t, 2H), 4,29-4,32 (d, 2H), 4,86-4,97 (m, 1H), 5,19-5,28 (m, 1H), 6,67-6,72 (dd, 2H), 6,76 (s, 1H), 6,97-7,00 (d, 1H). MS (ES^-) m/z 336,1 $[M-H]^-$.

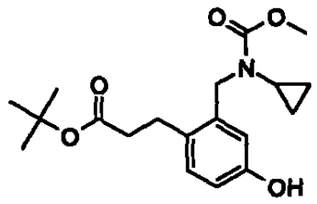
Los siguientes compuestos intermedios se prepararon de una forma sustancialmente similar a la de la Preparación 16.

<u>Éster terc-butílico del ácido 3-[4-hidroxi-2-(isobutoxicarbonilamino-metil)-fenil]-propiónico</u>



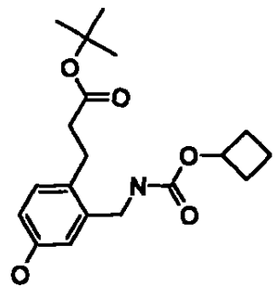
MS (ES$^-$) m/z 350 [M-H]$^-$.

Éster terc-butílico del ácido 3-[2-(ciclopropilmetoxicarbonilamino-metil)-4-hidroxi-fenil]-propiónico



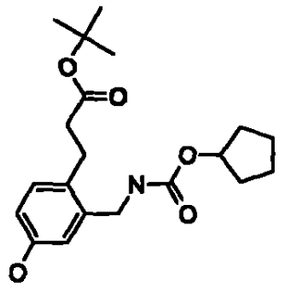
HRMS Calculado para $C_{19}H_{26}NO_5$: m/z 348,1811. Encontrado: 348,1817.

Éster terc-butílico del ácido 3-[2-(ciclobutoxicarbonilamino-metil)-4-hidroxi-fenil]-propiónico



HRMS Calculado para $C_{19}H_{26}NO_5$: m/z 348,1811. Encontrado: 348,1817.

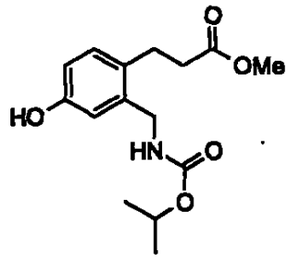
Éster terc-butílico del ácido 3-[2-(ciclopentiloxicarbonilamino-metil)-4-hidroxi-fenil]-propiónico



MS (ES^-) m/z 362 $[M-H]^-$.

Preparación 17

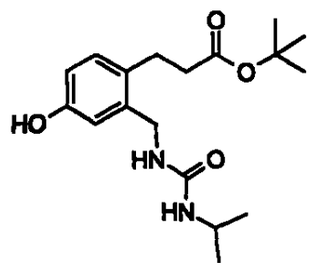
Éster metílico del ácido 3-[4-hidroxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



Una solución de éster terc-butílico del ácido 3-[4-hidroxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (3,0 mmol, 1,0g) en CH_2Cl_2 (10 ml) se trató con CF_3CO_2H al 90%/H_2O (20 ml) a temperatura ambiente. La mezcla se agitó durante 3 h y se concentró. El residuo se disolvió en MeOH (20 ml), se trató con H_2SO_4 conc. (1 ml), y se calentó a reflujo durante 14 h. La mezcla se enfrió y se concentró. El residuo se disolvió en agua/acetato de etilo y se neutralizó con K_2CO_3. La capa orgánica se secó (Na_2SO_4), y se concentró para dar el compuesto del título (0,76 g, 86 %). HRMS Calculado para $C_{15}H_{22}NO_5$: m/z 296,1498. Encontrado: 296,1504,

Preparación 18

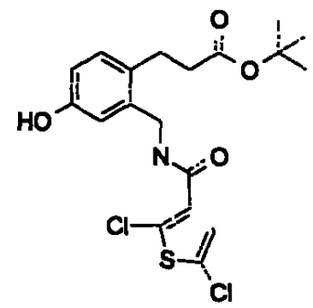
Éster terc-butílico del ácido 3-[4-hidroxi-2-(3-isopropil-ureidometil)-fenil]-propiónico



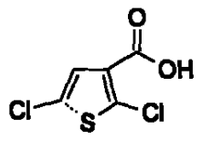
Una suspensión de éster terc-butílico del ácido 3-(2-aminometil-4-hidroxi-fenil)-propiónico (2,24 g, 8,91 mmol) en CH_2Cl_2 (30 ml) se trató con isocianato de isopropilo (1,1 ml, 11 mmol). La mezcla de reacción se diluyó con agua, el CH_2Cl_2 se retiró a presión reducida, y la capa acuosa se extrajo con EtOAc. La capa orgánica se secó ($MgSO_4$) y se concentró para dar el compuesto del título en forma de un sólido blanco (2,6 g, 87%). MS (ES^+) m/z 337 $[M+H]^+$.

Preparación 19

Éster terc-butílico del ácido 3-(2-{[(2,5-dicloro-tiofeno-3-carbonil)-amino]-metil}-4-hidroxi-fenil)-propiónico



Etapa A: Ácido 2,5-dicloro-tiofeno-3-carboxílico



Una mezcla de te 1-(2,5-dicloro-tiofen-3-il)-etanona (10 g, 51,26 mmol) y NaOCl al 9,5% (150 ml, 230 mmol, 4,5 eq., blanco comercial) se trató con NaOH 5 N (1 ml, 5 mmol, 0,1 eq.). La mezcla se agitó vigorosamente y se calentó a 55 °C. La temperatura interna se controló minuciosamente y se retiró el calor para controlar la exotermia. Después de 6 h a 61°C, el material de partida se había consumido completamente. La mezcla se enfrió a 0°C y se inactivó cuidadosamente con una solución acuosa al 20% de $NaHSO_3$ (20 ml). a 0°C y se añadió HCl 6 M (12 ml) para ajustar el PH a 1,5. La mezcla se extrajo con EtOAc (300 ml y 3 x 50 ml). Las capas orgánicas combinadas se lavaron con salmuera (200 ml), se secaron (Na_2SO_4), y se concentraron para dar un sólido blanco (8,8 g).

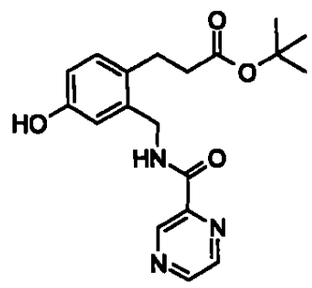
Etapa B: Éster terc-butílico del ácido 3-(2-{[(2,5-dicloro-tiofeno-3-carbonil)-amino]-metil}-4-hidroxi-fenil)-propiónico

Una solución del ácido 2,5-dicloro-tiofeno-3-carboxílico (12,9 g, 65,5 mmol) y 4-metilmorfolina (7,17 ml, 65,2 mmol) en THF seco (400 ml) se enfrió a -15°C. se añadió cloroformiato de isobutilo (8,46 ml, 65,2 mmol). La mezcla se agitó durante 3 min y se añadió trietilamina (9,1 ml, 65 mmol). Se añadió una solución de éster terc-butílico del ácido 3-(2-aminometil-4-hidroxi-fenil)-propiónico (16,4 g, 65,3 mmol) en DMF (130 ml) pre-enfriada a -15°C, mediante una cánula durante 15 min. Después de agitar durante 1 h, La TLC indicó que la reacción se había completado. La mezcla de reacción se dejó calentar a temperatura ambiente. Los sólidos se retiraron por filtración y se lavaron con

THF (100 ml). El filtrado se diluyó con Et_2O (500 ml) y se lavó con agua (250 ml) y después con salmuera (150 ml). La capa orgánica se secó (Na_2SO_4) y se concentró. El aceite pardo bruto se purificó por cromatografía en gel de sílice (hexanos/EtOAc 2/1) y recristalización (tolueno) para producir el compuesto del título en forma de un sólido blanco cristalino (22,3 g, 79,6%). MS (ES^+) m/z 430,1 $[M+H]^+$.

Preparación 20

Éster terc-butílico del ácido 3-(4-hidroxi-2-{[(pirazina-2-carbonil)-amino]-metil}-fenil)-propiónico

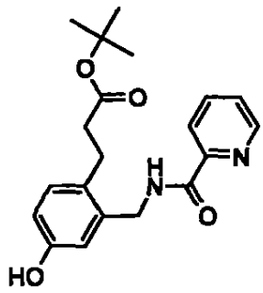


A una solución de ácido pirazina-2-carboxílico (0,570 g, 4,60 mmol) en CH_2Cl_2 (50 ml) se le añadió EDC (0,960 g, 5,01 mmol) y HOBt (0,620 g, 4,60 mmol) a temperatura ambiente. La mezcla se agitó durante 10 min, y se añadió éster terc-butílico del ácido 3-(2-aminometil-4-hidroxi-fenil)-propiónico (1,05 g, 4,18 mmol). La mezcla de reacción se agitó durante 18 h a temperatura ambiente, se trató con agua (50 ml), y se extrajo con CH_2Cl_2 (2 x 50 ml). Las capas orgánicas combinadas se secaron (Na_2SO_4), se concentraron, y se purificaron por cromatografía en gel de sílice (EtOAc/hexanos; 1:1 a 1:0) para obtener el compuesto del título (1,05 g, 70%). ^1H RMN (400 MHz, $CDCl_3$): d1,40 (s, 9H), 2,52 (t, 2 H, J = 7,6 Hz), 2,91 (t, 2H, J = 7,6 Hz), 4,66 (d, 2H, J = 6,4 Hz), 6,73 (dd, 1H, J = 2,9, 7,8 Hz), 6,83 (d, 1H, J = 2,4 Hz), 7,07 (d, 1H, J =

8,3 Hz), 8,17 (s a, 1H), 8,49 (dd, 1H, *J* = 1,5, 2,4 Hz), 8,73 (d, 1H, *J* = 2,4 Hz), 9,41 (d, 1H, *J* = 1,5 Hz). MS (ES) m/z 356,1 ([M-H]$^-$).

Los siguientes compuestos intermedios se prepararon de una forma sustancialmente similar a la de la Preparación 20.

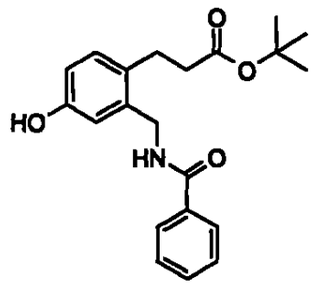
Éster terc-butílico del ácido 3-(4-hidroxi-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



^{1}H-RMN($CDCl_3$): 1,40 (s, 9H), 2,51 (t, *J* = 7,6 Hz, 2H), 2,91 (t, *J* = 7,6 Hz, 2H), 4,64 (d, *J* = 5,9 Hz, 2H), 6,72 (d, *J* = 7,8 Hz, 1H), 6,85 (s, 1H), 7,06 (d, *J* = 8,2 Hz, 1H), 7,41 (t, *J* = 7,6 Hz, 1H), 7,84 (t, *J* = 7,0 Hz, 1H), 8,20 (d, *J* = 7,4 Hz, 1H), 8,38 (s a, 1H), 8,50 (d, *J* = 3,5 Hz, 1 H); MS (ES) m/z 348 (M+H).

Preparación 21

Éster terc-butílico del ácido 3-[2-(benzoilamino-metil)-4-hidroxi-fenil]propiónico

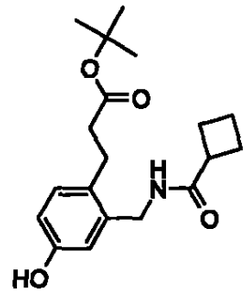


Una suspensión de éster terc-butílico del ácido 3-(2-aminometil-4-hidroxi-fenil)-propiónico (0,36 g, 1,43 mmol) en CH_2Cl_2 (10 ml) se enfrió en un

baño de agua enfriada con hielo y se trató con trietilamina (0,40 ml, 0,28 mmol) y después gota a gota con cloruro de benzoílo (0,18 ml, 1,55 mmol). La solución resultante se agitó durante 30 min, y el baño de refrigeración se retiró. Después de 30 min, la solución se concentró, y el residuo se repartió entre EtOAc (50 ml) y HCl 1 N (10 ml). La capa orgánica se lavó con salmuera (10 ml), se secó (Na_2SO_4), y se concentró para dar un sólido. La mezcla bruta se purificó por cromatografía radial (hexanos:EtOAc 3:1 a 2:1) para dar el compuesto del título en forma de un sólido blanco (325 mg, 64%): ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,26 (s, 9H), 2,54 (t, J = 7,1 Hz, 2H), 2,81 (t, J = 6,8 Hz, 2H), 4,55 (d, J = 2H), 6,68 (dd, J = 8,3, 2,4 Hz, 1H), 6,86 (d, J = 2,9 Hz, 1H), 6,96 (d, J = 8,3 Hz, 1H), 7,25-7,29 (m, 2H), 7,34-7,37 (m, 1H), 7,49 (s a, 1H), 7,16-7,79 (m, 2H); MS (ES) m/z 356,2 (M+H).

El siguiente compuesto intermedio se prepara de una forma similar a la descrita en la Preparación 21.

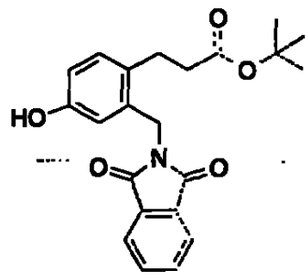
Éster terc-butílico del ácido 3-[2-[(ciclobutanocarbonil-amino)-metil]-4-hidroxi-fenil]-propiónico



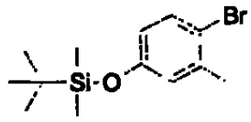
MS (ESI) m/z 334,2 $(M+H)^+$.

Preparación 22

Éster terc-butílico del ácido 3-[2-(1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil)-4-hidroxi-fenil]-propiónico

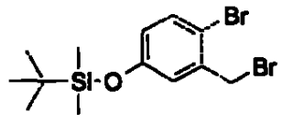


Etapa A: (4-Bromo-3-metil-fenoxi)-terc-butil-dimetil-silano



Un matraz de 12 l se cargó con 4-bromo-3-metil fenol (428 g, 2,29 mol), CH_2Cl_2 (7,5 l), trietilamina (480 ml, 3,45 mol), y cloruro de terc-butildimetilsililo (324 g, 2,15 mol). A la solución se le añadió 4-dimetilaminopiridina (15,0 g, 0,123 mol). La mezcla de reacción se agitó a temperatura ambiente durante una noche. La reacción se lavó con cloruro amónico saturado (2,2 l) y después agua DI (0,9 l). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró para dar el producto bruto (699 g). Este material se purificó por cromatografía en gel de sílice (heptano) para dar el compuesto del título (637 g, 98,5%).

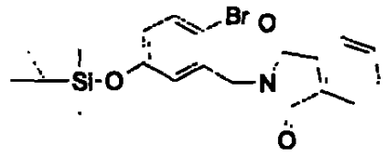
Etapa B: (4-Bromo-3-bromometil-fenoxi)-terc-butil-dimetil-silano



Se combinaron (4-bromo-3-metil-fenoxi)-terc-butil-dimetil-silano (255 g, 0,846 mol), dicloroetano (2,5 l), N-bromosuccinimida (165 g, 0,927 mol) y 2,2'-azobisisobutironitrilo (19,0 g, 0,116 mol) en un matraz de 5 l. La mezcla se desgasificó por evacuación y purga con N_2 (5 x). La mezcla de reacción se calentó a 47°C, y el calor se retiró. Se produjo una exotermia a 76°C. El

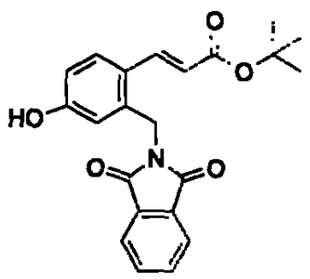
análisis por GC mostró un 6,5% de material de partida sin reaccionar. El calor se aplicó de nuevo, y la reacción se mantuvo a reflujo (83°C) durante 15 min. Después de enfriar a 8°C, se añadió heptano (1,0 l). La suspensión resultante se agitó a 4 °C durante 30 min y se filtró. El filtrado se evaporó a sequedad. El residuo se trató con heptano (1 l), se puso en el liofilizador durante una noche, y se filtró. El filtrado se concentró para dar el compuesto del título (326 g, 101%).

Etapa C: 2-[2-Bromo-5-(terc-butil-dimetil-silaniloxi)-bencil]-isoindol-1,3-diona



Un matraz de 12 l se cargó con (4-bromo-3-bromometil-fenoxi)-terc-butil-dimetil-silano (568 g 1,49 mol), DMF (3,1 l), y ftalimida potásica (316 g 1,71 mol). Se produjo una exotermia a 34 °C. Después de 40 min, la mezcla de reacción se enfrió a 18°C. Se añadieron éter (6,2 l) y agua DI (4,9 l) y las capas se separaron. La capa orgánica se lavó con solución saturada de NaCl (2 l), se secó (Na_2SO_4), se filtró, y se concentró. El residuo se recristalizó en heptano (1,5 l) para dar el compuesto del título (454 g, 68%).

Etapa D: Éster terc-butílico del ácido 3-[2-(1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil)-4-hidroxi-fenil]-acrílico



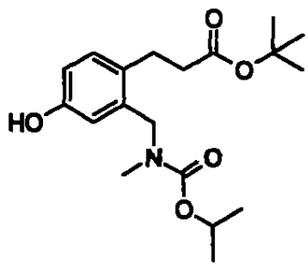
Un matraz de 12 l se cargó con 2-[2-bromo-5-(terc-butil-dimetil-silaniloxi)-bencil]-isoindol-1,3-diona (461 g, 1,03 mol), propionitrilo (7 l), tri-*orto*-tolil fosfina (76,0 g, 0,250 mol) y diisopropil etil amina (365 ml, 2,10 mol). La mezcla de reacción se desgasificó/se purgó con N_2 (3x), y se añadió acrilato de terc-butilo (465 ml, 3,17 mol). Después de desgasificar/purgar una vez, se añadió acetato de paladio (II) (28,0 g, 0,125 mol). La mezcla agitada se desgasificó/purgó con N_2 tres veces y se calentó a 95°C durante 20 h. La mezcla se filtró a través de una torta hyflo, se lavó con acetonitrilo, y se concentró hasta un aceite pardo (841 g). El residuo se disolvió en THF (3,5 l), y se añadió fluoruro de tetrabutilamonio (TBAF, 650 ml, 0,65 mol, 1M en THF). Después de 1 h, se añadió más TBAF (95 ml). La mezcla se agitó en el evaporador rotatorio durante 10 min y se concentró para dar el producto bruto (987 g). Este material se purificó por cromatografía en gel de sílice (tolueno/acetato de etilo, 100/0 a 75/25) para dar el compuesto del título (340 g, 86,8%).

Etapa E: Éster terc-butílico del ácido 3-[2-(1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil)-4-hidroxi-fenil]-propiónico

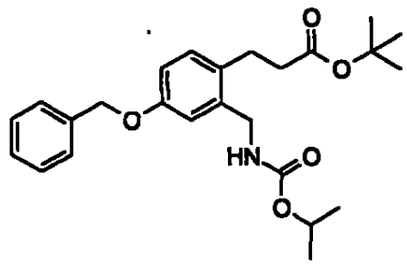
Un autoclave de 1 galón se cargó con éster terc-butílico del ácido 3-[2-(1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil)-4-hidroxi-fenil]-acrílico (196 g, 0,517 mol), acetato de etilo (2,6 l) y paladio al 5% sobre carbono (75 g). El autoclave se mantuvo a 25°C en 60 psi (413,68 kPa) de hidrógeno durante 21 h. La temperatura de la reacción se aumentó a 40 °C, y la presión se aumentó a 75 psi (517,10 kPa) durante 5 h. La mezcla se filtró a través de una capa de hyflo y se concentró para dar el compuesto del título (186 g, 94,4 %): MS (ESI) m/z 380,2 $(M-H)^-$.

Preparación 23

Éster terc-butílico del ácido 3-[4-hidroxi-2-[(isopropoxicarbonil-metil-amino)-metil]-fenil]-propiónico



Etapa A: Éster terc-butílico del ácido 3-[5-benciloxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



A una solución de éster terc-butílico del ácido 3-[5-hidroxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (14,8 mmol) en DMF (100 ml) se le añadió Cs_2CO_3 (29,6 mmol) y bromuro de bencilo (16,3 mmol). La mezcla de reacción se agitó durante una noche a temperatura ambiente y se diluyó con EtOAc (200 ml). La mezcla se lavó con salmuera (100 ml) y agua (100 ml). La capa orgánica se secó (Na_2SO_4) y se concentró para dar un aceite amarillo (6,8 g). MS [ES] m/z 428 $(M+H)^+$.

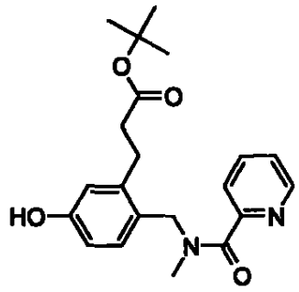
Etapa B: Éster terc-butílico del ácido 3-[5-hidroxi-2-[(isopropoxicarbonil-metil-amino)-metil]-fenil]-propiónico

A una solución de éster terc-butílico del ácido 3-[5-benciloxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (6,3 g, 0,015mol) en DMF (100

ml) se le añadió NaH (29,4 mmol, dispersión en aceite al 60%). La mezcla de reacción se agitó a 0°C durante 15 min, se trató con yoduro de metilo (4,18 g, 29,4 mmol), y se agitó durante una noche en una atmósfera de N_2 a temperatura ambiente. La mezcla se concentró y se trituró con hexanos (200 ml). El residuo se diluyó con EtOAc (200 ml), y la solución se lavó con agua (200 ml) y salmuera (200 ml), se secó (Na_2SO_4), y se concentró para dar un aceite amarillo (5,2 g). El material se disolvió en EtOAc (100 ml), y se añadió Pd al 5%/C (0,725 g). La mezcla de reacción se agitó en una atmósfera de hidrógeno en un aparato Parr a 60 psi (413,68 kPa) durante una noche a 40°C. La mezcla se filtró y se concentró para dar el compuesto del título (2,1 g). MS [ES] m/z 352 $(M+H)^+$.

El siguiente compuesto intermedio se prepara de una forma sustancialmente similar a la descrita en la Preparación 23.

Éster terc-butílico del ácido 3-(5-hidroxi-2-[[metil-(piridina-2-carbonil)-amino]-metil]-fenil)-propiónico



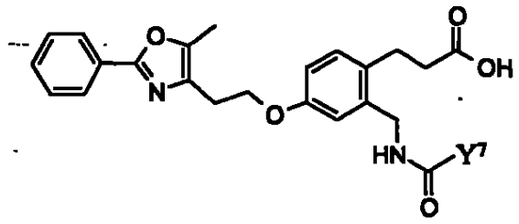
MS [ES] m/z 371 $(M+H)^+$.

Se usan los Siguientes Procedimientos Generales para preparar los compuestos de la presente invención, como se muestra a continuación.

Procedimientos Generales I y II

Procedimiento General I

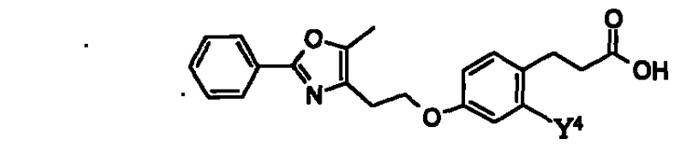
Procedimiento General para la Síntesis Paralela de Carboxamidas a partir de Ácidos Carboxílicos

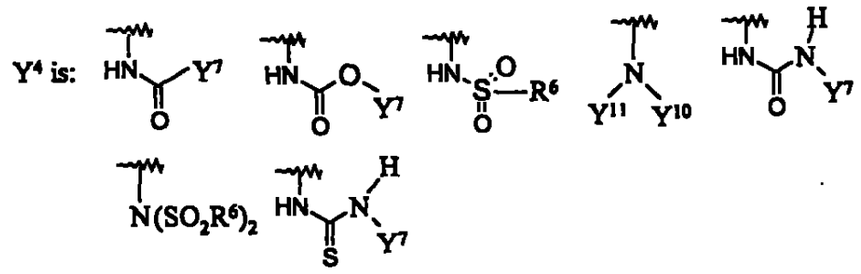


Se disolvió éster terc-butílico del ácido 3-{2-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico:sal de ácido acético (704 mg, 1,4 mmol) en CH_2Cl_2 (25 ml) y se lavó con una solución saturada de $NaHCO_3$ (15 ml). La capa orgánica se secó ($NaSO_4$), se filtró, y se concentró para dar éster terc-butílico del ácido 3-{2-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (636 mg, 1,4 mmol). Esta amina (0,1 mmol, 0,1 M en CH_2Cl_2) se añadió a ácido carboxílico (1,4 eq) en un vial de dracma (1,772 gramos). Se añadieron N-hidroxibenzotriazol hidrato (1,4eq, 0,17 M en CH_2Cl_2/DMF 10/1; HOBt) y EDC (1,4 eq, 0,18 M CH_2Cl_2), y los viales se taparon y se agitaron durante 18 h. DMF (0,5 ml) y se añadió trietilamina (0,5 ml) y los viales se agitaron durante 72 h. Se añadió salmuera (1 ml) y las mezclas se transfirieron a un cartucho ChemElute y se eluyeron con CH_2Cl_2. El disolvente se retiró en una atmósfera de N_2. El residuo se trató con una mezcla de CH_2Cl_2/TFA/agua 60/35/5 (1 ml), se agitó durante un corto espacio de tiempo, y se dejó en reposo a temperatura ambiente durante 2 h. El disolvente se retiró en una atmósfera de N_2. El residuo se trató con CCl_4 al 10%/CH_2Cl_2 (1 ml) y se concentró en una atmósfera de N_2 (2x). Los productos brutos se secaron al vacío y se purificaron por HPLC dirigida de masas.

Procedimiento General II

Procedimiento General para la Síntesis Paralela de Carboxamidas, Carbamatos, Sulfonamidas, Ureas y Tioureas a partir de Cloruros de Ácido Carboxílico, Cloroformiatos, Cloruros de Sulfonilo, Isocianatos e Isotiocianatos

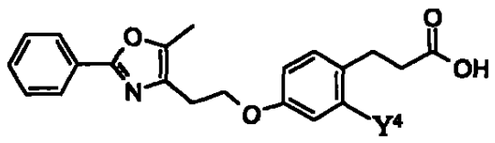




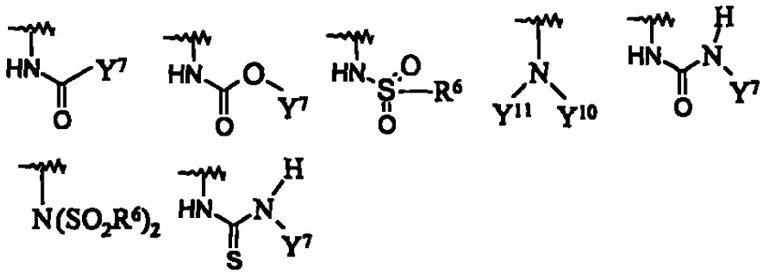
Se disolvió éster terc-butílico del ácido 3-{2-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico: sal del ácido acético (720 mg, 1,4 mmol) en CH_2Cl_2 (25 ml) y se lavó con una solución saturada de $NaHCO_3$ (15 ml). La capa orgánica se secó ($NaSO_4$), se filtró, y se concentró para dar éster terc-butílico del ácido 3-{2-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (586 mg, 92%). Esta amina (0,1 mmol, 0,1 M en CH_2Cl_2) y cloruro de ácido carboxílico, cloroformiato, cloruro de sulfonilo, isocianato o isotiocianato (1 eq), y trietilamina (0,2 ml) se pusieron en un vial de 1 dracma. Los viales se taparon y se agitaron durante 18 h. Se añadió DMF (0,5 ml) a las mezclas de reacción incompletas y los viales se agitaron durante 2 h. Se añadió salmuera (1 ml) y la mezclas se transfirieron a un cartucho ChemElute y se eluyeron con CH_2Cl_2. El disolvente se retiró en una atmósfera de N_2. El residuo se trató con una mezcla de CH_2Cl_2/TFA/agua 60/35/5 (1 ml), se agitó durante un corto espacio de tiempo, y se dejó en reposo a temperatura

ambiente durante 2 h. El disolvente se retiró en una atmósfera de N_2. El residuo se trató con CCl_4 al 10%/CH_2Cl_2 (1 ml) y se concentró en una atmósfera de N_2 (2x). Los productos brutos se secaron al vacío y se purificaron por HPLC dirigida de masas.

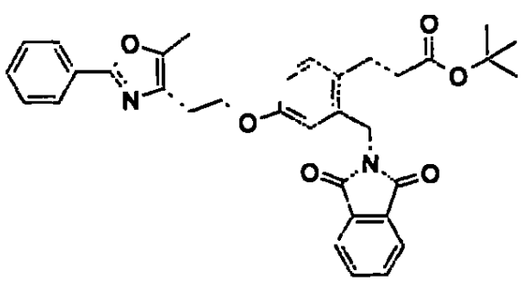
Ejemplo 1



Y^4 is:



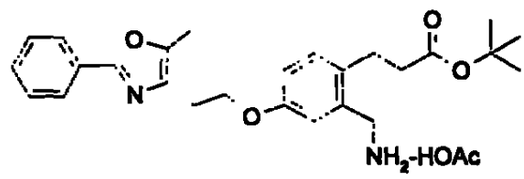
Etapa A: Éster terc-butílico del ácido 3-{2-(1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



Un matraz de 3 bocas, 2 l, se cargó con éster terc-butílico del ácido 3-[2-(1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil)-4-hidroxi-fenil]-propiónico (67,9 g, 0,178mol), 2-(5-metil-2-fenil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (76,6 g, 0,214 mol) y DMF (680 ml). Se añadió carbonato de cesio

(75,4 g, 0,231 mol) y la mezcla de reacción se calentó a 55 °C durante 18 h. Después de enfriar, se añadieron acetato de etilo (890 ml) y agua DI (1200 ml), la mezcla se agitó, y las capas se separaron. La capa acuosa se extrajo de nuevo con acetato de etilo (740 ml). Las capas orgánicas se combinaron y se lavaron con NaOH 1 N (375 ml) y después con una solución saturada de NaCl (2 x 375 ml). La solución orgánica se secó (Na_2SO_4), se filtró, y se concentró hasta un aceite (107 g). El aceite bruto se disolvió en tolueno (50 ml), y se añadió heptano (~100 ml) hasta que permaneció la turbidez incluso con agitación. La mezcla se calentó a 50 °C sobre un evaporador rotatorio para producir una solución. Se añadieron cristales seminales y se continuó la rotación a temperatura ambiente durante una noche. La suspensión de producto se puso en el congelador durante una noche y se filtró. El compuesto del título se secó en una estufa de vacío a 35 °C (71,4 g, 70,8 %).

Etapa B: Éster terc-butílico del ácido 3-{2-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico: sal del ácido acético

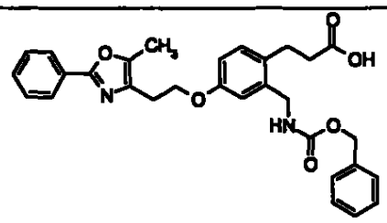


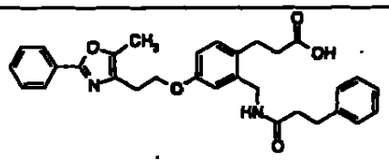
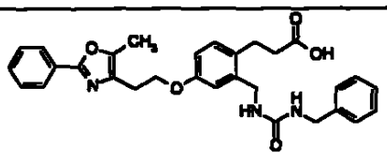
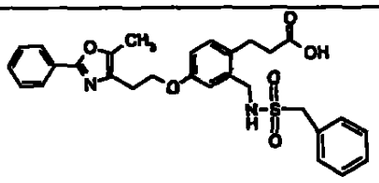
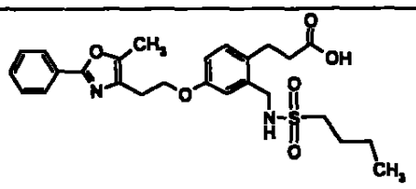
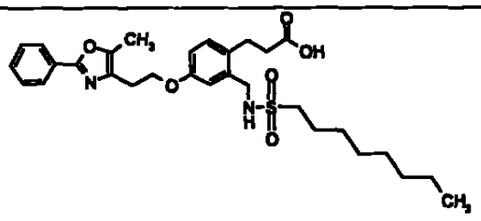
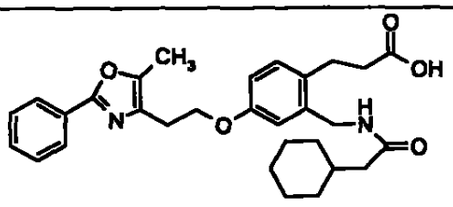
Un matraz de 3 bocas y 3 l se cargó con éster terc-butílico del ácido 3-{2-(1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (71,0 g, 0,125 mol) e isopropanol (IPA, 1,35 l). Después de calentar a 40 °C y añadir IPA (250 ml), aún no se obtuvo una solución. Después de enfriar a <30 °C, se añadió cuidadosamente en porciones borohidruro sódico (25,6 g, 0,677 mol). Al baño se le añadió agua corriente y la reacción se dejó en agitación durante una noche. Se usó una espátula para

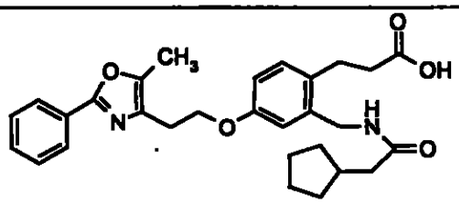
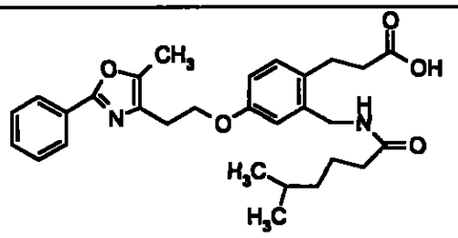
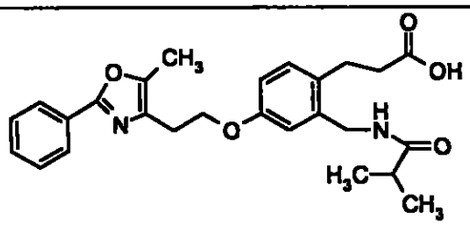
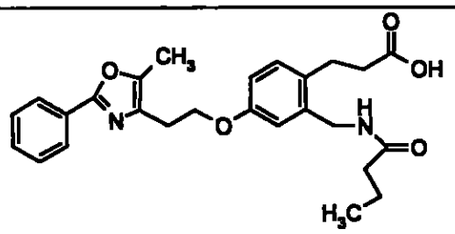
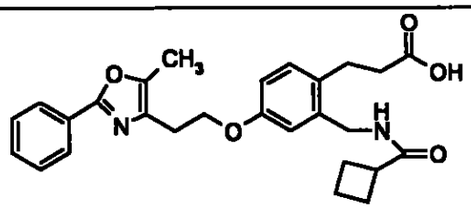
romper los sólidos en la suspensión espesa, y se añadió IPA (200 ml). Se añadió ácido acético glacial (130 ml, 2,27 mol) gota a gota durante 2 h. La mezcla de reacción se calentó a reflujo durante 10 h, se dejó enfriar durante el fin de semana, y se concentró para dar el producto bruto (237 g). Se añadió CH_2Cl_2 (100 ml) para dar un gel espeso que se vertió en una columna de gel de sílice 60 equilibrada con CH_2Cl_2. Se usó metanol para disolver el material bruto. La elución con CH_2Cl_2/MeOH (1/1) dio la mezcla del producto (182 g). Se añadió acetato de etilo (200 ml) y se formó un precipitado. La mezcla se calentó a 40 °C, y la solución se enfrió a 0 °C. El producto bruto se filtró, se lavó con heptano/EtOAc (1:1, 2 x 100 ml), y se secó para producir un sólido esponjoso blanco (35,4 g, 57%). El filtrado se concentró (116 g) y se purificó de nuevo por cromatografía en gel de sílice (CH_2Cl_2/MeOH 100/0 a 80/20) para dar más producto en forma de un aceite de color ámbar (13,9 g, 22%).

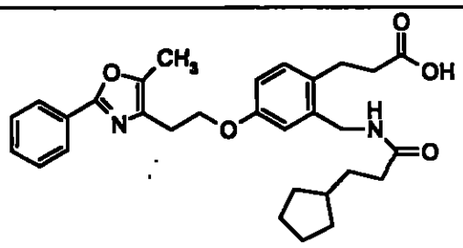
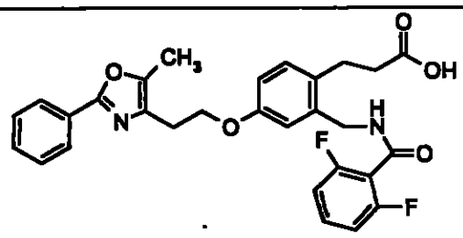
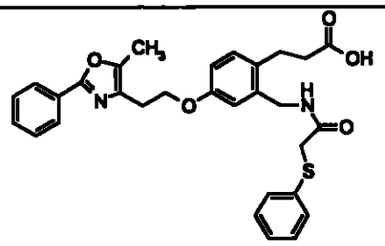
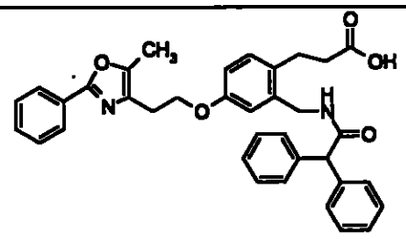
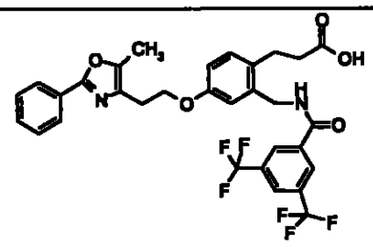
Ejemplos 2- 230

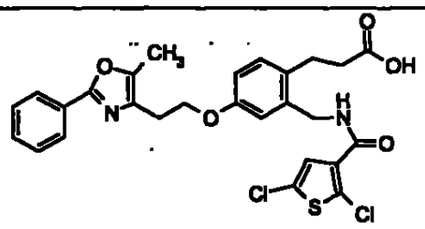
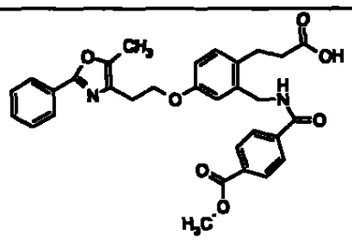
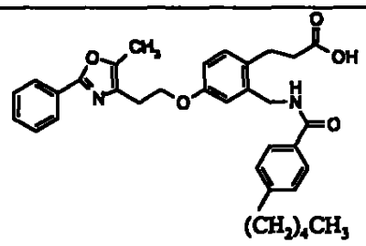
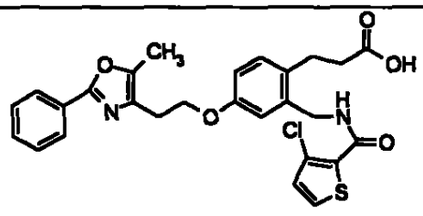
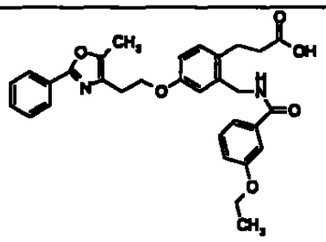
Los Ejemplos 2-230 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 1 y en los Procedimientos Generales I y II.

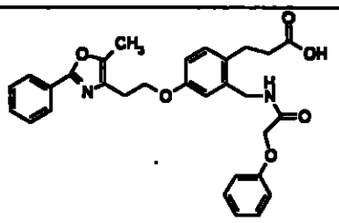
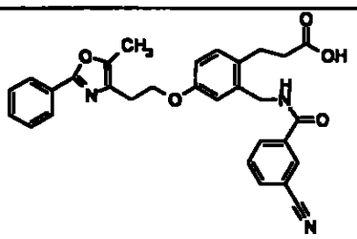
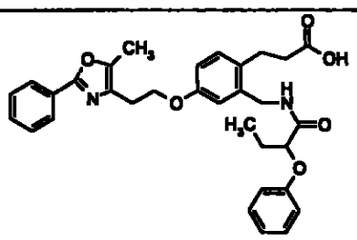
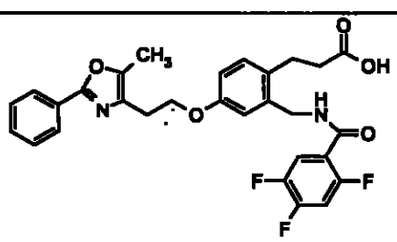
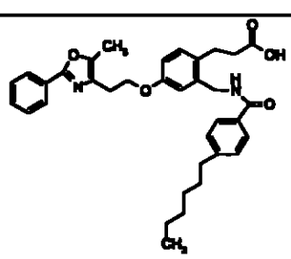
No	Compuestos	MS (ES+)	Procedimiento General
2		515,5 FIA	II

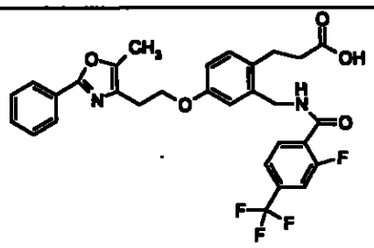
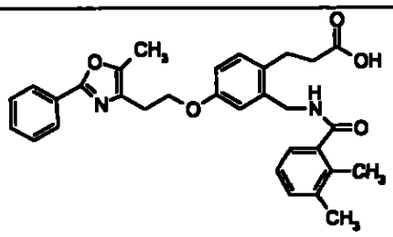
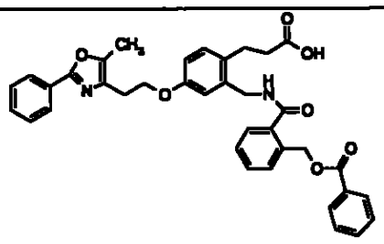
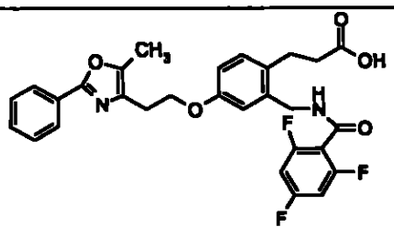
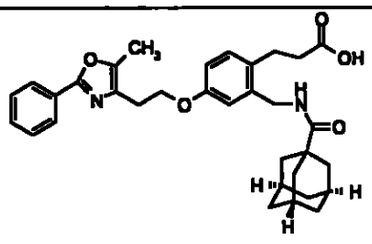
No	Compuestos	MS (ES+)	Procedimiento General
3		513,5 FIA	I
4		514,4 FIA	II
5		535,2 FIA	II
6		501,3 FIA	II
7		557,1 FIA	II
8		505,3	II

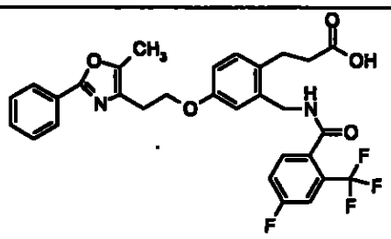
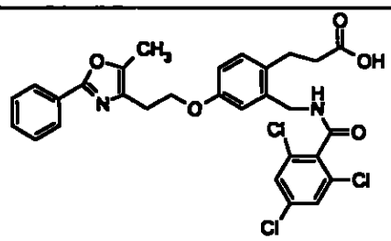
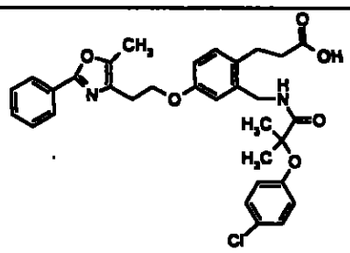
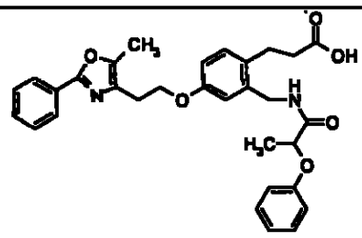
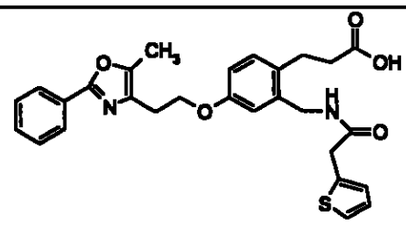
No	Compuestos	MS (ES+)	Procedimiento General
9		491,3	I
10		493,3	I
11		451,2	I
12		451,2	II
13		463,3	II

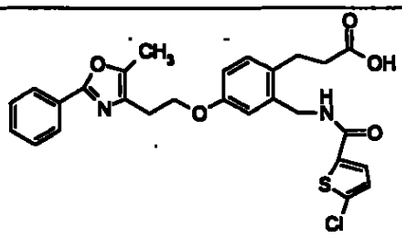
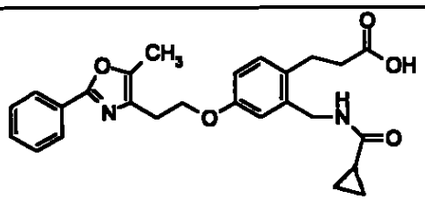
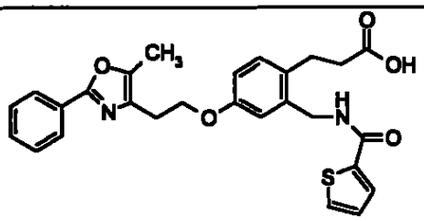
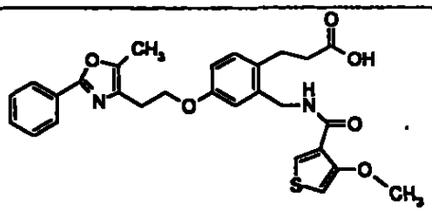
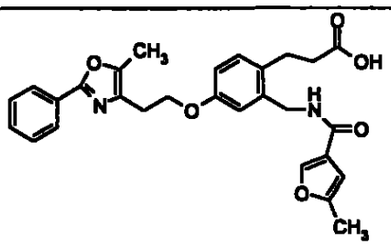
No	Compuestos	MS (ES+)	Procedimiento General
14		505,3	II
15		521,6	II
16		531,6	II
17		575,7	II
18		621,6	II

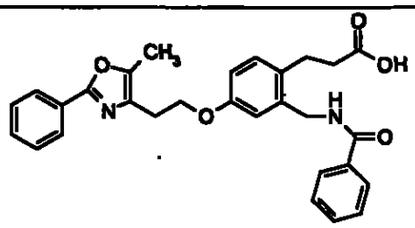
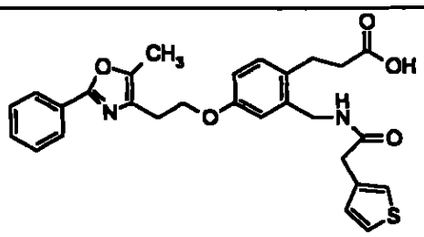
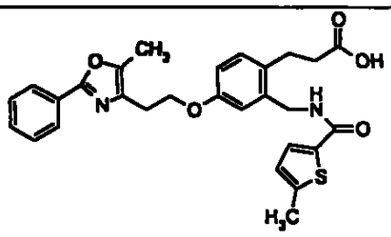
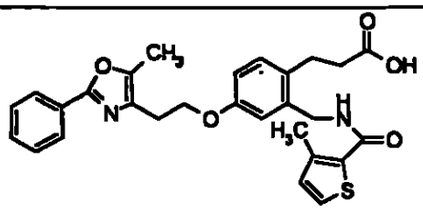
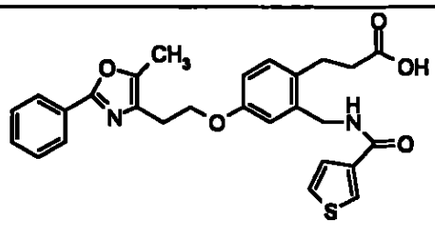
No	Compuestos	MS (ES+)	Procedimiento General
19		559,8	II
20		543,7	II
21		555,4	II
22		525,2	II
23		529,3	II

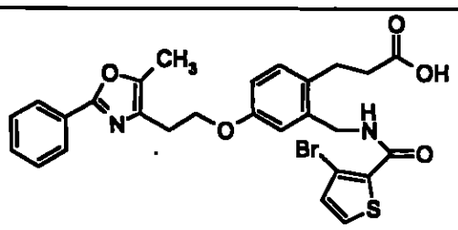
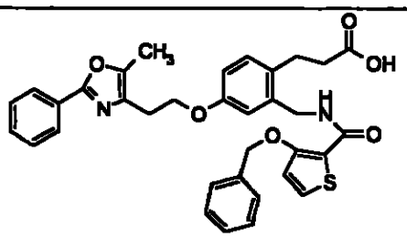
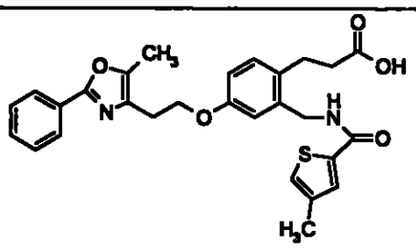
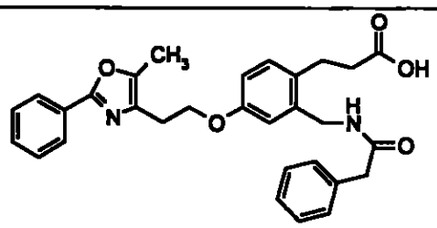
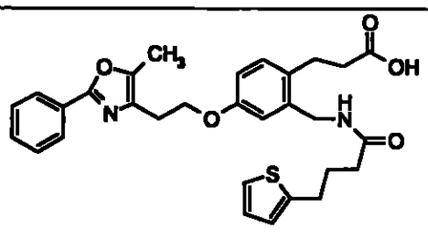
No	Compuestos	MS (ES+)	Procedimiento General
24		515,3	II
25		510,6	II
26		543,7	II
27		539,3	II
28		569,4	II

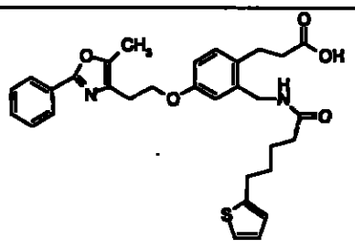
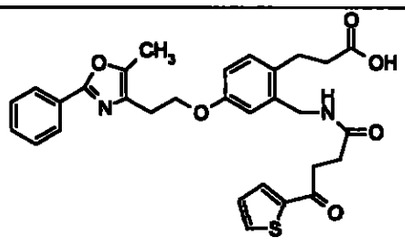
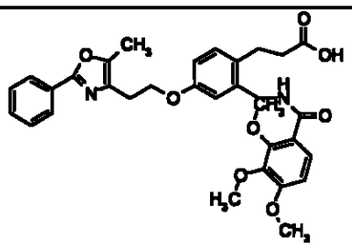
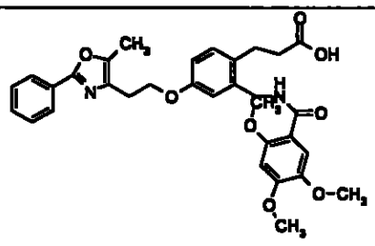
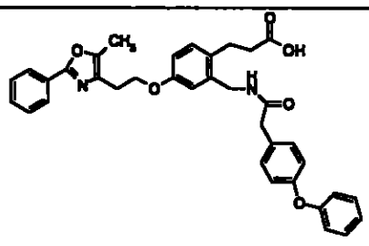
No	Compuestos	MS (ES+)	Procedimiento General
29		571,3	II
30		513,4	II
31		619,4	II
32		539,3	II
33		543,4	II

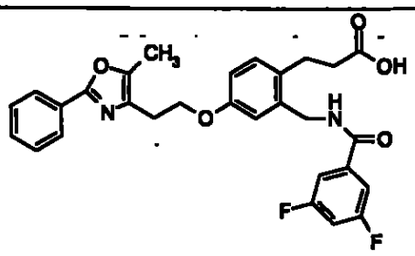
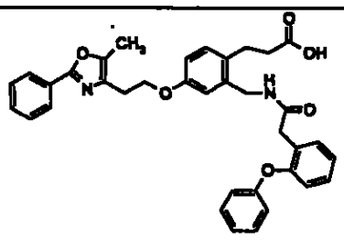
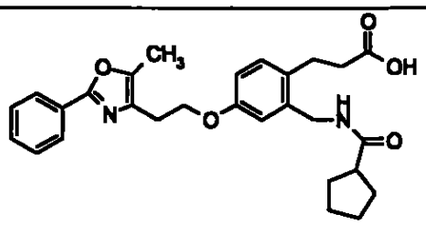
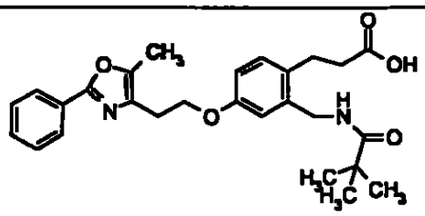
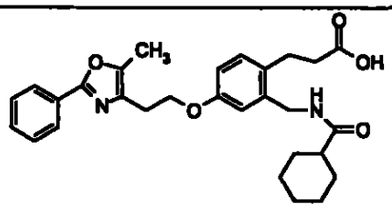
No	Compuestos	MS (ES+)	Procedimiento General
34		571,3	II
35		589,2	II
36		577,3	II
37		529,7	I
38		505,3	I

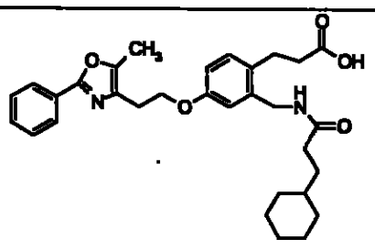
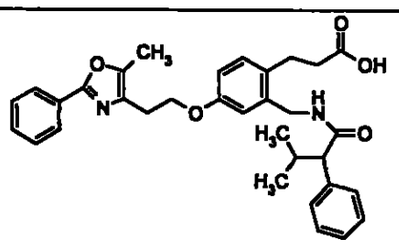
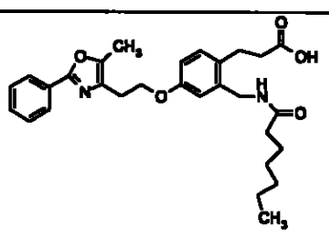
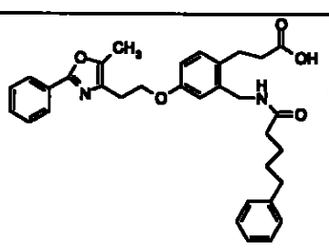
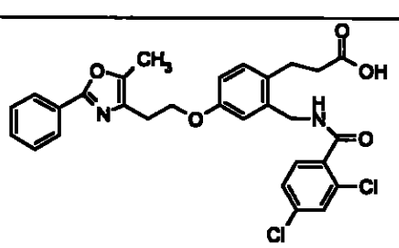
No	Compuestos	MS (ES+)	Procedimiento General
39		525,2	I
40		549,3	I
41		491,3	I
42		521,3	I
43		489,3	I

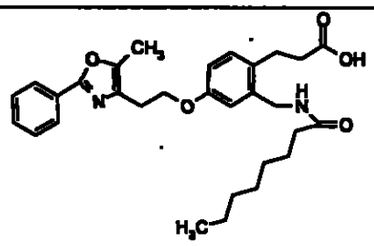
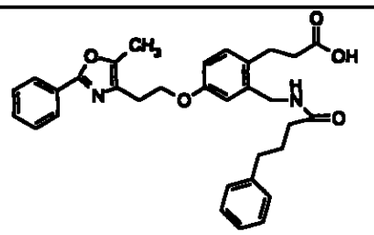
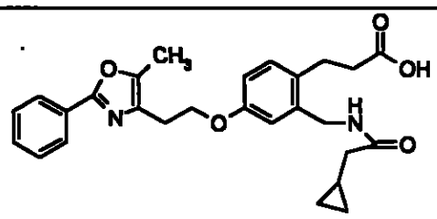
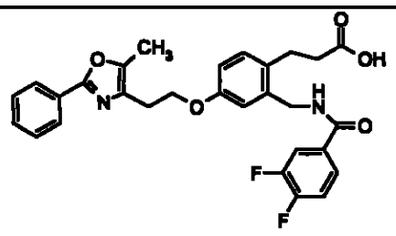
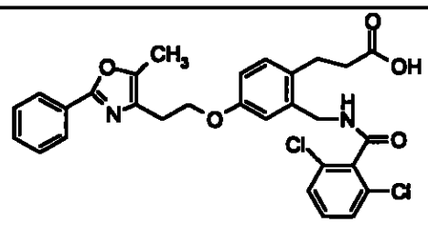
No	Compuestos	MS (ES+)	Procedimiento General
44		485,3	I
45		505,3	I
46		505,3	I
47		505,3	I
48		491,3	I

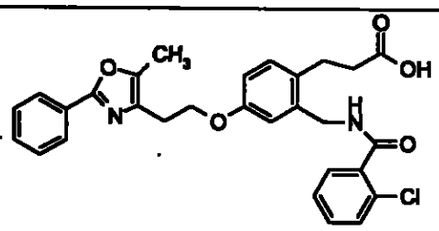
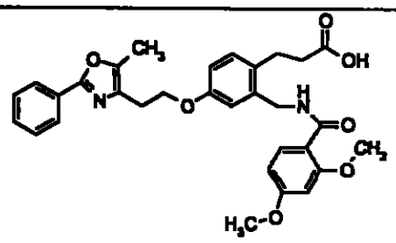
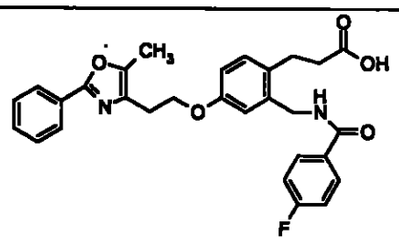
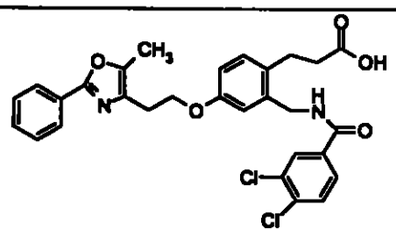
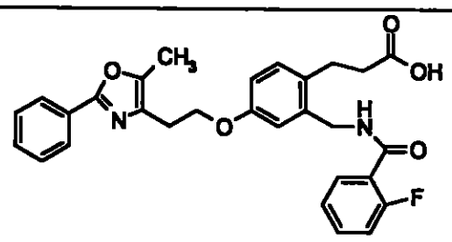
No	Compuestos	MS (ES+)	Procedimiento General
49		571,2	I
50		597,4	I
51		505,3	I
52		499,3	I
53		533,3	I

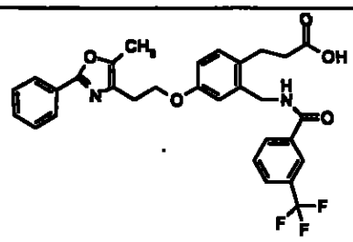
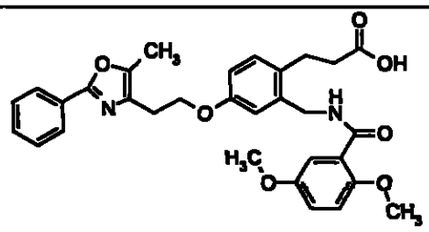
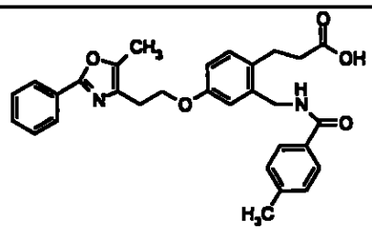
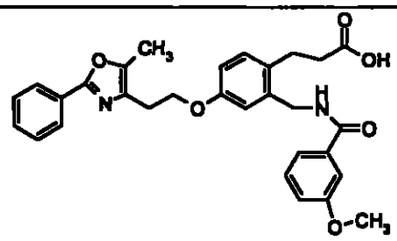
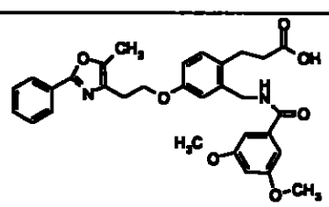
No	Compuestos	MS (ES+)	Procedimiento General
54		547,3	I
55		547,3	I
56		575	I
57		575	I
58		591	I

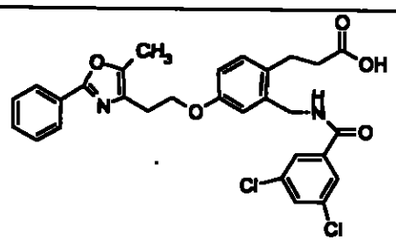
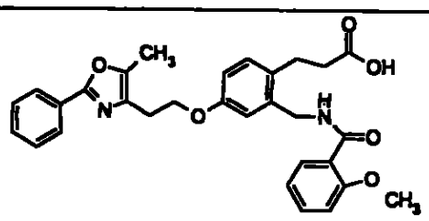
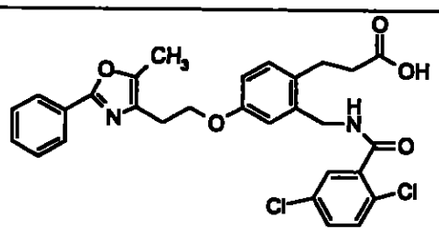
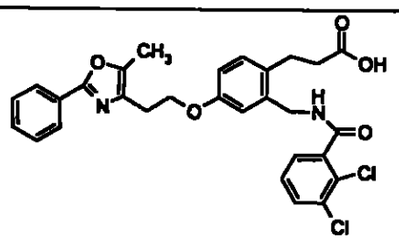
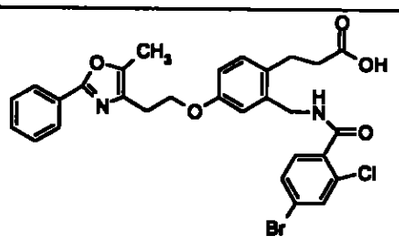
No	Compuestos	MS (ES+)	Procedimiento General
59		521	I
60		591	I
61		477,2	I
62		465	I
63		491	I

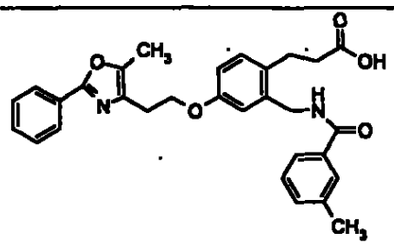
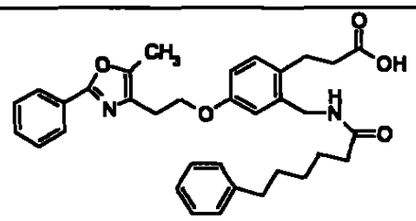
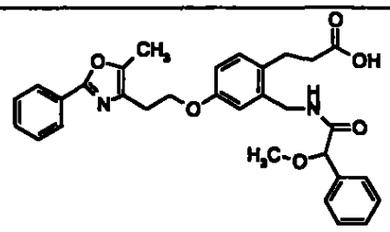
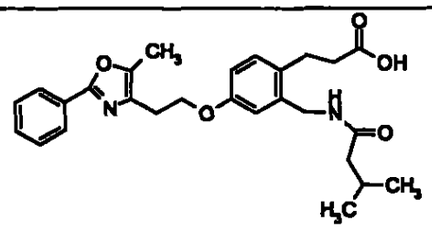
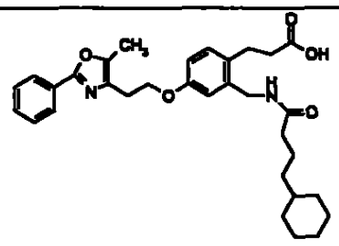
No	Compuestos	MS (ES+)	Procedimiento General
64		519	I
65		541	I
66		493	I
67		541	I
68		554	I

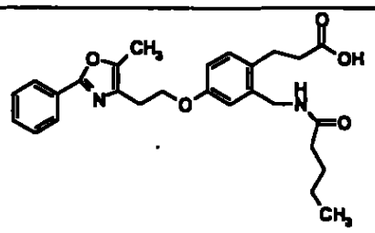
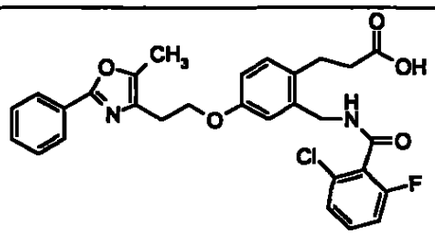
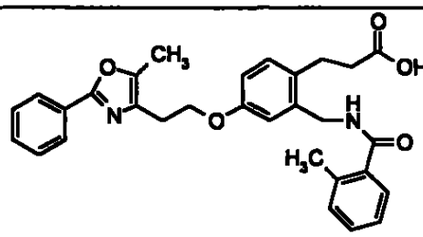
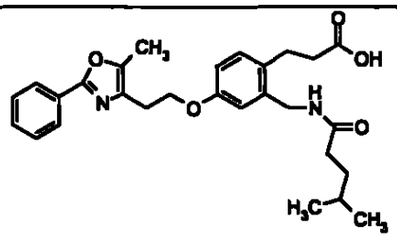
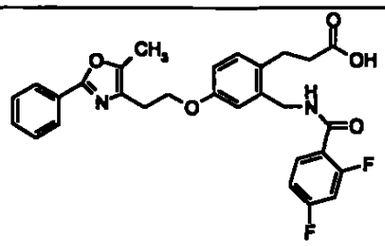
No	Compuestos	MS (ES+)	Procedimiento General
69		507	I
70		527	I
71		463	I
72		521	I
73		554	I

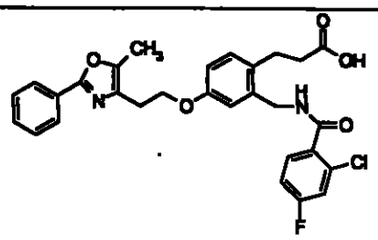
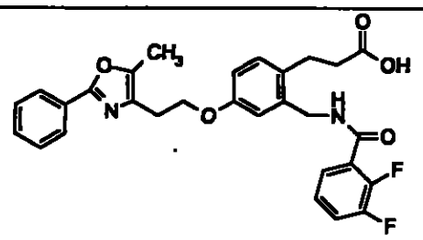
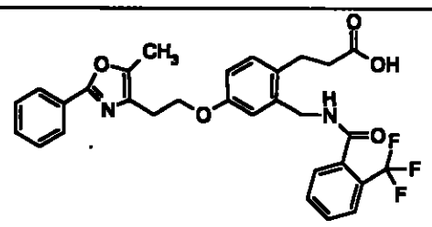
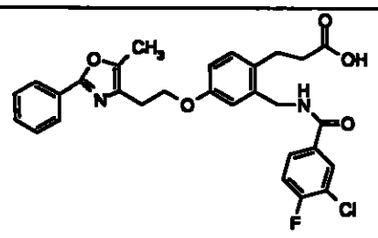
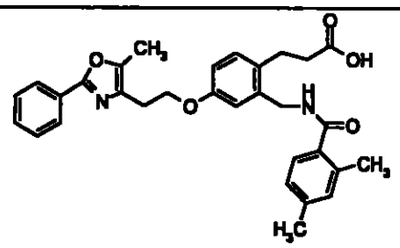
No	Compuestos	MS (ES+)	Procedimiento General
74		520	I
75		545	I
76		503	I
77		554	I
78		503	I

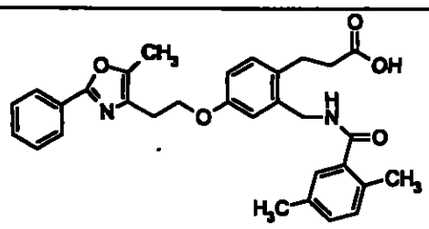
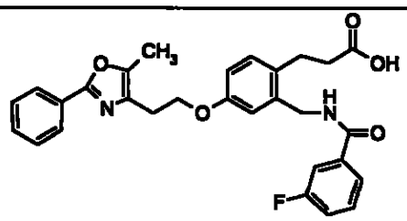
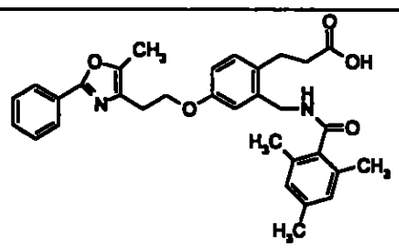
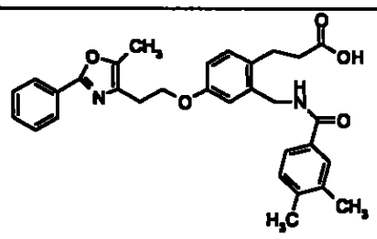
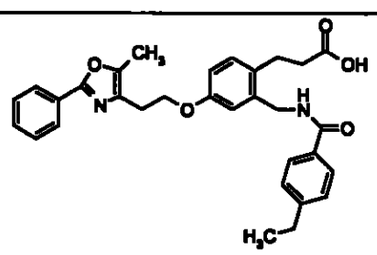
No	Compuestos	MS (ES+)	Procedimiento General
79		553	I
80		545	I
81		499	I
82		515,2	I
83		545,3	I

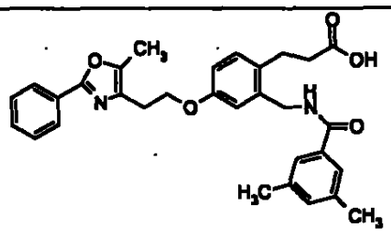
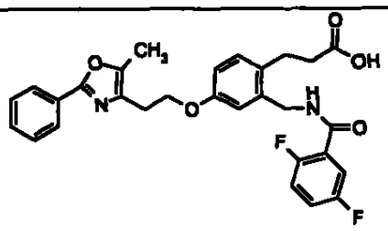
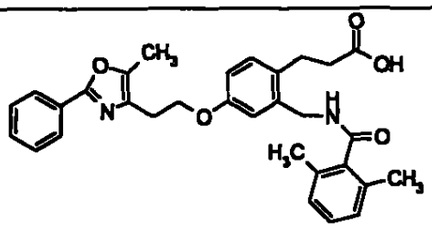
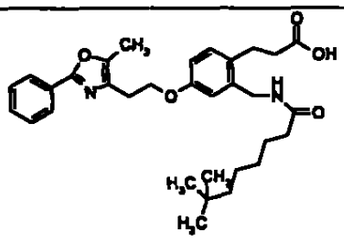
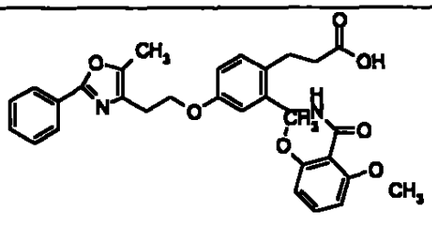
No	Compuestos	MS (ES+)	Procedimiento General
84		554	I
85		515	I
86		554	I
87		554	I
88		598	I

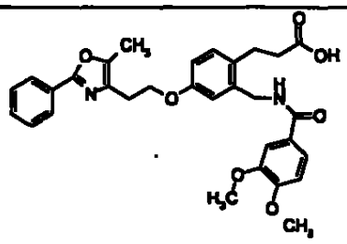
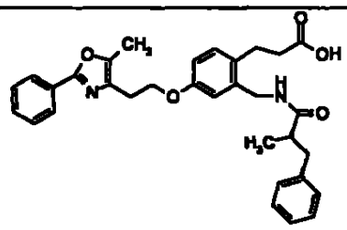
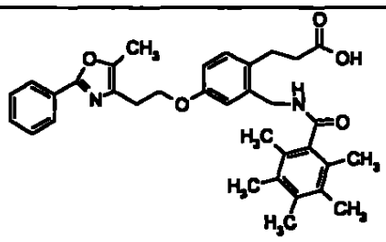
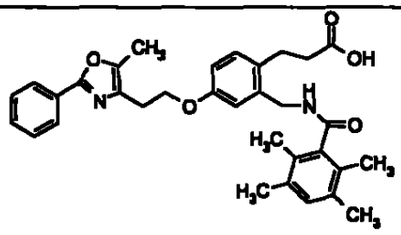
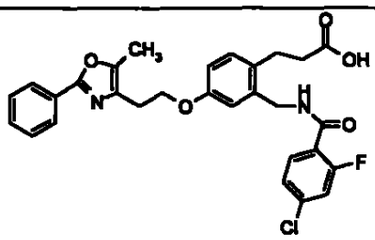
No	Compuestos	MS (ES+)	Procedimiento General
89		499	I
90		555	I
91		529	I
92		465	I
93		533	I

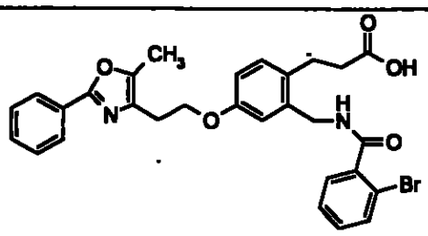
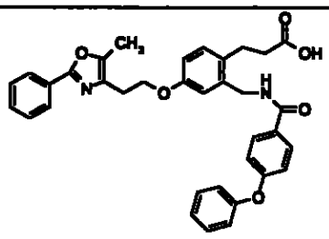
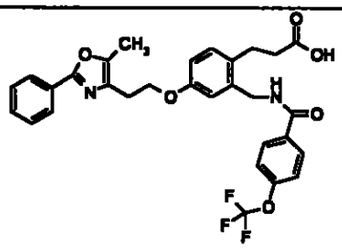
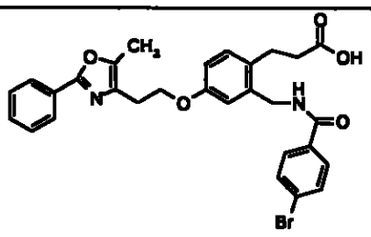
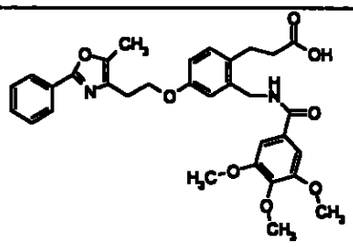
No	Compuestos	MS (ES+)	Procedimiento General
94		465	I
95		538	I
96		499	I
97		479	I
98		521	I

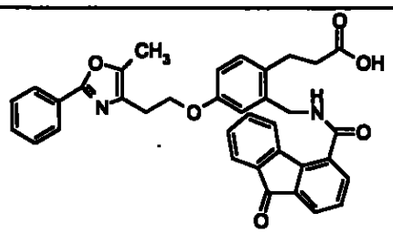
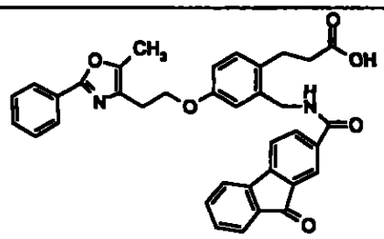
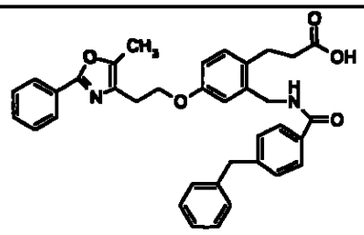
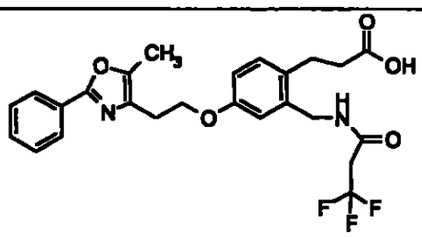
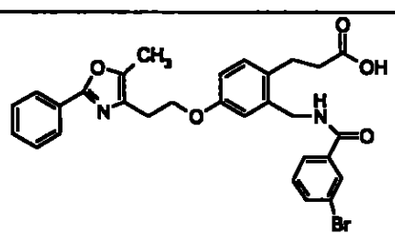
No	Compuestos	MS (ES+)	Procedimiento General
99		538	I
100		521	I
101		553	I
102		538	I
103		513	I

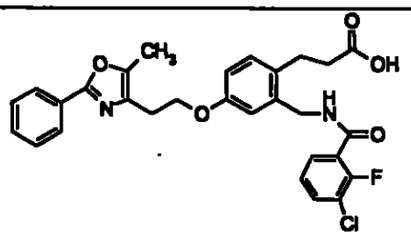
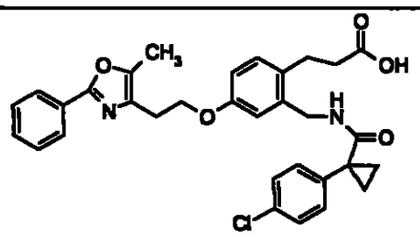
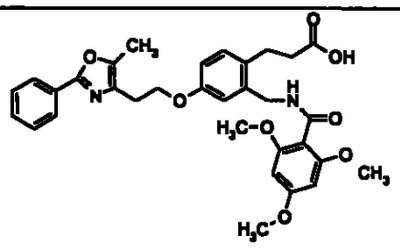
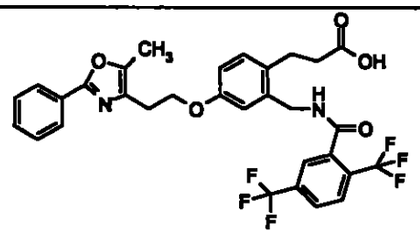
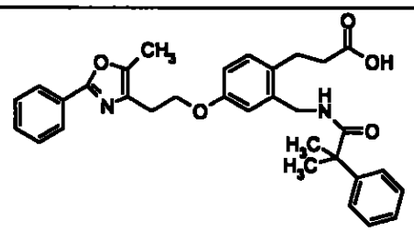
No	Compuestos	MS (ES+)	Procedimiento General
104		513	I
105		503	I
106		527	I
107		513	I
108		513	I

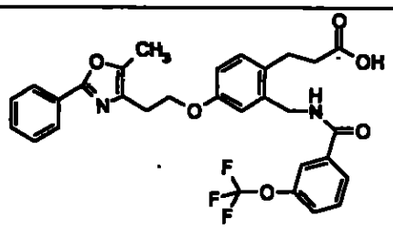
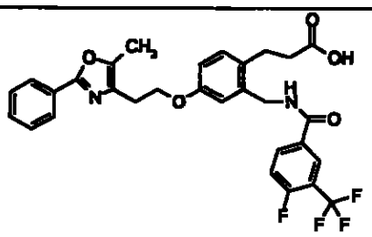
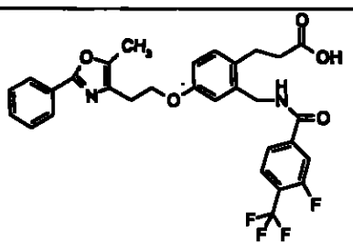
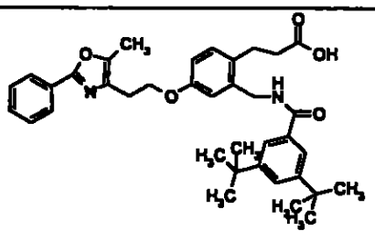
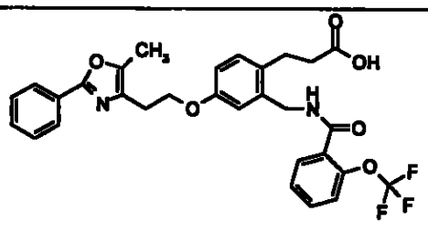
No	Compuestos	MS (ES+)	Procedimiento General
109		513	I.
110		521	I
111		513	I
112		535	I
113		545	I

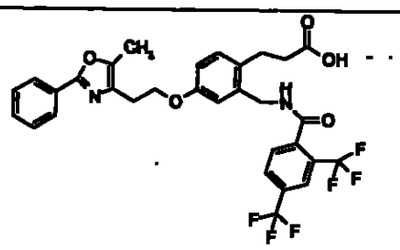
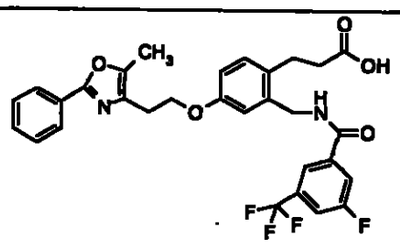
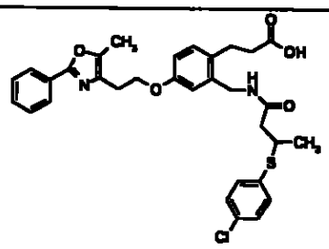
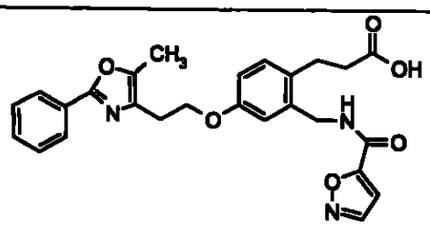
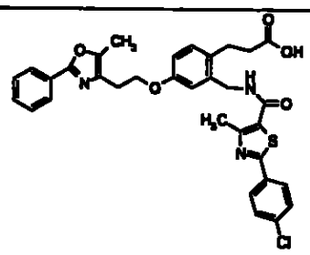
No	Compuestos	MS (ES+)	Procedimiento General
114		545	I
115		527	I
116		555	I
117		541	I
118		538	I

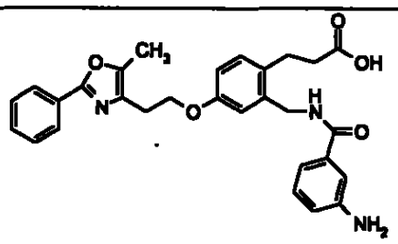
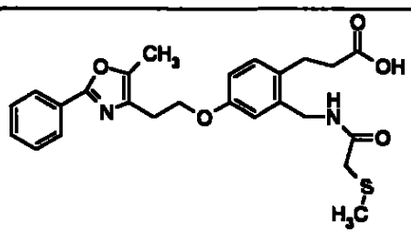
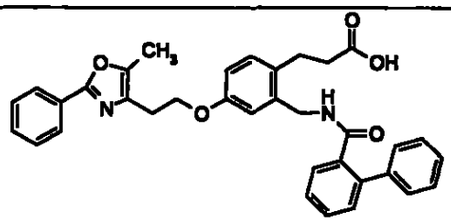
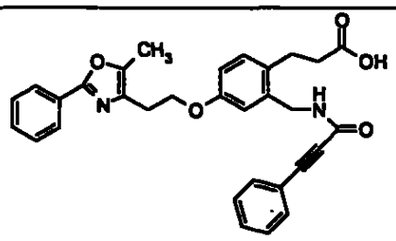
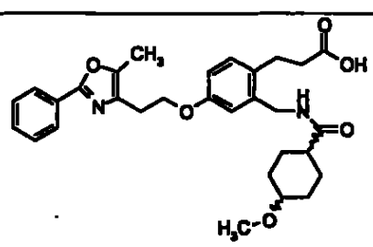
No	Compuestos	MS (ES+)	Procedimiento General
119		564	I
120		577	I
121		569	I
122		564	I
123		575	I

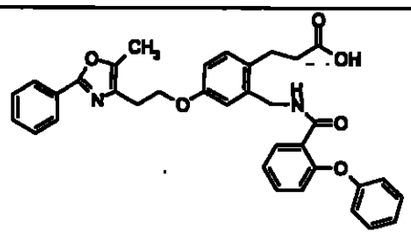
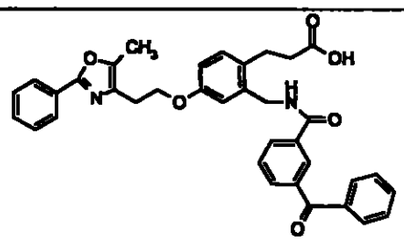
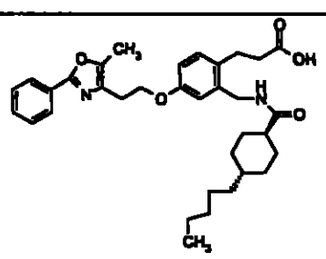
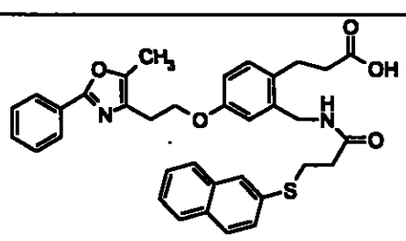
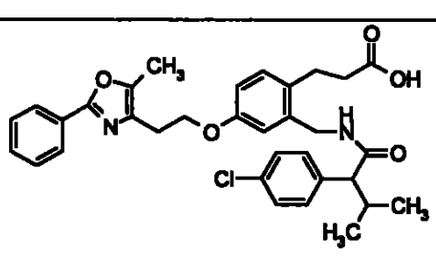
No	Compuestos	MS (ES+)	Procedimiento General
124		587	I
125		587	I
126		575	I
127		491	I
128		564	I

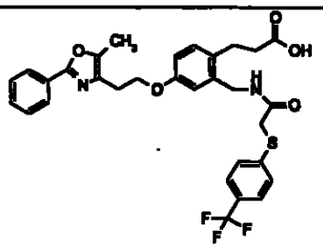
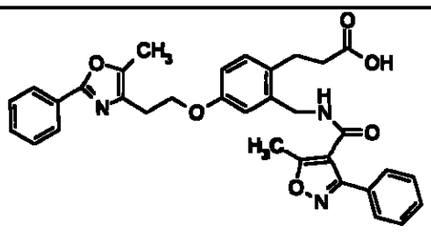
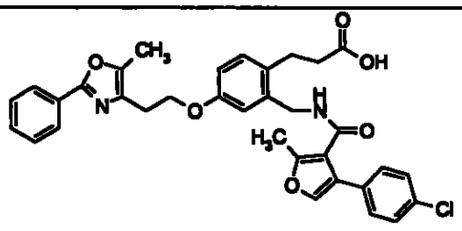
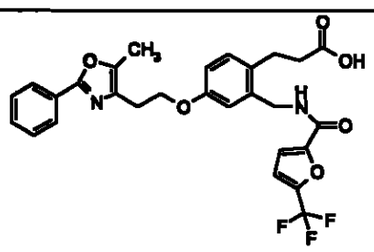
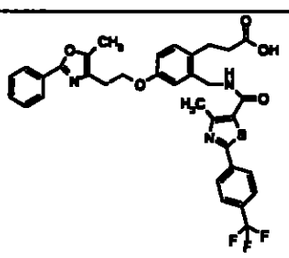
No	Compuestos	MS (ES+)	Procedimiento General
129		538	I
130		560	I
131		575	I
132		621	I
133		527	I

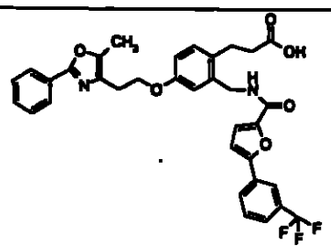
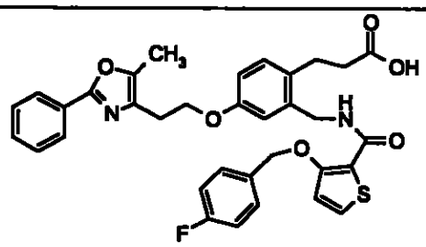
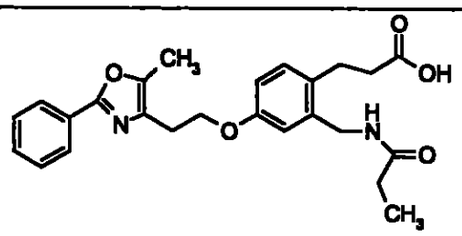
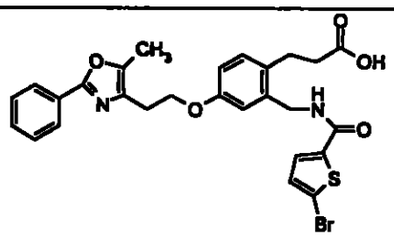
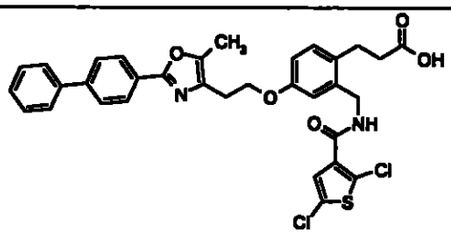
No	Compuestos	MS (ES+)	Procedimiento General
134		569	I
135		571	I
136		571	I
137		597	I
138		569	I

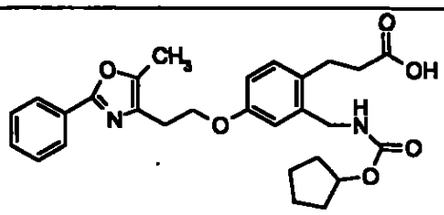
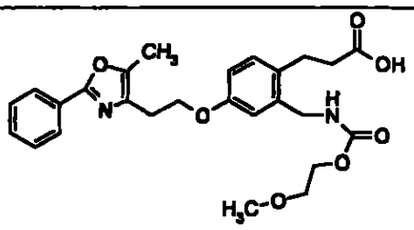
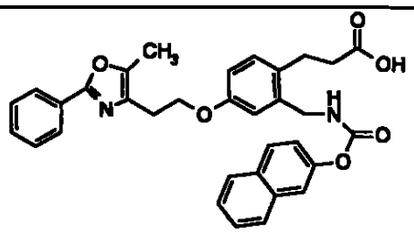
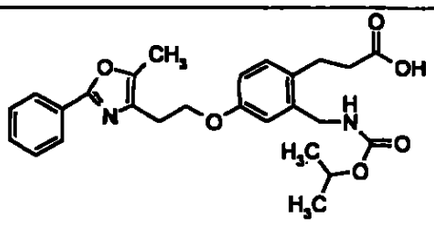
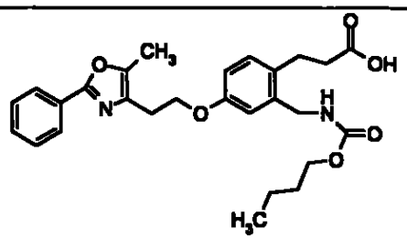
No	Compuestos	MS (ES+)	Procedimiento General
139		621	I
140		571	I
141		594	I
142		476	I
143		617	I

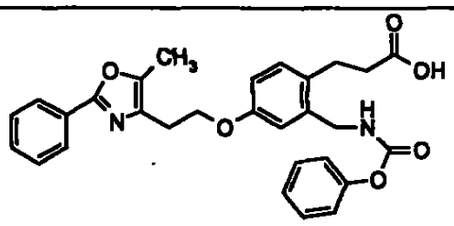
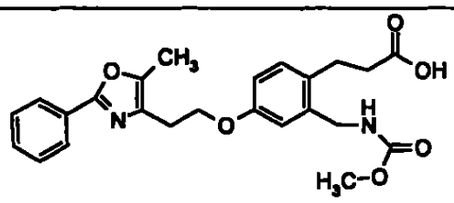
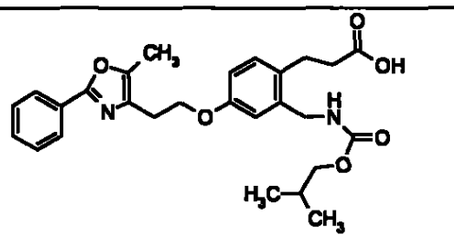
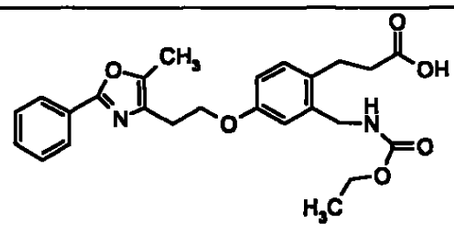
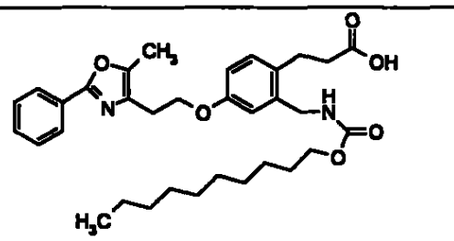
No	Compuestos	MS (ES+)	Procedimiento General
144		500	I
145		469	I
146		561	I
147		509	I
148		521	I

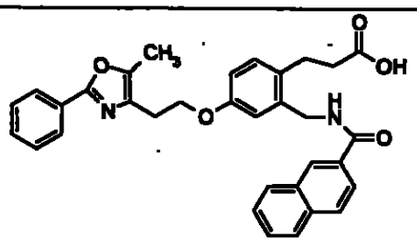
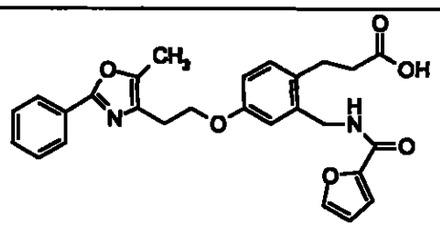
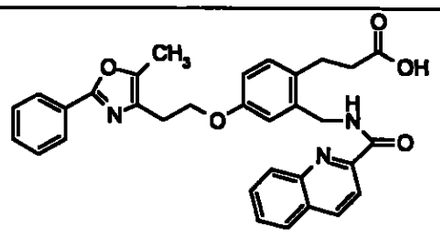
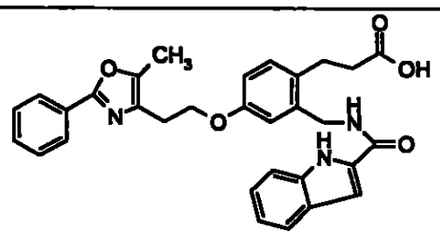
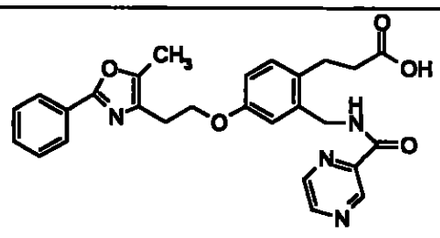
No	Compuestos	MS (ES+)	Procedimiento General
149		577	I
150		589	I
151		561	I
152		595	I
153		575	I

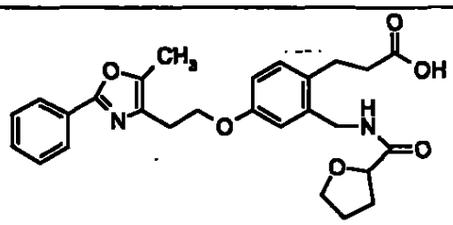
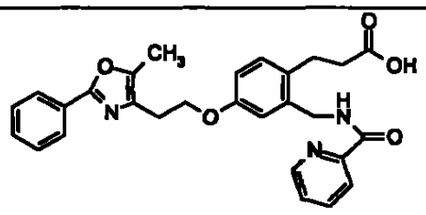
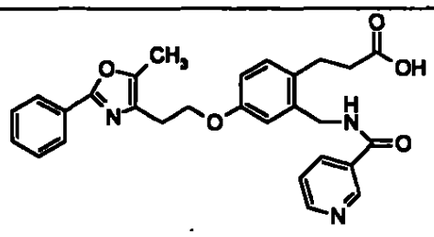
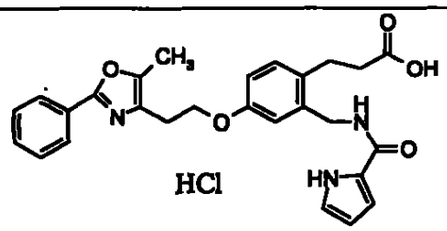
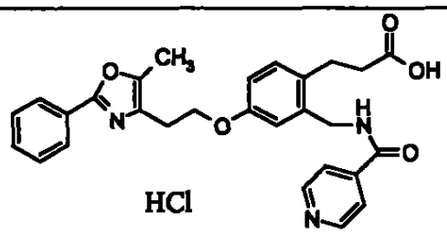
No	Compuestos	MS (ES+)	Procedimiento General
154		599	I
155		566	I
156		599	I
157		543	I
158		650	I

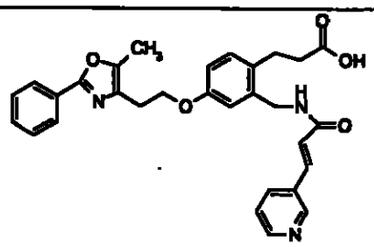
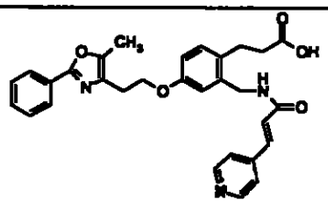
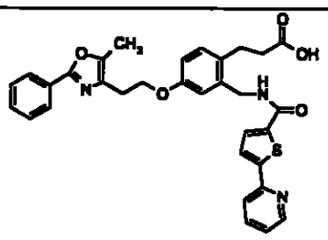
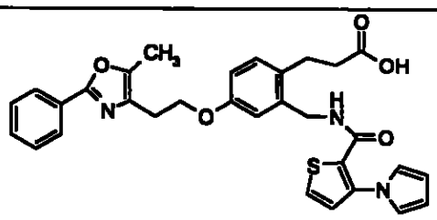
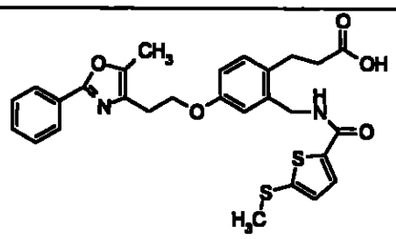
No	Compuestos	MS (ES+)	Procedimiento General
159		619	I
160		615	I
161		437,2	I
162		571,2	I
163		véase el texto	I

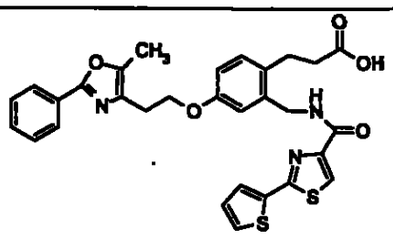
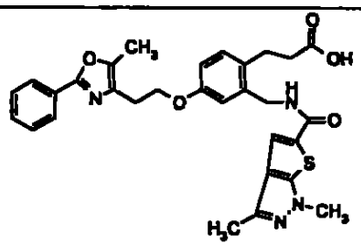
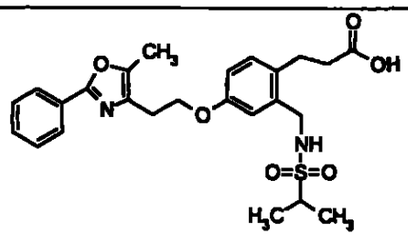
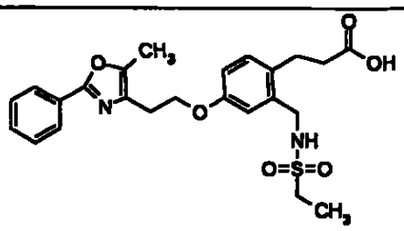
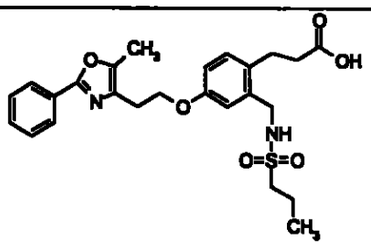
No	Compuestos	MS (ES+)	Procedimiento General
164		493,2	II
165		483,2	II
166		551,2	II
167		467,2	II
168		481,2	II

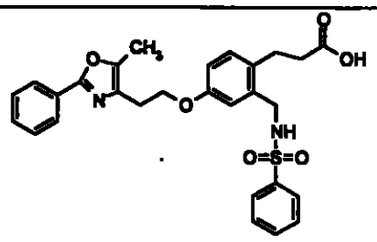
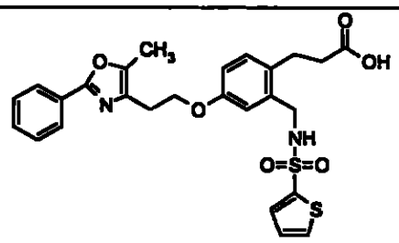
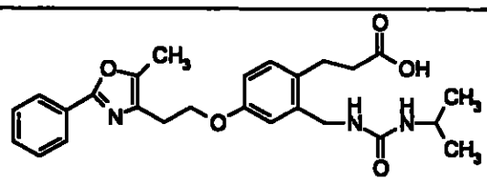
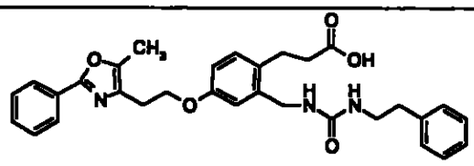
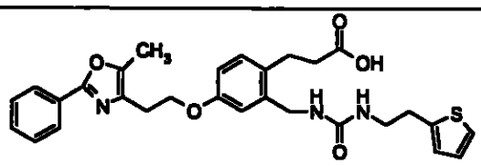
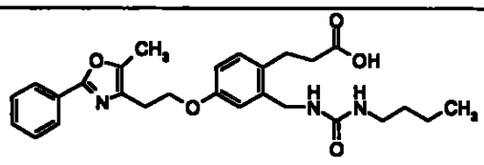
No	Compuestos	MS (ES+)	Procedimiento General
169		501,2	II
170		439,2	II
171		481,3	II
172		453,2	II
173		565,4	II

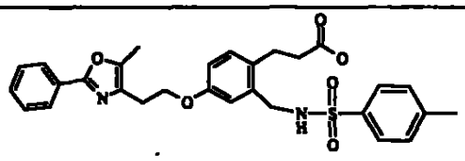
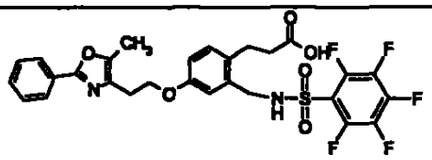
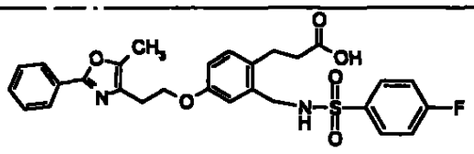
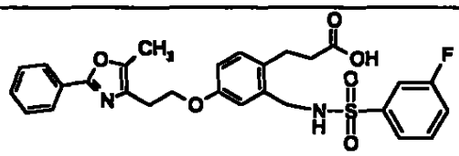
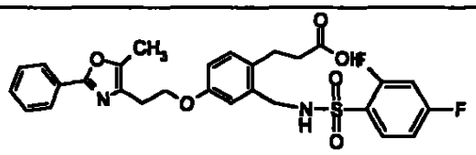
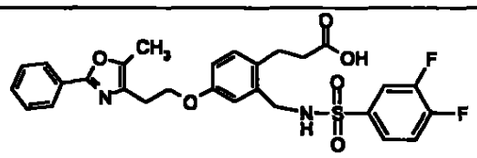
No	Compuestos	MS (ES+)	Procedimiento General
174		535,2	II
175		475,2	I
176		536,2	I
177		524,2	I
178		487,2	I

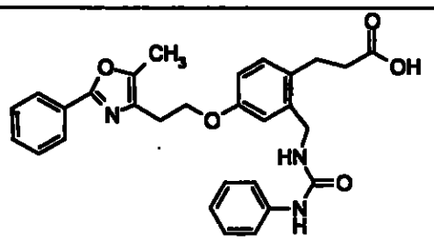
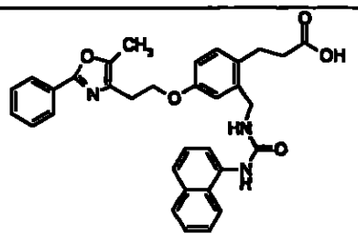
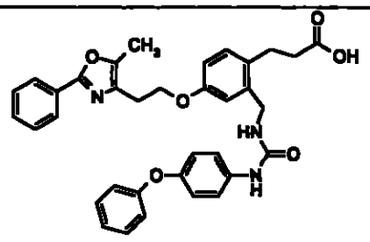
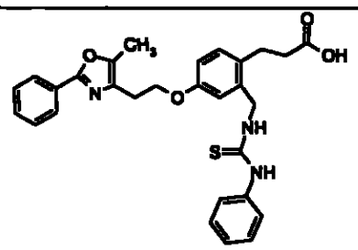
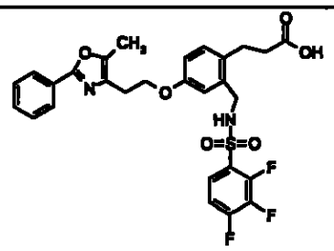
No	Compuestos	MS (ES+)	Procedimiento General
179		479,2	I
180		486,2	I
181		486,2	I
182		474,2	I
183		486,2	I

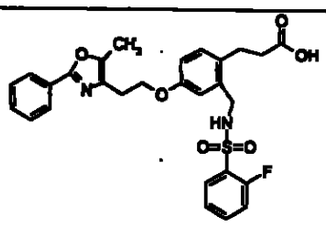
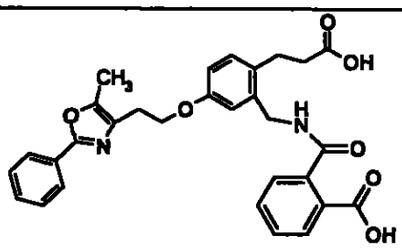
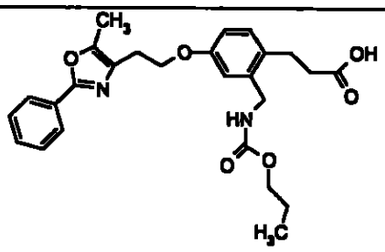
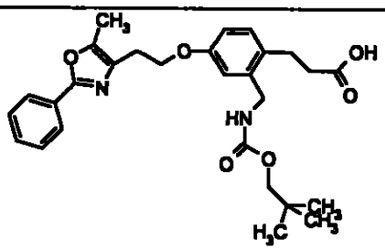
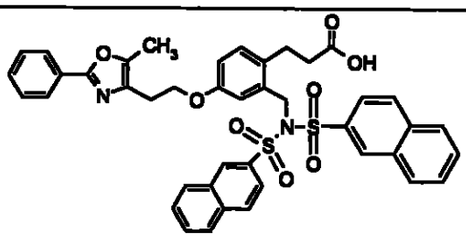
No	Compuestos	MS (ES+)	Procedimiento General
184		512	I
185		512,2	I
186		568,1	I
187		556,1	I
188		537,1	I

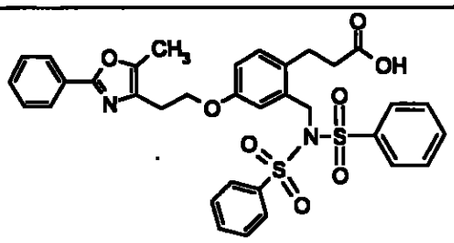
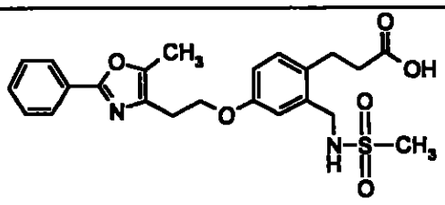
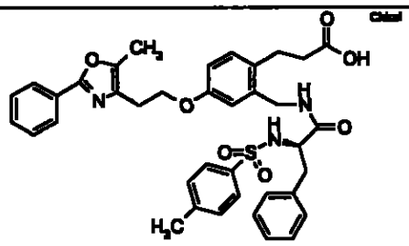
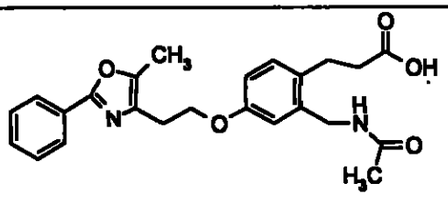
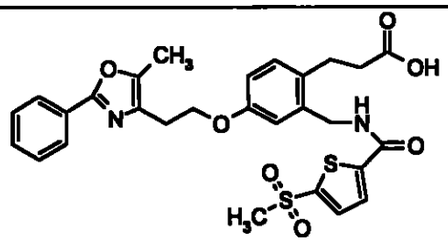
No	Compuestos	MS (ES+)	Procedimiento General
189		574,1	I
190		559,1	I
191		487,3	II
192		473,0	II
193		487,3	II

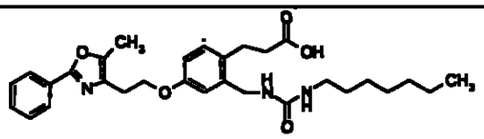
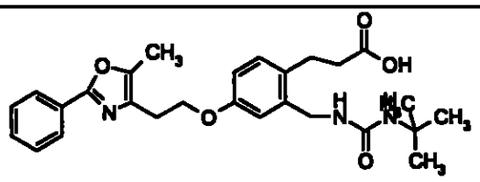
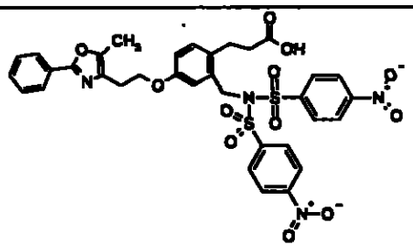
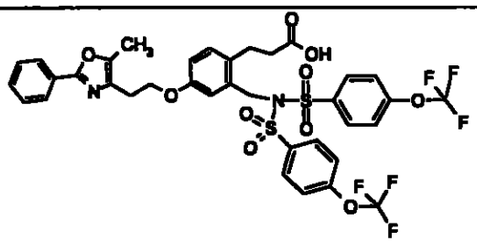
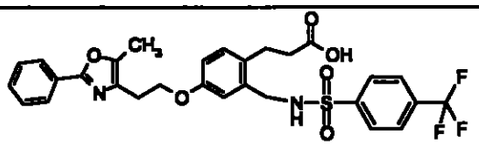
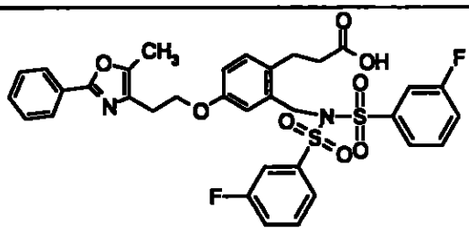
No	Compuestos	MS (ES+)	Procedimiento General
194		521,3	II
195		527,2	II
196		466,3	II
197		528,3	II
198		534,3	II
199		480,3	II

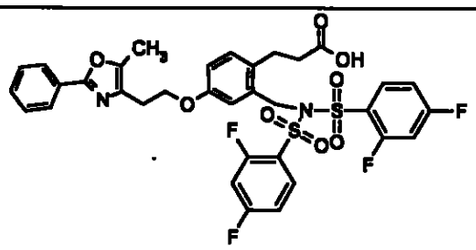
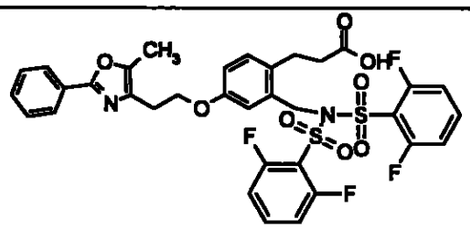
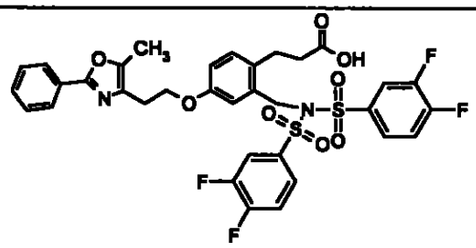
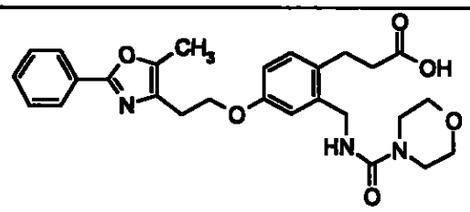
No	Compuestos	MS (ES+)	Procedimiento General
200		535,2	II
201		611,1	II
202		539,2	II
203		539,1	II
204		557,1	II
205		557,1	II

No	Compuestos	MS (ES+)	Procedimiento General
206		500,2	II
207		550,2	II
208		592,2	II
209		516,1	II
210		575,1	II

No	Compuestos	MS (ES+)	Procedimiento General
211		539,2	II
212		529	II
213		467,3	II
214		495,3	II
215		761,2 (FIA)	II

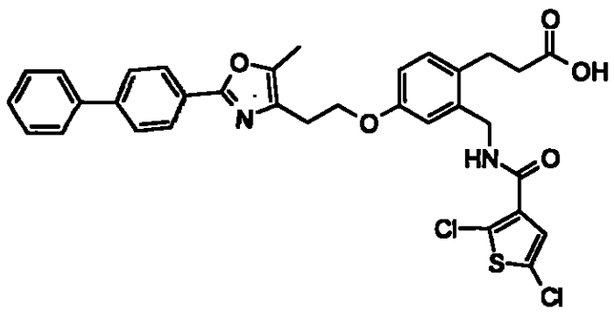
No	Compuestos	MS (ES+)	Procedimiento General
216		661,1 (FIA)	II
217		459,4 (FIA)	II
218		682	II
219		423	I
220		569	I

No	Compuestos	MS (ES+)	Procedimiento General
221		552	II
222		480	II
223		751	II
224		829	II
225		589	II
226		697	II

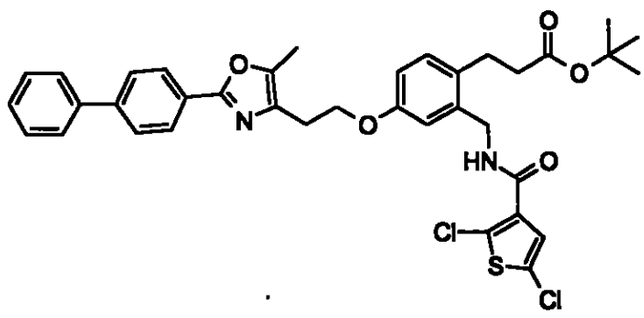
No	Compuestos	MS (ES+)	Procedimiento General
227		733	II
228		733	II
229		733	II
230		494,1	II

Ejemplo 231

Ácido 3-(4-[2-(2-Bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-{[(2,5-dicloro-tiofeno-3-carbonil)-amino]-metil}-fenil)-propiónico



Etapa A: Éster terc-butílico del ácido 3-(4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-{[(2,5-dicloro-tiofeno-3-carbonil)-amino]-metil}-fenil)-propiónico



Una mezcla de éster terc-butílico del ácido 3-(2-{[(2,5-dicloro-tiofeno-3-carbonil)-amino]-metil}-4-hidroxi-fenil)-propiónico (280 mg, 0,651 mmol) y 2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (498 mg, 1,15 mmol) se hizo reaccionar de acuerdo con el Procedimiento Convencional A para dar, después de cromatografía radial (hexanos/ EtOAc 98:2 a 90:10), el compuesto del título en forma de un sólido blanco (367 mg, 82%). ^{1}H RMN (400 MHz, $CDCl_3$): d1,36 (s, 9 H), 2,37 (s, 3 H), 2,55 (t, 2H, J = 7,3 Hz), 2,87 (t, 2H, J = 7,3 Hz), 2,96 (t, 2 H, J = 6,6 Hz), 4,22 (t, 2H, J = 6,8 Hz), 4,58 (d, 2H, J

= 5,4 Hz), 6,80 (dd, 1H, J = 8,3 Hz, J = 2,4 Hz), 6,88 (d, 1H, J = 2,9 Hz), 6,97 (t, 1H, J = 5,9 Hz), 7,10 (d, 1 H, J = 8,8 Hz), 7,13 (s, 1 H), 7,36 (t, 1H, J = 7,3 Hz), 7,45 (t, 2H, J = 7,8 Hz), 7,63 (d, 2 H, J = 8,3 Hz), 7,65 (d, 2H, J = 6,3 Hz), 8,02 (d, 2H, J = 7,8 Hz). MS (ES) m/e 691,2 [M+1].

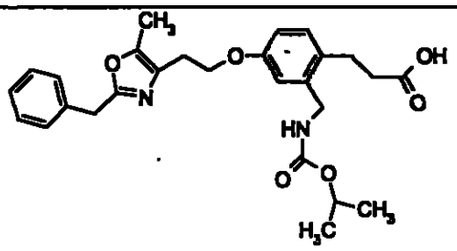
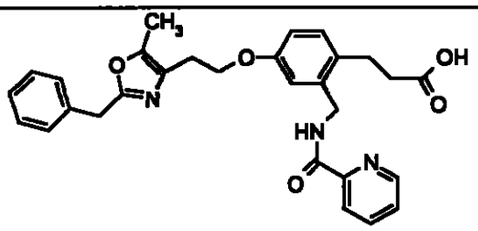
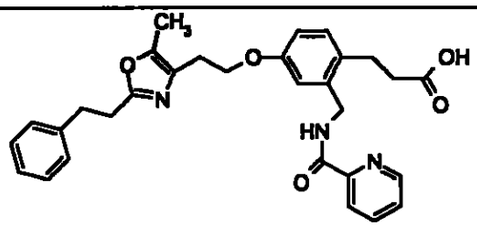
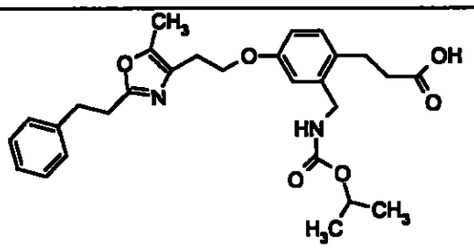
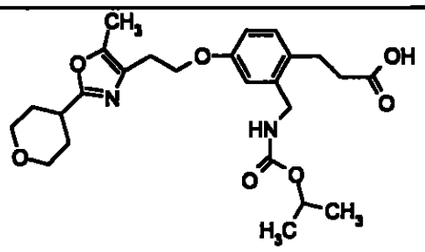
Etapa B: Ácido 3-(4-[2-(2-Bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-{[(2,5-dicloro-tiofeno-3-carbonil)-amino]-metil}-fenil)-propiónico

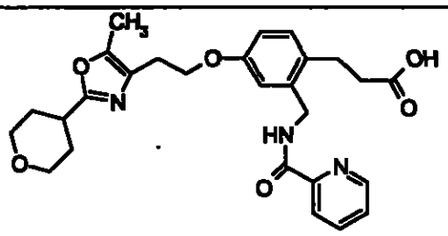
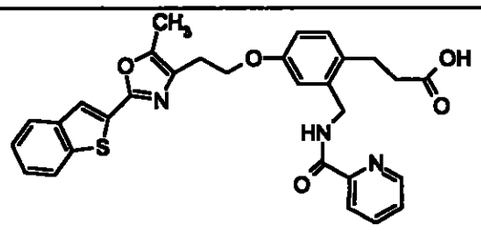
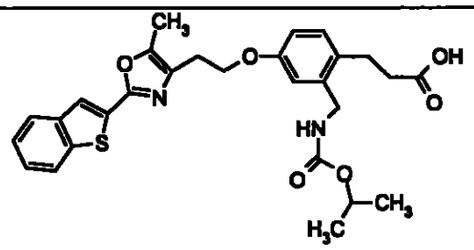
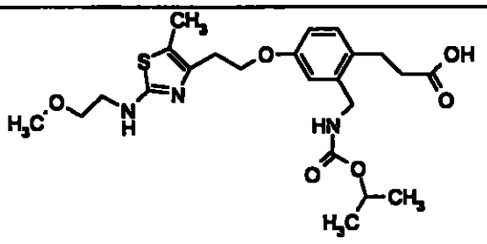
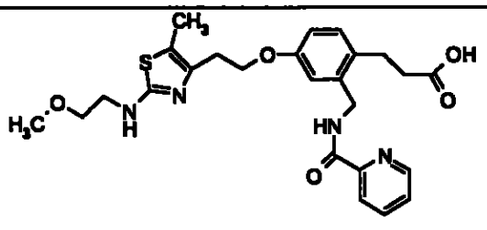
Una solución de éster terc-butílico del ácido 3-(4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-{[(2,5-dicloro-tiofeno-3-carbonil)-amino]-metil}-fenil)-propiónico (367 mg, 0,531 mmol) en CH_2Cl_2 (20 ml) se trató con anisol (2,0 ml) y después con TFA (6,0 ml). La mezcla se agitó a temperatura ambiente durante 2 h y se concentró. El residuo se co-evaporó tres veces con CCl_4, se secó al vacío, se trituró con éter, y se filtró para obtener el compuesto del título en forma de un sólido blanco (301 mg, 73%). ^{1}H RMN (400 MHz, DMSO-d6): d2,25 (s, 3 H), 2,38 (t, 2H, J = 8,3 Hz), 2,71 (t, 2H, J = 7,3 Hz), 2,82 (t, 2H, J = 6,3 Hz), 4,07 (t, 2H, J = 6,6 Hz), 4,28 (d, 2H, J = 4,9 Hz), 6,68 (d, 1H, J = 9,3 Hz), 6,77 (s, 1H), 7,00 (d, 1H, J = 8,3 Hz), 7,24 (s, 1H), 7,29 (t, 1 H, J = 5,9 Hz), 7,39 (t, 2H, J = 7,8 Hz), 7,63 (t, 2H, J = 7,8 Hz), 7,71 (d, 2 H, J = 8,3 Hz), 7,88 (d, 2H, J = 8,3 Hz), 8,69 (t, 2H, J = 5,9 Hz). MS (ES) m/e 635,1 [M+1].

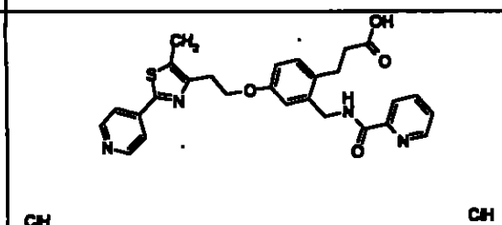
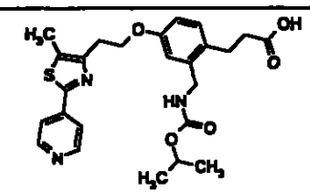
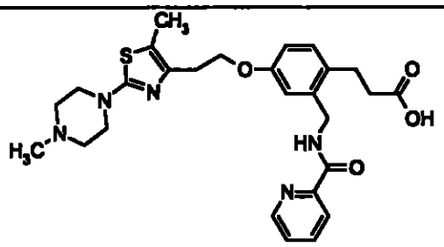
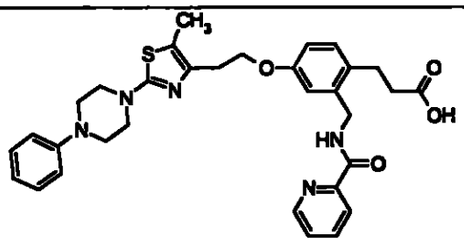
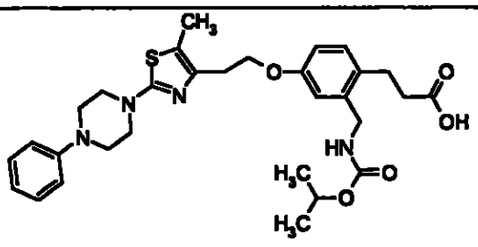
Ejemplos 232-318

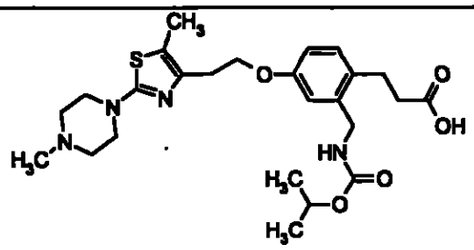
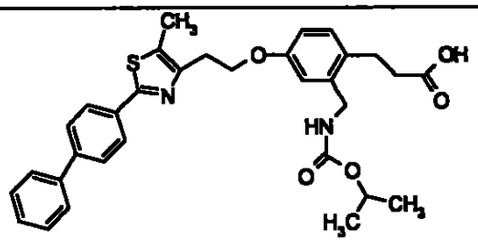
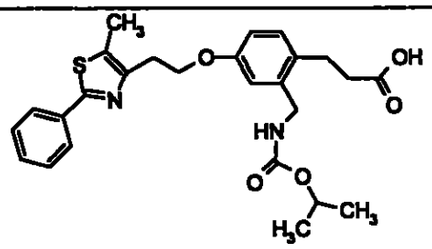
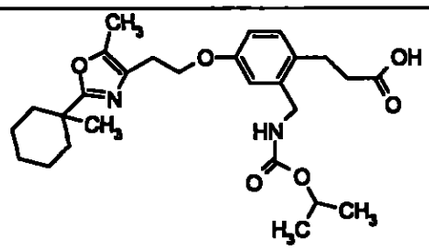
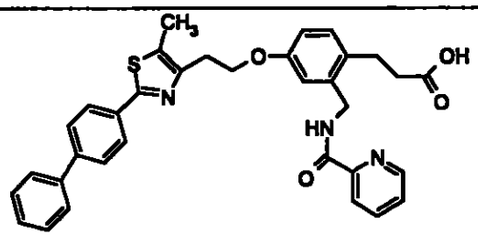
Los ejemplos 232-318 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 231 y el procedimiento de acoplamiento convencional A y los procedimientos de hidrólisis convencional C a E.

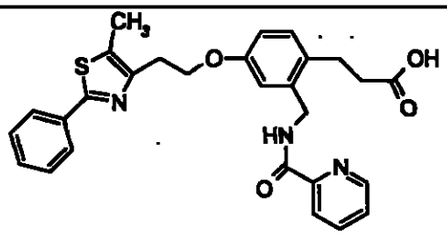
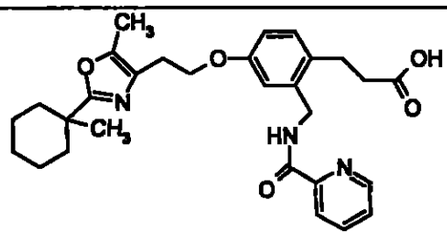
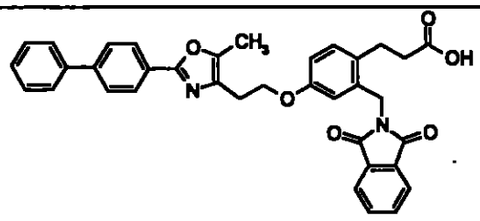
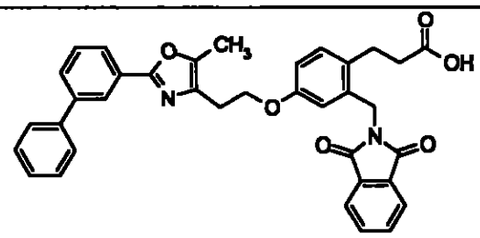
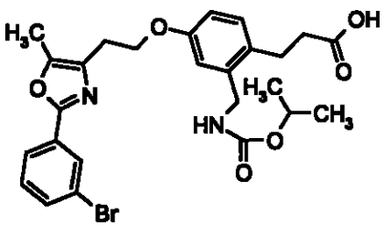
No.	Compuestos	MS (ES+)

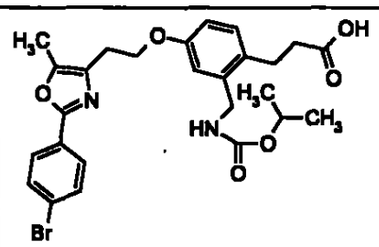
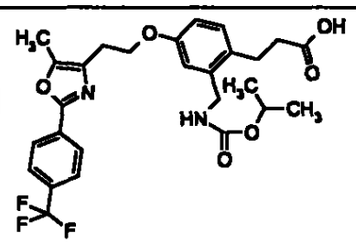
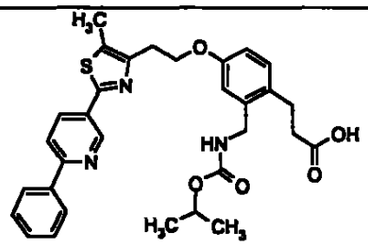
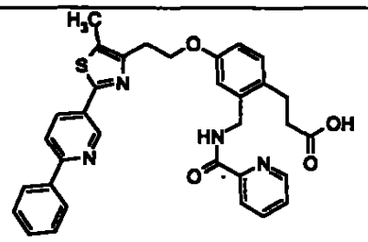
No.	Compuestos	MS (ES+)
232		481,3
233		500,3
234		514,3
235		495,3
236		475,1

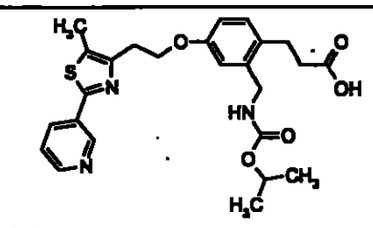
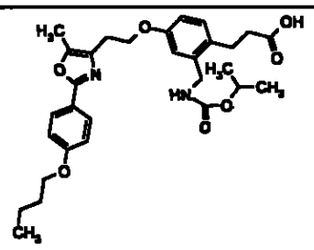
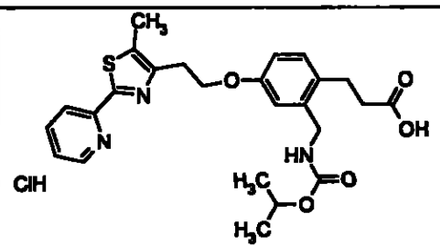
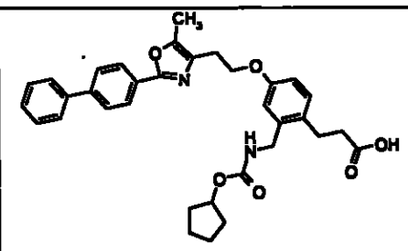
No.	Compuestos	MS (ES+)
237		494,3
238		542,2
239		523,3
240		480,3
241		499,2

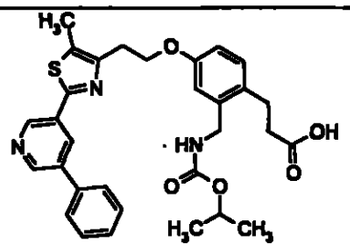
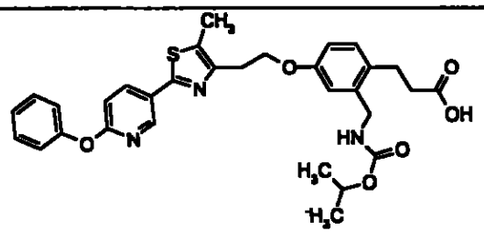
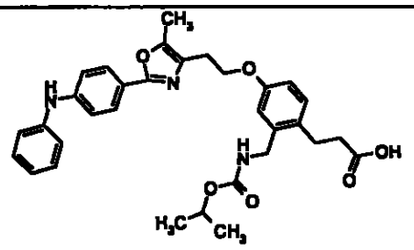
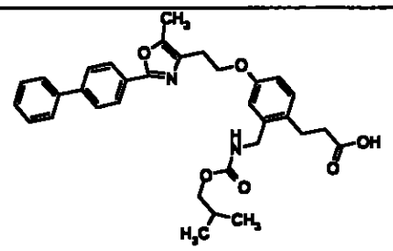
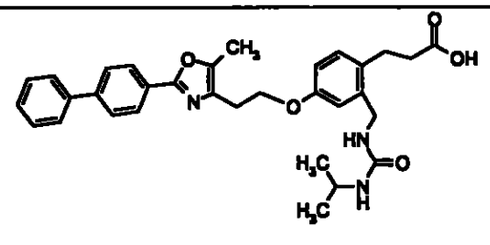
No.	Compuestos	MS (ES+)
242		503
243		484
244		524,4
245		586,3
246		567,3

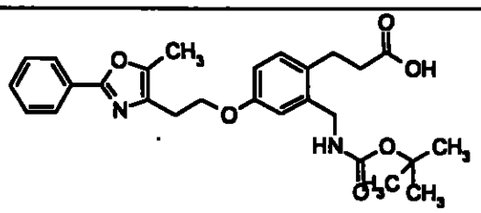
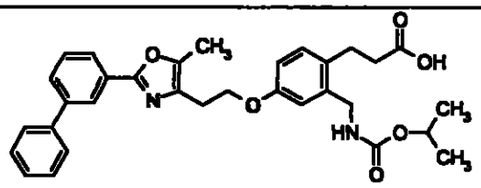
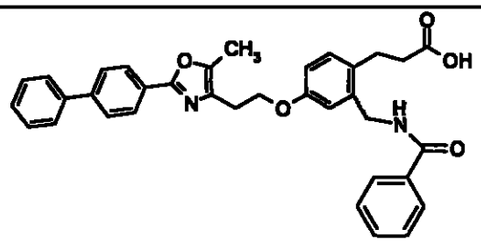
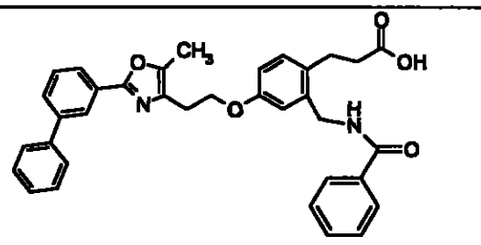
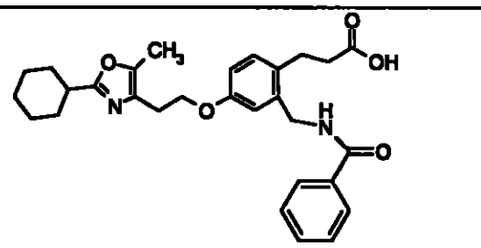
No.	Compuestos	MS (ES+)
247		505,3
248		559,2
249		483,2
250		487,3
251		578,3

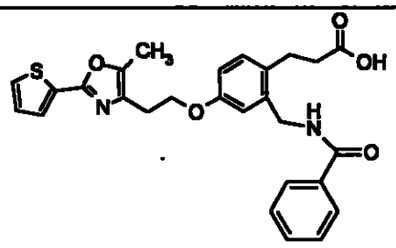
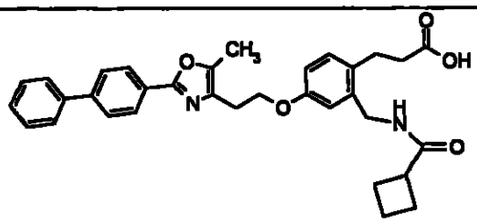
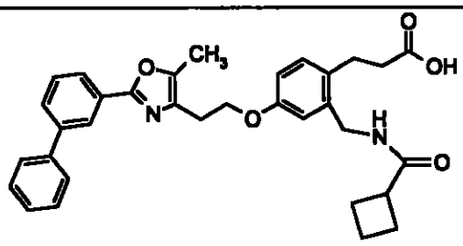
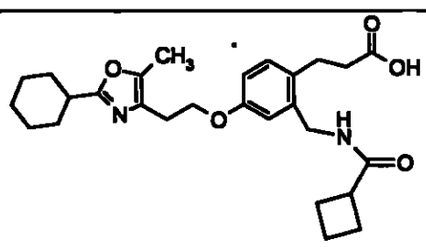
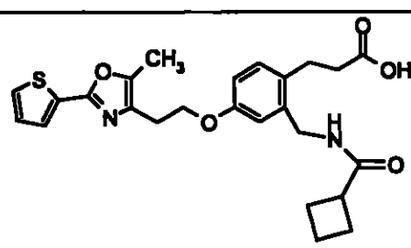
No.	Compuestos	MS (ES+)
252		502,2
253		503,3
254		587,2
255		587,2
256		545/547

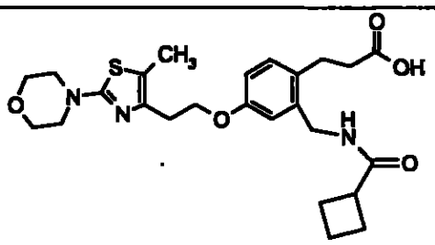
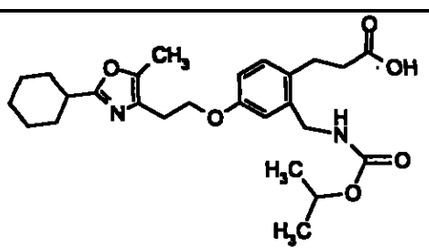
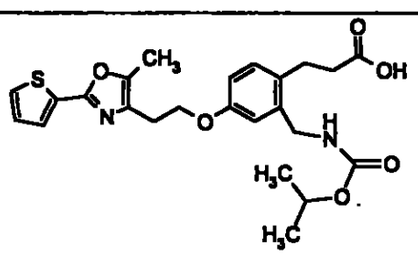
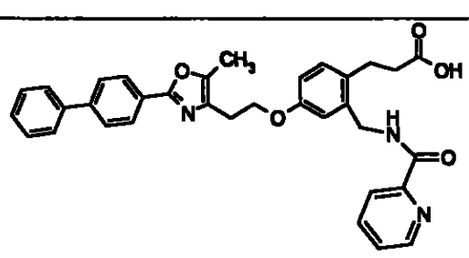
No.	Compuestos	MS (ES+)
257		545/547
258		535
259		560
260		579

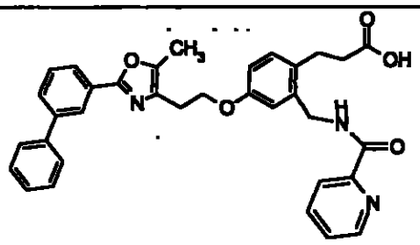
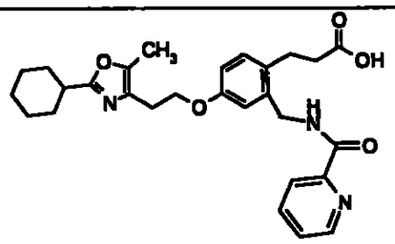
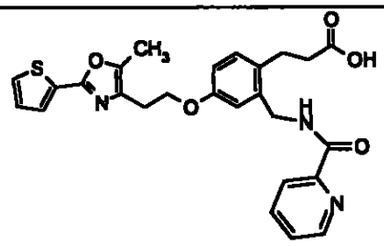
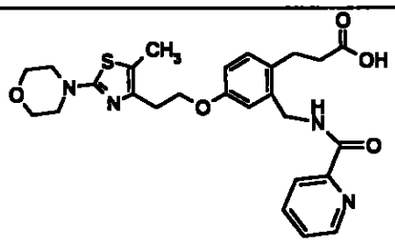
No.	Compuestos	MS (ES+)
261	 ClH	484
262		539
263	 ClH	484
264		569

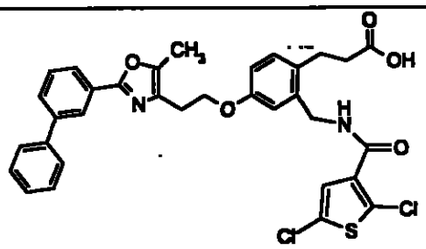
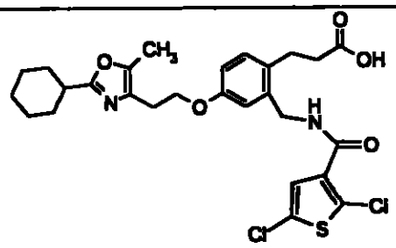
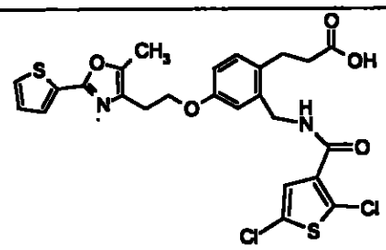
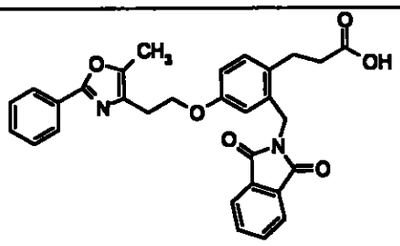
No.	Compuestos	MS (ES+)
265		560
266		576,1
267		558,4
268		557,2
269		542

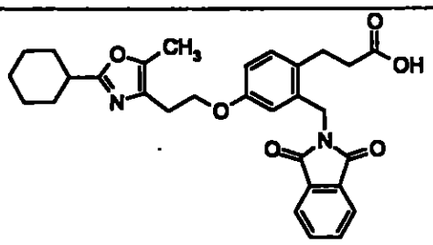
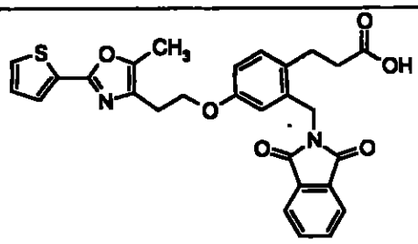
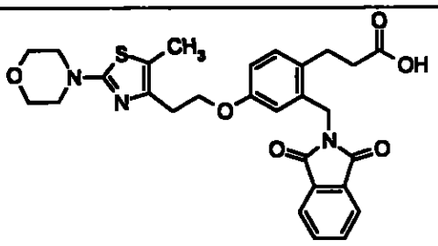
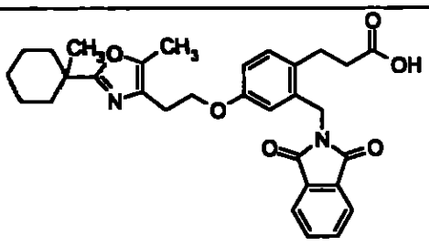
No.	Compuestos	MS (ES+)
270		481,3
271		543,2
272		561,3
273		561,3
274		491,3

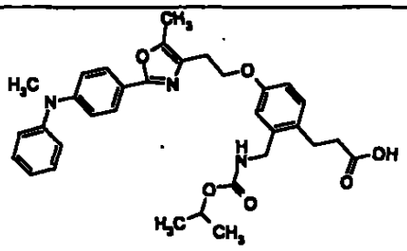
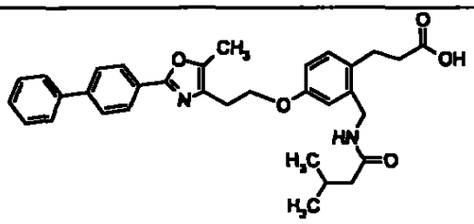
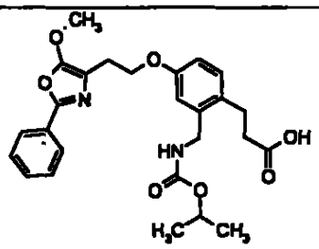
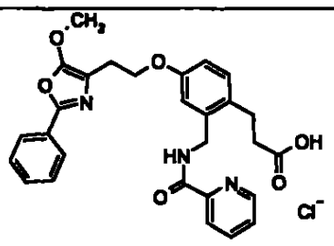
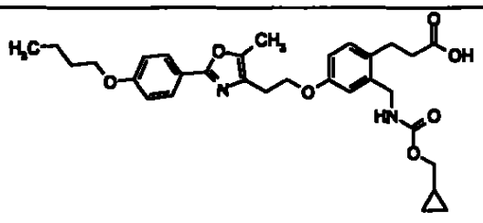
No.	Compuestos	MS (ES+)
275		491,2
276		539,3
278		539,3
279		469,3
280		469,3

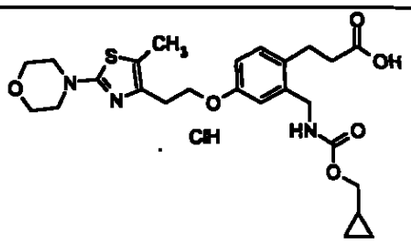
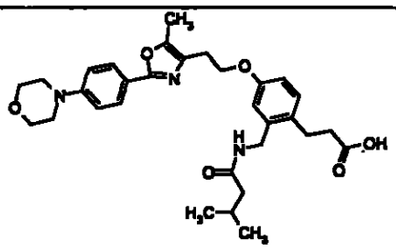
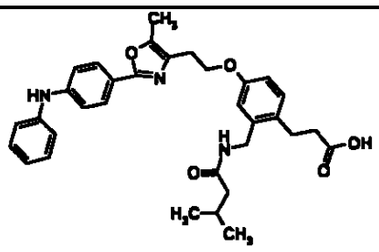
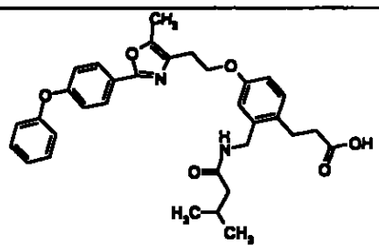
No.	Compuestos	MS (ES+)
281		488,1
282		473,3
283		473,2
284		562,2

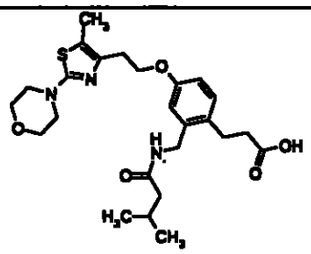
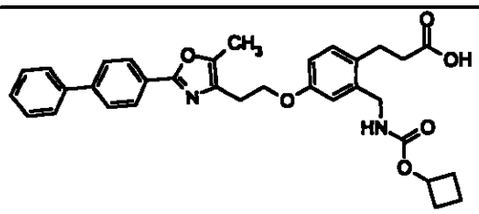
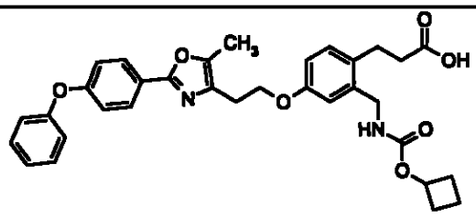
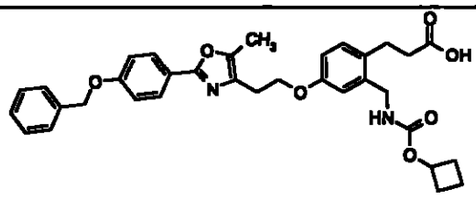
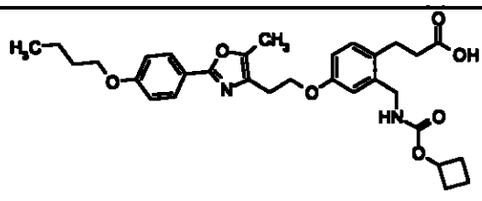
No.	Compuestos	MS (ES+)
285		562,3
286		492,2
287		492,2
288		511,2

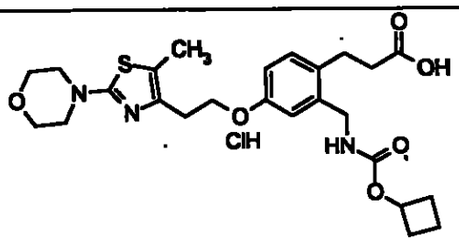
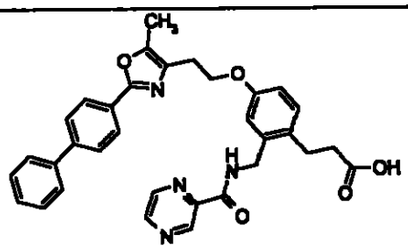
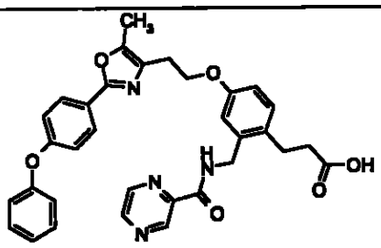
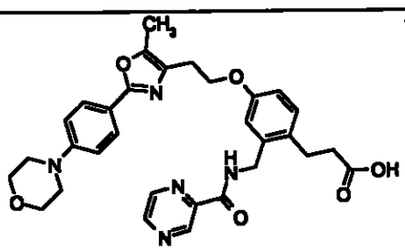
No.	Compuestos	MS (ES+)
289		635,2
290		565,2
291		565
292		511

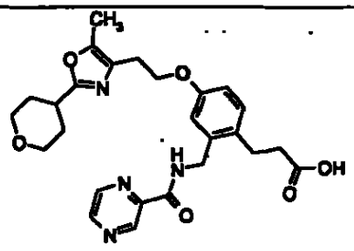
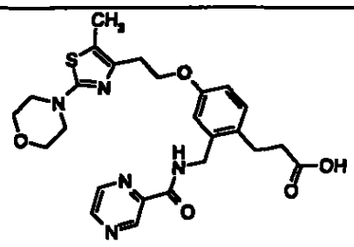
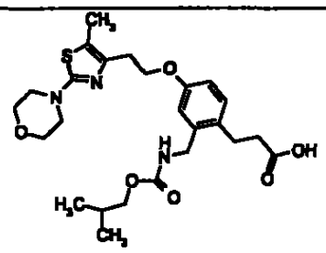
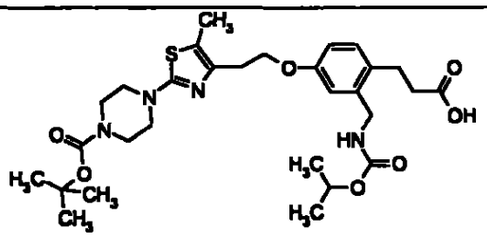
No.	Compuestos	MS (ES+)
293		517
294		517
295		536
296		531

No.	Compuestos	MS (ES+)
297		572,2
298		541
299		483
300		502
301		551,2770 (HRMS)

No.	Compuestos	MS (ES+)
302		504,2171 (HRMS)
303		550,2
304		554
305		557,2

No.	Compuestos	MS (ES+)
306		490,2
307		555,2426 (HRMS)
308		571,2436 (HRMS)
309		585,2595 (HRMS)
310		551,2753 (HRMS)

No.	Compuestos	MS (ES+)
311		504,2144 (HRMS)
312		563,2
313		579,2
314		572,2

No.	Compuestos	MS (ES+)
315		495,2
316		512,2
317		506,2
318		^{1}H RMN

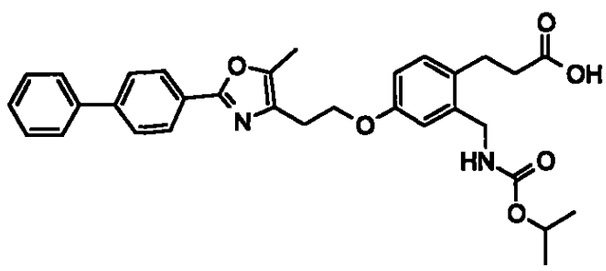
^{1}H RMN datos para el Ejemplo 318:

(400 MHz, $CDCl_3$): d 6,98 (1H, d, J = 7,9 Hz), 6,71 (1H, s), 6,68 (1H, d, J = 7,9 Hz), 4,97 (1H, m), 4,86 (2H, m), 4,31 (2H, s a), 4,08 (2H, t, J = 6,5 Hz), 3,45

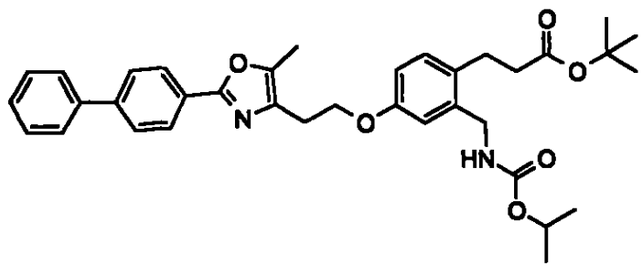
(4H, m), 3,27 (4H, m), 2,86 (4H, m), 2,55 (2H, s a), 2,18 (3H, s), 1,42 (9H, s), 1,16 (6H, d, J = 7,2 Hz).

Ejemplo 319

Ácido {4-[2-(5-Metil-2-(4-fenil)fenil-oxazol-4-il)-etoxi]-2-(isopropilcarbamato)-metil}-propiónico



Etapa A: Éster terc-butílico del ácido {4-[2-(5-metil-2-(4-fenil)fenil-oxazol-4-il)-etoxi]-2-(isopropilcarbamato)metil}-propiónico



Se hicieron reaccionar éster terc-butílico del ácido 3-[4-hidroxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (258 mg, 0,763 mmol) y 2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (654 mg, 1,51 mmol) de acuerdo con el Procedimiento Convencional A. La purificación por cromatografía radial (CH_2Cl_2/EtOAc 98/2 a 90/10) dio el compuesto del título con un rendimiento cuantitativo. ^1H RMN (400 MHz, $CDCl_3$): δ1,14 (d, 6H, J = 5,9 Hz), 1,31 (s, 9 H), 2,30 (s, 3 H), 2,39 (t, 2H, J = 7,6 Hz), 2,89 (t, 2H, J = 6,6 Hz), 4,14 (t, 2H, J = 6,6 Hz), 4,25 (d, 2H, J = 5,4 Hz), 4,85 (heptuplete,

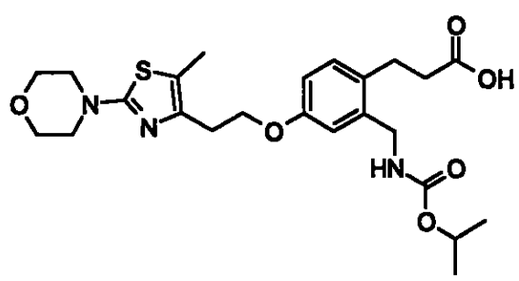
1H, J = 5,8 Hz), 6,67 (dd, 1H, J = 8,3 Hz, J = 2,4 Hz), 6,75 (d, 1H, J = 2,4 Hz), 6,99 (d, 1H, J = 8,3 Hz), 7,26-7,30 (m, 1 H), 7,37 (t, 2H, J = 7,6 Hz), 7,53-7,58 (m, 4 H), 7,95 (d, 2H, J = 8,3 Hz). MS (ES) m/e 599,4 [M+1].

Etapa B: Ácido {4-[2-(5-metil-2-(4-fenil)fenil-oxazol-4-il)-etoxi]-2-(isopropilcarbamato)metil}-propiónico

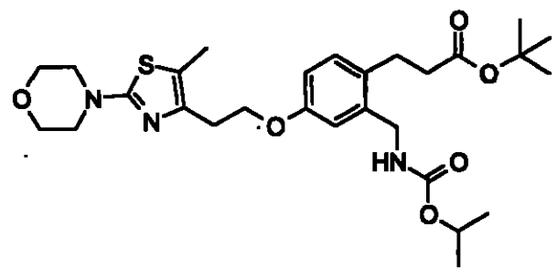
Una solución de ácido {4-[2-(5-metil-2-(4-fenil)fenil-oxazol-4-il)-etoxi]-2-(isopropilcarbamato)metil}-propiónico (414 mg, 0,763 mmol) en CH_2Cl_2 (10 ml) se trató con anisol (1,0 ml) y después con ácido trifluoroacético (TFA, 3,0 ml). La solución se agitó a temperatura ambiente durante 2 h y se concentró. El residuo se co-evaporó dos veces con CCl_4, se secó al vacío, se trituró con éter, y se filtró para obtener el compuesto del título en forma de un sólido blanco (287 mg, 69%). ^{1}H RMN (400 MHz, CDCl3) δ 1,11 (d, 6H, J = 5,9 Hz), 2,28 (s, 3 H), 2,46 (t, 2H, J = 7,6 Hz), 2,79 (t, 2H, J = 7,6 Hz), 2,86 (t, 2H, J = 6,6 Hz), 4,11 (t, 2H, J = 6,8 Hz), 4,24 (d, 2H, J = 5,4 Hz), 4,82 (heptuplete, 1H, J = 6,1 Hz), 5,05 (s a, 1 H), 6,66 (dd, 1H, J = 2,4, 8,3 Hz), 6,73 (d, 1H, J = 2,4 Hz), 6,99 (d, 1H, J = 8,3 Hz), 7,24-7,28 (m, 1 H), 7,35 (t, 2H, J = 7,6 Hz), 7,51-7,56 (m, 4 H), 7,98 (d, 2H, J = 8,3 Hz). MS (ES) m/e 543,1 [M+1].

Ejemplo 320

Ácido 3-{2-(isopropoxicarbonilaminometil)-4-[2-(5-metil-2-morfolin-4-il-tiazol-4-il)etoxi]-fenil}propiónico



Etapa A: Éster terc-butílico del ácido 3-{2-(isopropoxicarbonilamino-metil)-4-[2-(5-metil-2-morfolin-4-il-tiazol-4-il)-etoxi]-fenil}-propiónico



Se hicieron reaccionar éster terc-butílico del ácido 3-[4-hidroxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (272 mg, 0,806 mmol) y 2-(5-metil-2-morfolin-4-il-tiazol-4-il)-etil éster del ácido tolueno-4-sulfónico (522 mg, 1,36 mmol) de acuerdo con el Procedimiento Convencional A. La purificación usando cromatografía radial (CH_2Cl_2/EtOAc 98:2 a 75:25) dio el compuesto del título en forma de un sólido blanco (387 mg, 98%). ^{1}H RMN (400 MHz, $CDCl_3$) d1,14 (d, 6H, J = 5,9 Hz), 1,32 (s, 9 H), 2,16 (s, 3 H), 2,39 (t, 2H, J = 7,6 Hz), 2,77 (t, 2H, J = 7,6 Hz), 2,84 (t, 2H, J = 7,1 Hz), 3,28 (t, 4H, J = 4,9 Hz), 3,70 (t, 4H, J = 4,9 Hz), 4,08 (t, 2H, J = 7,1 Hz), 4,25 (d, 2H, J = 5,4 Hz), 4,83 (heptuplete, 1H, J = 4,9 Hz), 6,66 (dd, 1H, J = 2,4, 8,3 Hz), 6,72 (d, 1H, J = 2,4 Hz), 6,98 (d, 1H, J = 8,3 Hz). MS (ES) m/e 548,3 [M+1].

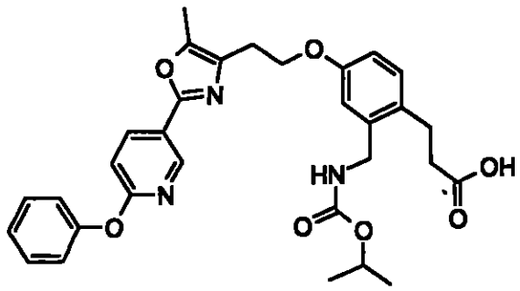
Etapa B: Ácido 3-{2-(isopropoxicarbonilaminometil)-4-[2-(5-metil-2-morfolin-4-il-tiazol-4-il)etoxi]-fenil}propiónico

Una solución de éster terc-butílico del ácido 3-{2-(isopropoxicarbonilamino-metil)-4-[2-(5-metil-2-morfolin-4-il-tiazol-4-il)-etoxi]-fenil}-propiónico (387 mg, 0,706 mmol) en CH_2Cl_2 (10 ml) se trató con anisol (1 ml) y después con TFA (3 ml). La solución se agitó a temperatura ambiente durante 2 h y se concentró. El residuo se co-evaporó dos veces con CCl_4, se

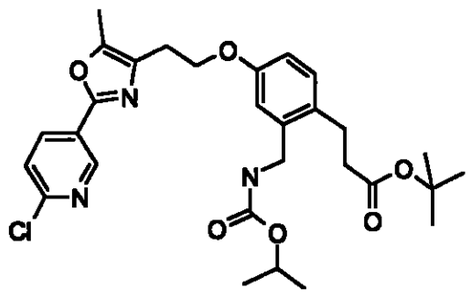
secó al vacío, se trituró con éter, y se filtró para obtener el compuesto del título en forma de un sólido blanco (236 mg, 60%), aislado como la sal del ácido trifluoroacético: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,12 (d, 6H, J = 6,4 Hz), 2,16 (s, 3H), 2,47 (t, 2H, J = 7,6 Hz), 2,79 (t, 2H, J = 7,6 Hz), 2,87 (t, 2H, J = 6,4 Hz), 3,35 (t, 4H, J = 4,9 Hz), 3,70 (t, 4H, J = 4,9 Hz), 4,07 (t, 2H, J = 6,6 Hz), 4,23 (d, 2H, J = 5,4 Hz), 4,82 (heptuplete, 1H, J = 6,1 Hz), 5,07 (s a, 1H), 6,63 (dd, 1H, J = 2,7, 8,6 Hz), 6,69 (d, 1H, J = 2,9 Hz), 6,98 (d, 1H, J = 8,3 Hz). MS (ES) m/e 492,1 [M+1].

Ejemplo 321

Ácido 3-(2-(2-isopropoxicarbonil-etil)-4-{2-[5-metil-2-(6-fenoxi-piridin-3-il)-oxazol-4-il]etoxi}-fenil)-propiónico



Etapa A: Éster t-butílico del ácido 3-(2-(2-isopropoxicarbonil-etil)-4-{2-[5-metil-2-(6-cloro-piridin-3-il)-oxazol-4-il]etoxi}-fenil)-propiónico



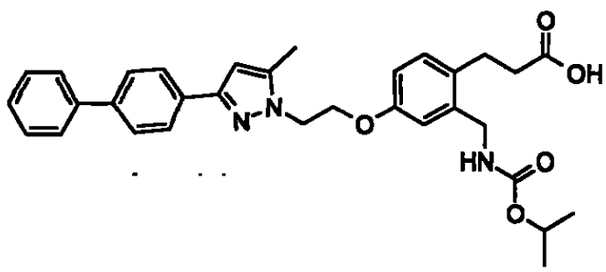
Tosilato de 2-[2-(6-cloro-piridin-3-il)-5-metil-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico (290 mg, 0,74 mmol) y éster t-butílico del ácido 3-[4-hidroxi-2-(2-isopropoxicarbonil-etil)-fenil]-propiónico (274 mg, 0,81 mmol) se convirtieron en el compuesto del título (183 mg, 44 %) de acuerdo con el Procedimiento Convencional A. MS (ESI) m/z 559 $(M+H)^+$.

Etapa B: Ácido 3-(2-(2-isopropoxicarbonil-etil)-4-{2-[5-metil-2-(6-fenoxi-piridin-3-il)-oxazol-4-il]etoxi}-fenil)-propiónico

A una suspensión de NaH (20 mg, 0,48 mmol) en DMF (10 ml) a temperatura ambiente se le añadió fenol (45 mg, 0,48 mmol). La mezcla se agitó a 60°C durante 20 min, y se añadió éster t-butílico del ácido 3-(2-(2-isopropoxicarbonil-etil)-4-{2-[5-metil-2-(6-cloro-piridin-3-il)-oxazol-4-il]etoxi}-fenil)-propiónico (180 mg, 0,32 mmol). La mezcla resultante se agitó a 60°C durante una noche, se enfrió, se diluyó con EtOAc, y se lavó con agua/salmuera (4x). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía en gel de sílice (hexanos/EtOAc 3/1 a 1/1) para producir el éster intermedio en forma de un aceite (60 mg, 30%). El compuesto del título se generó usando el procedimiento de hidrólisis convencional C. MS (ESI) m/z 560 $(M+H)^+$. ^1H RMN ($CDCl_3$, 250 MHz) δ 1,25 (d, J = 0,5 Hz, 6H), 2,42 (s, 3H), 2,65 (m, 2H), 2,96 (m, 4H), 4,38 (m, 2H), 4,18 (m, 2H), 4,38 (m, 1H), 5,00 (m, 2H), 6,82 (m, 3H), 6,96 (m, 1H), 7,12 (m, 1H), 7,20 (m, 2H), 7,45 (m, 2H), 8,28 (m, 1H), 8,80 (m, 1H).

Ejemplo 322

Ácido 3-[4-[2-(3-bifenil-4-il-5-metil-pirazol-1-il)-etoxi]-2-(isopropoxicarbonil-amino-metil)-fenil]-propiónico

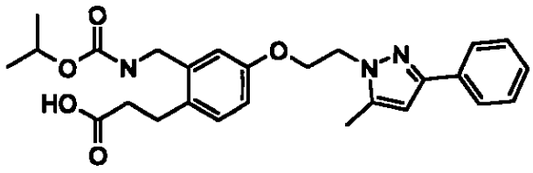


El compuesto del título se preparó a partir de éster terc-butílico del ácido 3-[4-hidroxi-2-(isopropoxicarbonil-amino-metil)-fenil]-propiónico (Prep 16) y 2-(3-bifenil-4-il-5-metil-pirazol-1-il)-etanol (Prep 11) usando el procedimiento de acoplamiento convencional B seguido del procedimiento de hidrólisis convencional C. MS [ES] m/e 542 $(M+1)^+$.

Los siguientes Ejemplos 323 a 333 siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 322.

Ejemplo 323

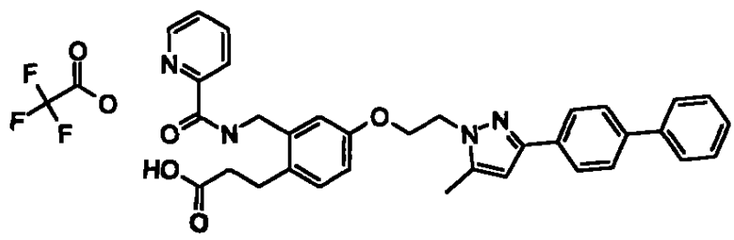
Ácido 3-{2-(Isopropoxicarbonilamino-metil)-4-[2-(5-metil-3-fenil-pirazol-1-il)-etoxi]-fenil}-propiónico



HRMS Calculado para $C_{26}H_{32}N_3O_5$: m/z 466,2342. Encontrado: 466,2331,

Ejemplo 324

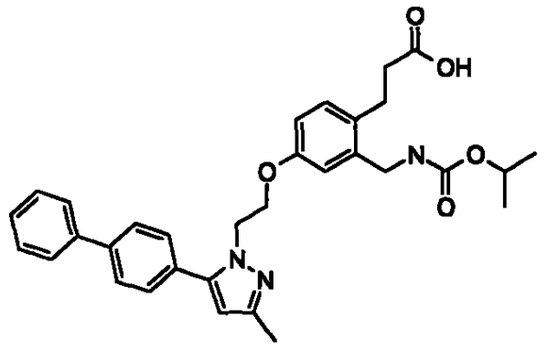
Trifluoroacetato del ácido 3-(4-[2-(3-bifenil-4-il-5-metil-pirazol-1-il)-etoxi]-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



HRMS Calculado para $C_{28}H_{30}N_4O_4$: m/z 486,2267. Encontrado: 486,2233,

Ejemplo 325

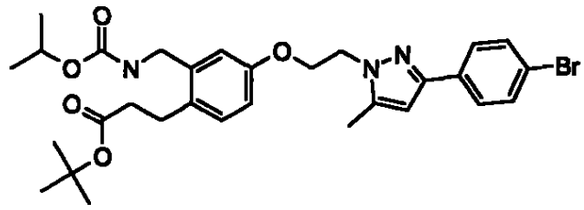
Ácido 3-[4-[2-(5-bifenil-4-il-3-metil-pirazol-1-il)-etoxi]-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



HRMS Calculado para $C_{32}H_{38}N_3O_5$: m/z 542,2655. Encontrado: 542,2678

Ejemplo 326

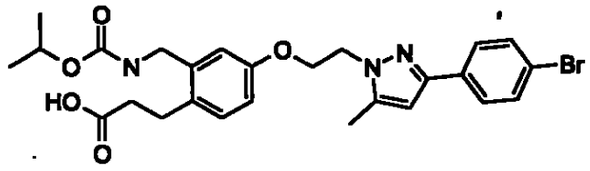
Éster terc-butílico del ácido 3-[4-{2-[3-(4-bromo-fenil)-5-metil-pirazol-1-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



HRMS Calculado para $C_{30}H_{36}BrN_3O_5$: m/z 600,2073. Encontrado: 600,2064.

Ejemplo 327

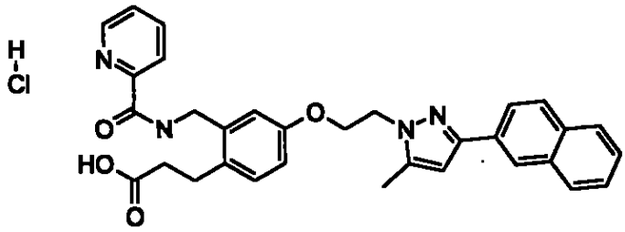
Ácido 3-[4-{2-[3-(4-bromo-fenil)-5-metil-pirazol-1-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



HRMS Calculado para $C_{26}H_{31}BrN_3O_5$: m/z 544,1447. Encontrado: 544,1456.

Ejemplo 328

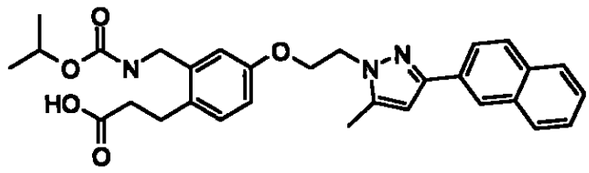
Clorhidrato del ácido 3-(4-[2-(5-Metil-3-naftalen-2-il-pirazol-1-il)-etoxi]-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



El compuesto anterior se prepara usando el procedimiento de hidrólisis convencional D. HRMS Calculado para $C_{32}H_{31}N_4O_4$: m/z 535,2345. Encontrado: 535,2343

Ejemplo 329

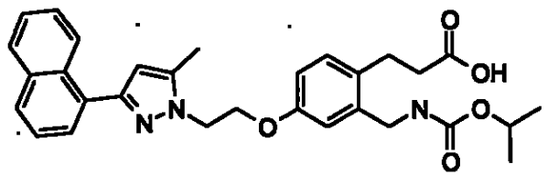
Ácido 3-{2-(isopropoxicarbonilamino-metil)-4-[2-(5-metil-3-naftalen-2-il-pirazol-1-il)-etoxi]-fenil}-propiónico



HRMS Calculado para $C_{30}H_{34}N_3O_5$: m/z 516,2498. Encontrado: 516,2485,

Ejemplo 330

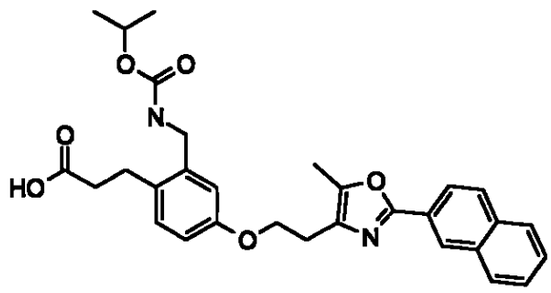
Ácido 3-{2-(Isopropoxicarbonilamino-metil)-4-[2-(5-metil-3-naftalen-1-il-pirazol-1-il)-etoxi]-fenil}-propiónico



HRMS Calculado para $C_{30}H_{34}N_3O_5$: m/z 516,2498. Encontrado: 516,2529.

Ejemplo 331

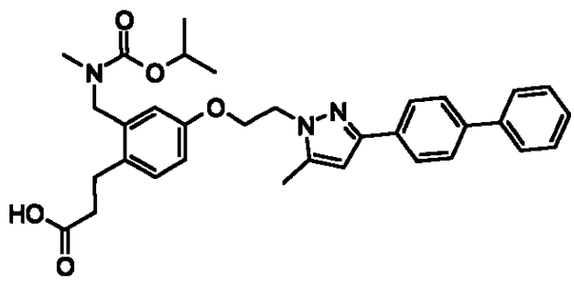
Ácido 3-{2-(isopropoxicarbonilamino-metil)-4-[2-(5-metil-2-naftalen-2-il-oxazol-4-il)-etoxi]-fenil}-propiónico



HRMS Calculado para $C_{30}H_{33}N_2O_6$: m/z 517,2339. Encontrado: 517,2328,

Ejemplo 332

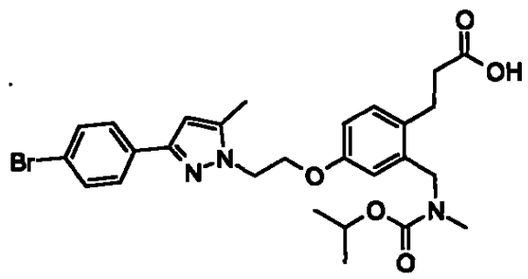
Ácido 3-{4-[2-(3-bifenil-4-il-5-metil-pirazol-1-il)-etoxi]-2-[(isopropoxi-carbonil-metil-amino)-metil]-fenil}-propiónico



HRMS Calculado para $C_{33}H_{38}N_3O_5$: m/z 556,2811. Encontrado: 556,2819

Ejemplo 333

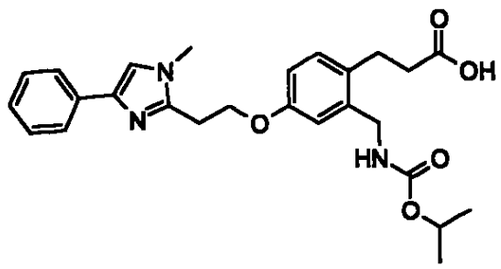
Ácido 3-{4-{2-[3-(4-bromo-fenil)-5-metil-pirazol-1-il]-etoxi}-2-[(isopropoxi-carbonil-metil-amino)-metil]-fenil}-propiónico



HRMS Calculado para $C_{27}H_{33}BrN_3O_5$: m/z 558,1604. Encontrado: 558,1608

Ejemplo 334

Ácido 3-{2-(isopropoxicarbonilamino-metil)-4-[2-(1-metil-4-fenil-1H-imidazol-2-il)-etoxi]-fenil}-propiónico

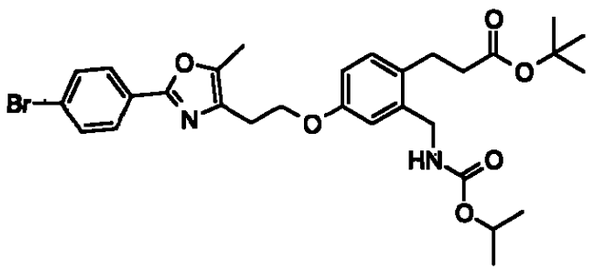


El compuesto del título se preparó a partir de éster terc-butílico del ácido 3-[4-hidroxi-2-(isopropoxicarbonil-amino-metil)-fenil]-propiónico (Prep 16) y 2-(1-Metil-4-fenil-1H-imidazol-2-il)-etanol (*J. Med. Chem.* 1998, *41* (25), 5037-5054) usando el procedimiento de acoplamiento convencional B seguido del procedimiento de hidrólisis convencional D produciendo un sólido finamente cristalino blanquecino. HRMS Calculado para C26H31N3O5: m/z 466,2342. Encontrado: 466,2355.

Modificaciones de Anillo de Arilo de Pieza de cabeza

Ejemplo 335

Éster terc-butílico del ácido 3-[4-{2-[2-(4-bromo-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonil-amino-metil)-fenil]-propiónico

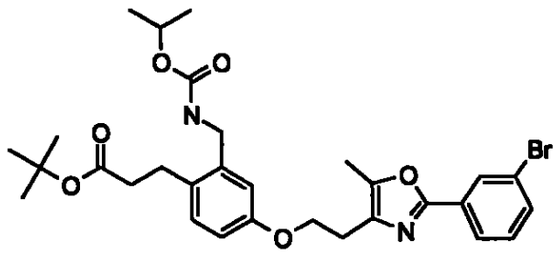


Se acoplaron 2-[2-(4-bromo-fenil)-5-metil-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico (5,06g, 11,6mmol) y éster terc-butílico del ácido 3-[4-hidroxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (3,01 g, 8,92 mmol) usando el Procedimiento Convencional A para dar el compuesto del título en forma de un sólido blanco (3,41 g, 64%). MS [ES] m/z 601,603 (M+H).

Los siguientes Ejemplos 336 a 337 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 335,

Ejemplo 336

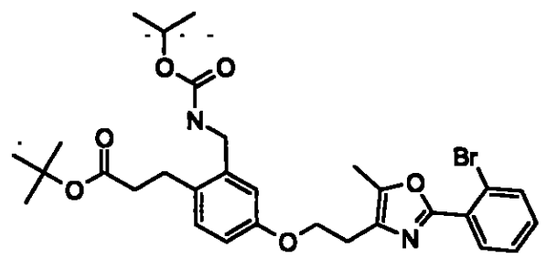
Éster terc-butílico del ácido 3-[4-{2-[2-(3-bromo-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxi-carbonilamino-metil)-fenil]-propiónico



MS [ES] m/z 601,603 (M+H).

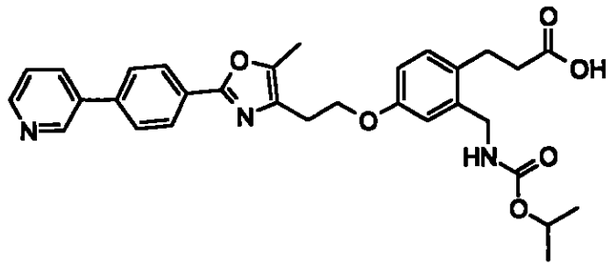
Ejemplo 337

Éster terc-butílico del ácido 3-[4-{2-[2-(2-bromo-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxi-carbonilamino-metil)-fenil]-propiónico.



Ejemplo 338

Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-piridin-3-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



Acoplamiento de Suzuki Usando Ácidos Aril Borónicos: Una mezcla de éster terc-butílico del ácido 3-[4-{2-[2-(4-bromo-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (450 mg, 0,75 mmol), ácido 3-piridinaborónico (120 mg, 0,97 mmol), trifenilfosfina (6 mg, 0,024 mmol), carbonato sódico acuoso 2 M (3 ml) en n-propanol (15 ml) se roció con nitrógeno durante 5 min. Se añadió acetato de paladio (2 mg, 0,008 mmol) y la reacción se calentó a reflujo en una atmósfera de nitrógeno durante 4 h. La mezcla de reacción se concentró y después se repartió entre agua/EtOAc. La capa orgánica se secó ($MgSO_4$) y se concentró para dàr el producto bruto (290 mg). Este material se purificó por cromatografía en

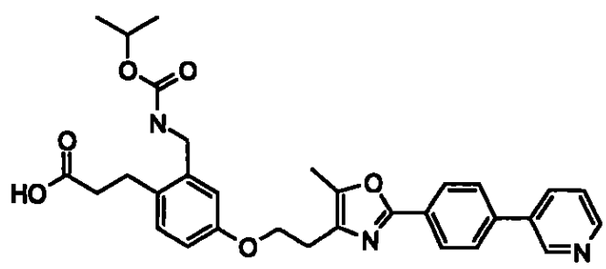
columna de gel de sílice para producir éster terc-butílico del ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-piridin-3-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico obtenido en forma de un sólido blanco (230 mg, 51%). ^{1}H RMN (CDCl3) d1,25 (d, 6H), 1,42 (s, 9H), 2,42 (s, 3H), 2,51 (t, 2H), 2,89 (t, 2H), 3,05 (t, 2H), 4,26 (t, 2H), 4,36 (d, 2H), 4,96 (m, 2H), 6,78 (dd, 1H), 6,87 (d, 1H), 7,21 (d, 1H), 7,47 (dd, 1H), 7,67 (d, 2H), 8,00 (dt, 1H), 8,12 (d, 2H), 8,65 (dd, 1H),8,94 (s, 1H). MS [EI+] m/z 600 (M+H).

Este éster (225 mg, 0,375 mmol) se disolvió en THF (15ml) y se trató con HCl 1 N (1ml). La mezcla se calentó a reflujo durante 7 h, se enfrió, y se concentró. El residuo se destiló azeotrópicamente dos veces con acetonitrilo y se secó en una estufa de vacío para dar el compuesto del título, aislado como la sal HCl (140 mg, 64%). ^{1}H RMN (DMSO-d_6) d1,15 (d, 6H), 2,41 (s, 3H), 2,45 (t, 2H), 2,76 (t, 2H), 2,95 (t, 2H), 4,17 (solapamiento t y d, 4H), 4,75 q, 1H), 6,77 (m, 2H), 7,07 (dd, 1H), 7,55 (t, 1H), 8,02 (m, 4H), 8,73 (d, 1H), 8,85 (d, 1H), 9,25 (s, 1H). MS [EI+] m/z 544 (M+H).

Los siguientes Ejemplos 339 a 367 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 338

Ejemplo 339

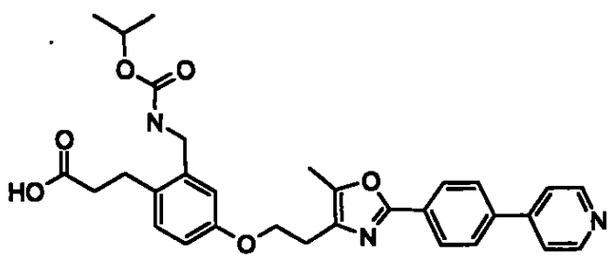
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(4-piridin-3-ilfenil)oxazol-4-il]etoxi} fenil) propiónico



MS (ES) m/z 544 (M+1).

Ejemplo 340

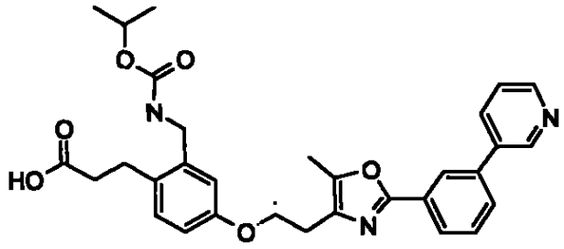
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(4-piridin-4-il-fenil)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 544 (M+1).

Ejemplo 341

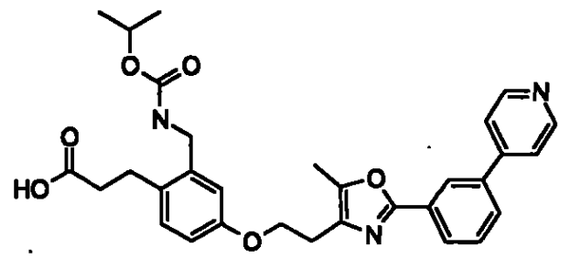
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(3-piridin-3-ilfenil)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 544 (M+1).

Ejemplo 342

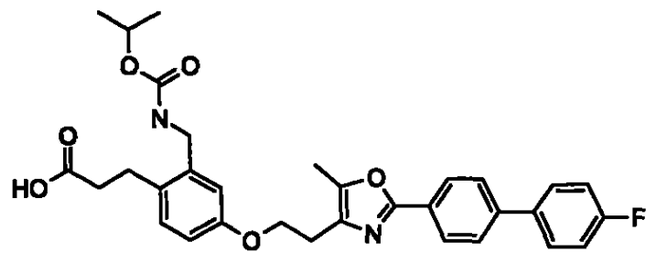
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(3-piridin-4-ilfenil)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 544 (M+1).

Ejemplo 343

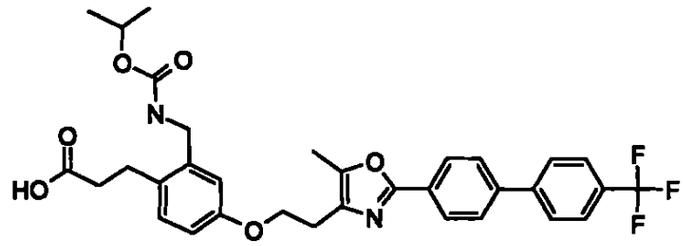
Ácido 3-[4-{2-[2-(4'-fluorobifenil-4-il)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 559 (M+1).

Ejemplo 344

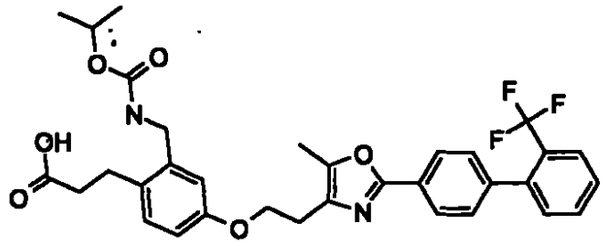
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(4'-trifluorometilbifenil-4-il)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 609 (M+1).

Ejemplo 345

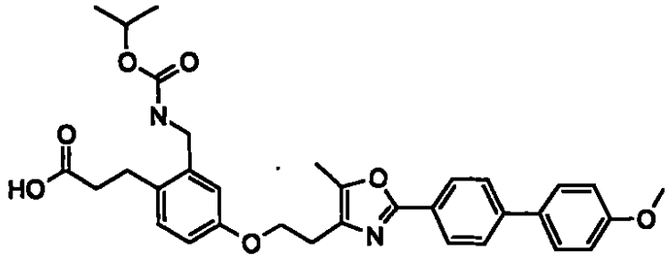
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(2'-trifluorometilbifenil-4-il)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 609 (M+1).

Ejemplo 346

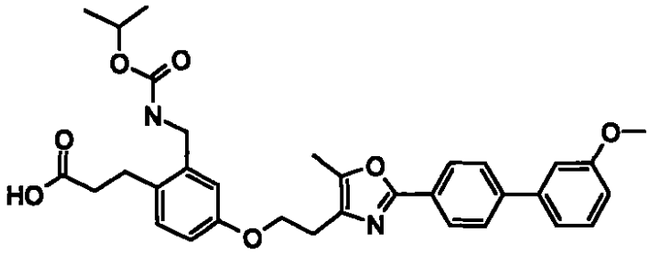
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[2-(4'-metoxibifenil-4-il)-5-metiloxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 571 (M+1).

Ejemplo 347

Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[2-(3'-metoxibifenil-4-il)-5-metiloxazol-4-il]etoxi}fenil) propiónico

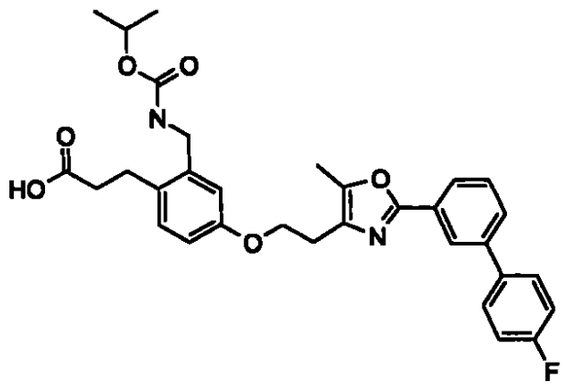


^{1}H-RMN (DMSO-d6) δ 1,16 (d, 6H), 2,39 (s, 3H), 2,45 (t, 2H), 2,76 (t, 2H), 2,95

(t, 2H), 3,85 s, 3H), 4,17 (m, 4H), 4,77 (m, 1H), 6,74-7,55 (m, 7H, 7,83 (d, 2H), 7,99 (d, 2H).

Ejemplo 348

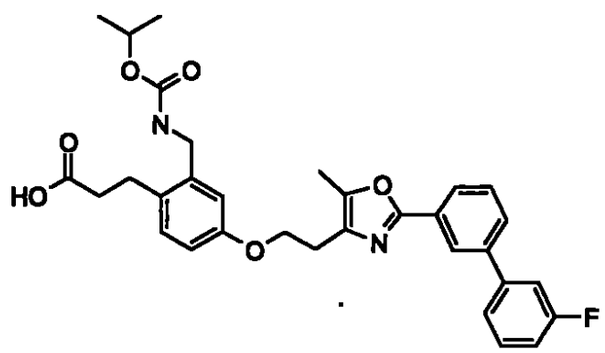
Ácido 3-[4-{2-[2-(4'-fluorobifenil-3-il)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 559 (M+1).

Ejemplo 349

Ácido 3-[4-{2-[2-(3'-fluorobifenil-3-il)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)fenil] propiónico

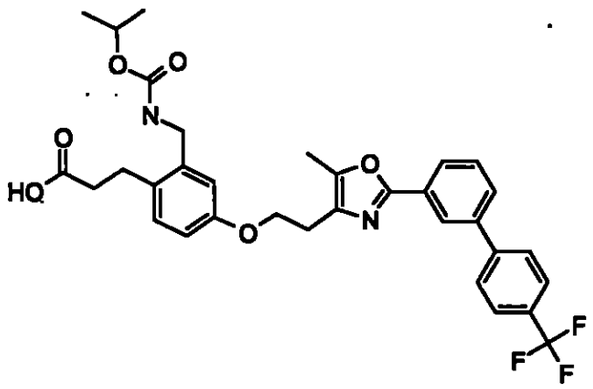


MS (ES) m/z 546 (M+1).

Ejemplo 350

Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(4'-trifluorometilbifenil-

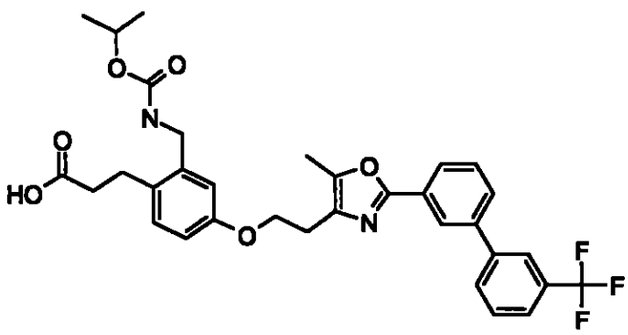
3-il)oxazol-4-il]etoxi}fenil) propiónico



^{1}H-RMN (DMSO-d6) δ 1,15 (d, 6H), 2,40 (s, 3H), 2,45 (t, 2H), 2,79 (t, 2H), 2,96 (t, 2H), 4,17 (m, 4H), 4,75 (m, 1H), 6,77 (m, 2H), 7,08 (d, 1H), 7,53 (m, 1H), 7,66 (m, 1H), 7,83-8,05 (m, 5H), 8,20 (s, 1H).

Ejemplo 351

Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(3'-trifluorometilbifenil-3-il)oxazol-4-il]etoxi}fenil) propiónico

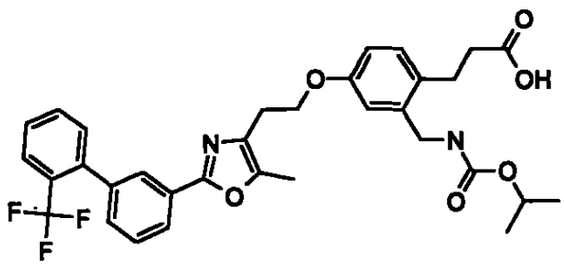


^{1}H-RMN (DMSO-d6) δ 1,14 (d, 6H), 2,40 (s, 3H), 2,45 (t, 2H), 2,67 (t, 2H), 2,95 (t, 2H), 4,16 (m, 4H), 4,74 (m, 1H), 6,77 (m, 2H), 7,09 d, 1H), 7,47-8,20 (m, 8H).

Ejemplo 352

Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(2'-trifluorometilbifenil-

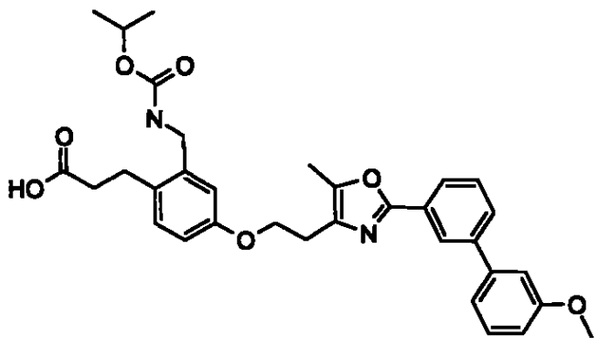
3-il)oxazol-4-il]etoxi}fenil) propiónico



^{1}H-RMN (DMSO-d6) δ 1,13 (d, 6H), 2,36 (s, 3H), 2,44 (t, 2H), 2,77 (t, 2H), 2,93 (t, 2H), 4,15 (m, 4H), 4,74 (m, 1H), 6,76 (m, 2H), 7,06 (d, 1H), 7,40-8,00 (m, 8H).

Ejemplo 353

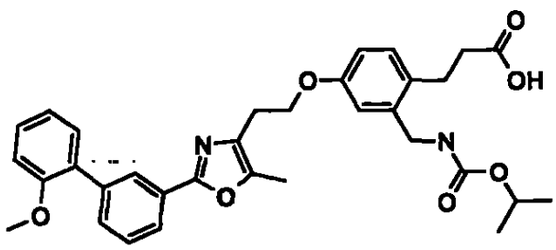
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[2-(3'-metoxibifenil-3-il)-5-metiloxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 573 (M+1).

Ejemplo 354

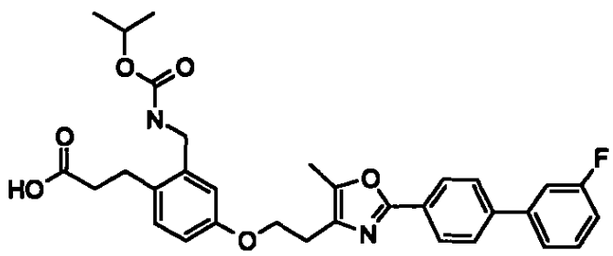
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[2-(2'-metoxibifenil-3-il)-5-metiloxazol-4-il]etoxi}fenil) propiónico



^{1}H-RMN (DMSO-d6) δ 1,13 (d, 6H), 2,40 (s, 2H), 2,45 (t, 2H), 2,78 (t, 2H), 2,93 (t, 2H), 3,80 (s, 3H), 4,16 (m, 4H), 4,75 (m, 1H), 6,76 (m, 2H), 7,07 (m, 2H), 7,16 (d, 1H), 7,32-8,05 (m, 6H).

Ejemplo 355

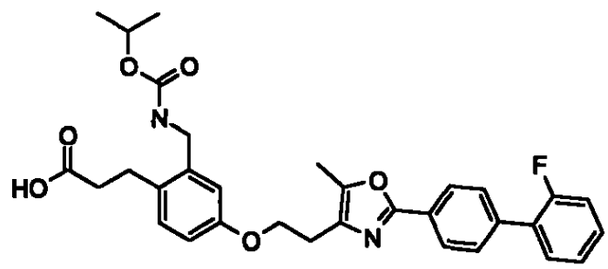
Ácido 3-[4-{2-[2-(3'-fluorobifenil-4-il)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 559 (M+1).

Ejemplo 356

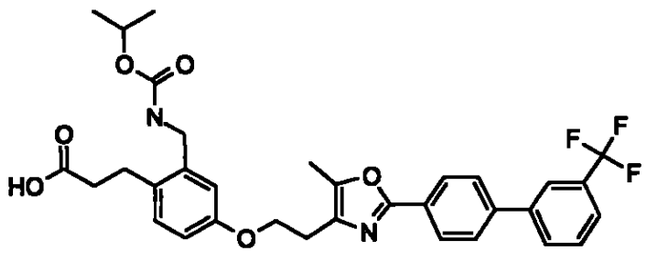
Ácido 3-[4-{2-[2-(2'-fluoro-bifenil-4-il)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilaminometil)-fenil]-propiónico



^{1}H-RMN (CDCl3) δ 1,25 (d, 6H), 2,41 (s, 3H), 2,65 (t, 2H), 2,95 (t, 2H), 3,01 (t, 2H), 4,24 (t, 2H), 4,38 (d a, 2H), 4,96 (m, 1H), 5,03 (s a, 1H), 6,78 (dd, 1H), 6,84 (d, 1H), 7,19-7,55 (m, 6H), 7,65 (dd, 2H), 8,06 dd, 2H).

Ejemplo 357

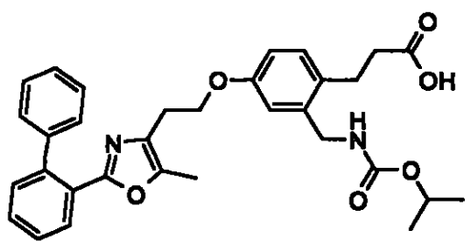
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(3'-trifluorometilbifenil-4-il)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 561 (M+1).

Ejemplo 358

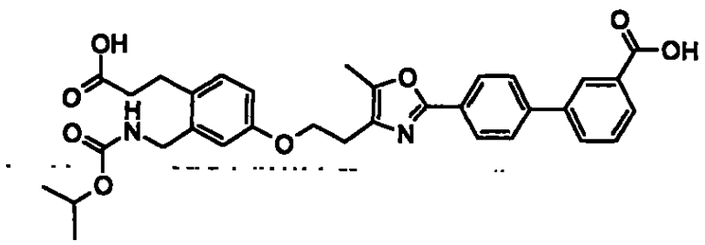
Ácido 3-[4-[2-(2-bifenil-2-il-5-metil-oxazol-4-il)-etoxi]-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 543,2 $(M+1)^+$.

Ejemplo 359

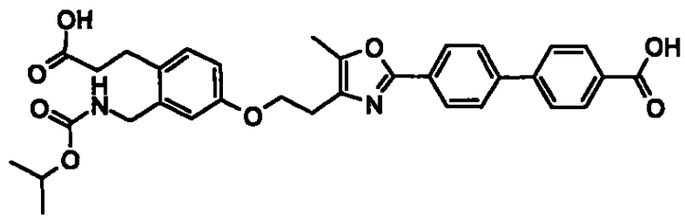
Ácido 4'-(4-{2-[4-(2-carboxi-etil)-3-(isopropoxicarbonilamino-metil)-fenoxi]-etil}-5-metil-oxazol-2-il)-bifenil-3-carboxílico



El compuesto anterior se prepara después de una etapa de hidrólisis adicional usando el Procedimiento Convencional E. MS (ES) m/z 587,3 $(M+1)^+$.

Ejemplo 360

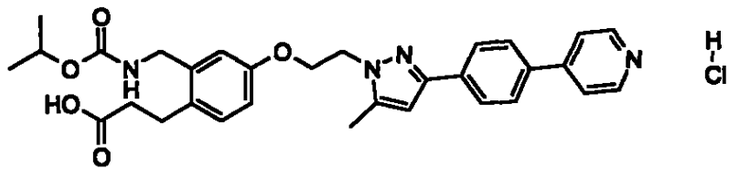
Ácido 4'-(4-{2-[4-(2-carboxi-etil)-3-(isopropoxicarbonilamino-metil)-fenoxi]-etil}-5-metil-oxazol-2-il)-bifenil-4-carboxílico



El compuesto anterior se prepara después de una etapa de hidrólisis adicional usando el Procedimiento Convencional E. MS (ES) m/z 587,2 $(M+1)^+$.

Ejemplo 361

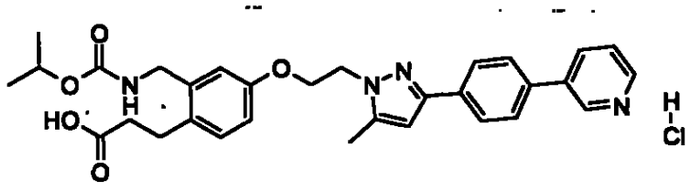
Clorhidrato del ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-3-(4-piridin-4-il-fenil)-pirazol-1-il]-etoxi}-fenil)-propiónico



HRMS Calculado para $C_{31}H_{35}N_4O_5$: m/z 543,2607. Encontrado: 543,2614,

Ejemplo 362

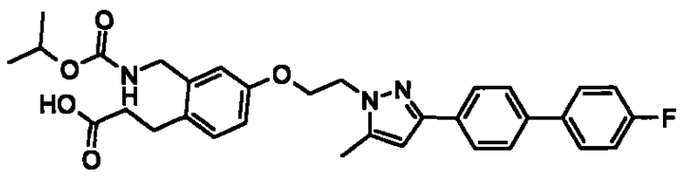
Clorhidrato del *ácido* 3-(2-(isopropoxicarbonilamino-metil)-4-[2-[5-metil-3-(4-piridin-3-il-fenil)-pirazol-1-il]-etoxi}-fenil)-propiónico



HRMS Calculado para $C_{31}H_{35}N_4O_5$: m/z 543,2607. Encontrado: 543,2612,

Ejemplo 363

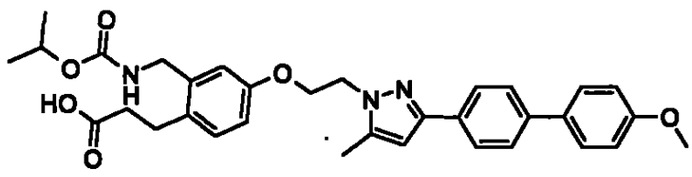
Ácido 3-[4-{2-[3-(4'-fluoro-bifenil-4-il)-5-metil-pirazol-1-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



HRMS Calculado para $C_{28}H_{35}FN_3O_5$: m/z 560,2561. Encontrado: 560,2575,

Ejemplo 364

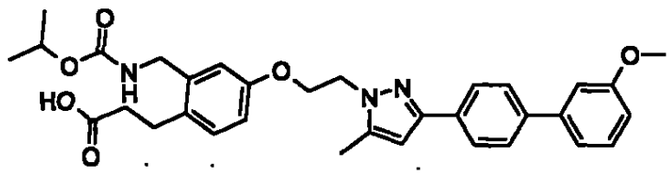
Ácido 3-[4-{2-[3-(4'-metoxi-bifenil-4-il)-5-metil-pirazol-1-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



HRMS Calculado para $C_{33}H_{38}N_3O_6$: m/z 572,2761. Encontrado: 572,2752,

Ejemplo 365

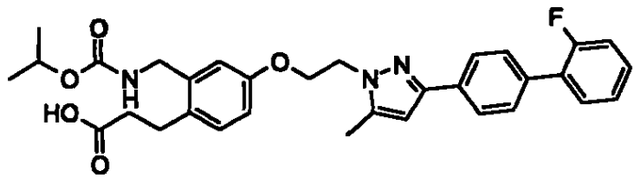
Ácido 3-[4-{2-[3-(3'-metoxi-bifenil-4-il)-5-metil-pirazol-1-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



HRMS Calculado para $C_{33}H_{38}N_3O_6$: m/z 572,2761. Encontrado: 572,2776,

Ejemplo 366

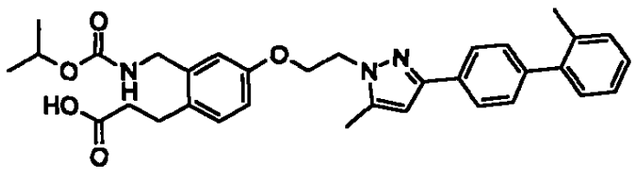
Ácido 3-[4-{2-[3-(2'-fluoro-bifenil-4-il)-5-metil-pirazol-1-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



HRMS Calculado para $C_{32}H_{35}FN_4O_5$: m/z 560,2561. Encontrado: 560,2540,

Ejemplo 367

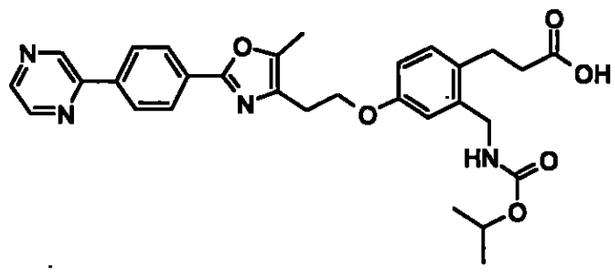
Ácido 3-[4-{2-[3-(2'-metil-bifenil-4-il)-5-metil-pirazol-1-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



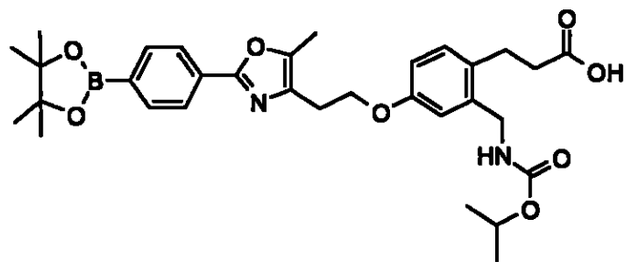
HRMS Calculado para $C_{33}H_{38}N_3O_5$: m/z 556,2811. Encontrado: 556,2802,

Ejemplo 368

Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-pirazin-2-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



Etapa A: Ácido 3-[2-(isopropoxicarbonilamino-metil)-4-(2-{5-metil-2-[4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico



Una solución de éster terc-butílico del ácido 3-[4-[2-[2-(4-bromo-fenil)-5-metil-oxazol-4-il]-etoxi]-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (4,00 g, 6,65 mmol) en DMSO (50 ml) se trató con bis(pinacolato)diborano (2,20 g, 8,64 mmol) y acetato potásico (1,96 g, 19,95 mmol). La solución se roció con nitrógeno durante 10 min, se añadió $Pd(dppf)Cl_2$ (980 mg, 1,20 mmol; 1:1 complejado con CH_2Cl_2), y la mezcla de reacción se calentó a 80 °C durante 4 h. La mezcla se repartió entre agua y acetato de etilo. La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró. La purificación por cromatografía en gel de sílice (9:1 hexanos:acetato de etilo) produjo el compuesto del título en forma de un aceite amarillo (2,81 g). ^1H RMN (300MHz $CDCl_3$) δ 1,25 (d, 6H), 1,26 (s, 9H), 1,37 (s, 12H), 2,40 (s, 3H), 2,51 (t, 2H), 2,88 (t, 2H), 2,98 (t, 2H), 4,26 (t, 2H), 4,35 (d, 2H), 4,97 (m a, 2H), 6,77 (dd, 1H), 6,85 (d, 1H), 7,10 (d, 1H), 7,87 (d, 2H), 7,99 (d, 2H). MS [EI+] 649 (M+H).

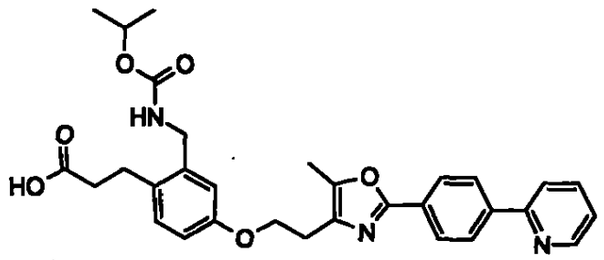
Etapa B: Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-pirazin-2-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico

Acoplamiento de Suzuki Usando Compuestos de Haloarilo: Se añadieron ácido 3-[2-(isopropoxicarbonilamino-metil)-4-(2-{5-metil-2-[4-(4,4,5,5-tetrametil-[1,3,2]-dioxaborolan-2-il)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico (500 g, 0,771 mmol), CsF (258 g, 1,69 mmol), $PdCl_2$(dppf) (0,057 g, 0,07 mmol), y 2-cloropirazina (.0971g, 0,85 mmol) a un matraz de 3 bocas y se disolvió en dioxano anhidro (25 ml). La mezcla de reacción se agitó a 100°C en una atmósfera de N_2 durante aproximadamente 12 h. La mezcla de reacción se diluyó con acetato de etilo (200 ml) y se lavó con NaCl saturado (100 ml) y agua (100 ml). La capa orgánica se filtró a través de Celite, se secó (Na_2SO_4), se filtró, y se concentró. El producto bruto (1,2 g) se purificó por cromatografía radial (10-70% EtOAc/hexanos) para dar el éster intermedio (0,312g): MS (ES) m/z 601 $(M+H)^+$. El éster se disolvió en de HCl 4 M/dioxano (10 ml). La mezcla se agitó en N_2 durante 16 h y se concentró para dar el compuesto del título (305 mg, 72%): MS (ES) m/z 545 $(M+H)^+$. Anal. Calculado para C 66,16%, H 5,92%, N 10,29%. Encontrado C 65,97%, H 6,07%, N 10,45%.

Los siguientes Ejemplos 369 a 382 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 368.

Ejemplo 369

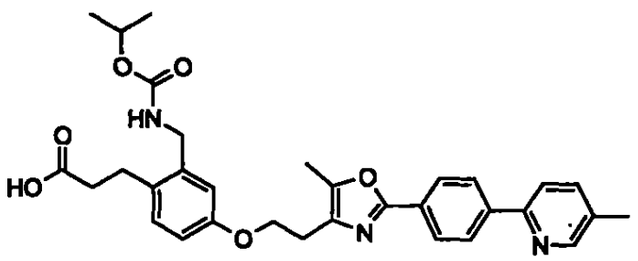
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(4-piridin-2-ilfenil)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 544 (M+1).

Ejemplo 370

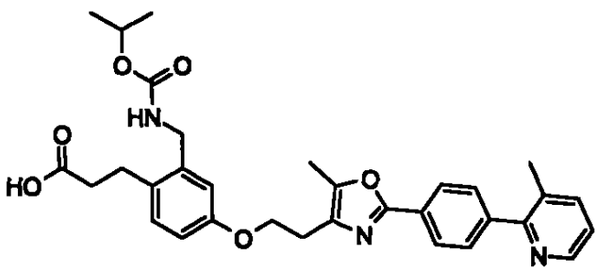
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(5-metilpiridin-2-il)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 558 (M+1).

Ejemplo 371

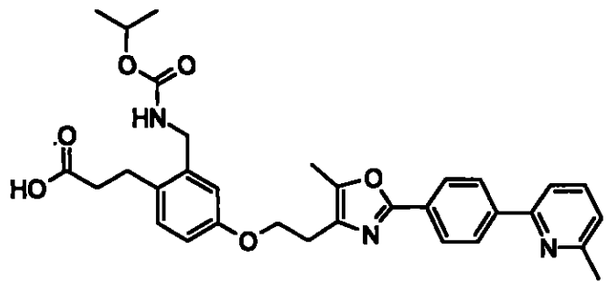
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(3-metilpiridin-2-il)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 558 (M+1).

Ejemplo 372

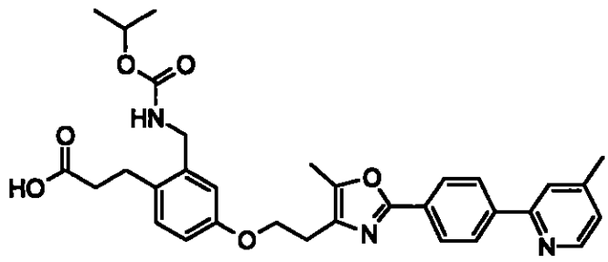
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(6-metilpiridin-2-il)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 492 (M+1).

Ejemplo 373

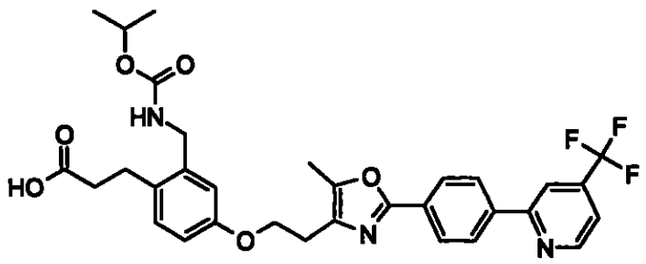
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(4-metilpiridin-2-il)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 558 (M+1).

Ejemplo 374

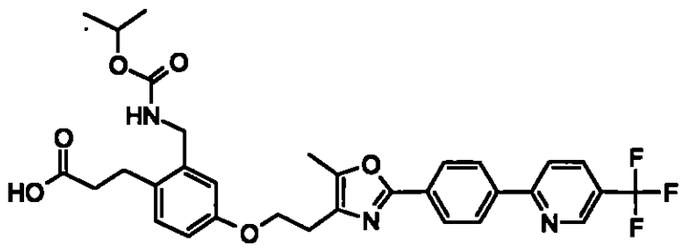
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(4-trifluorometilpiridin-2-il)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 612 (M+1).

Ejemplo 375

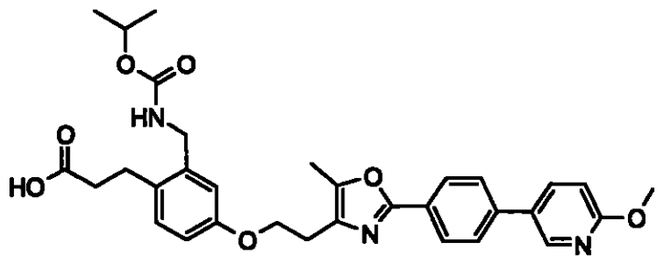
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(5-trifluorometilpiridin-2-il)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 612 (M+1).

Ejemplo 376

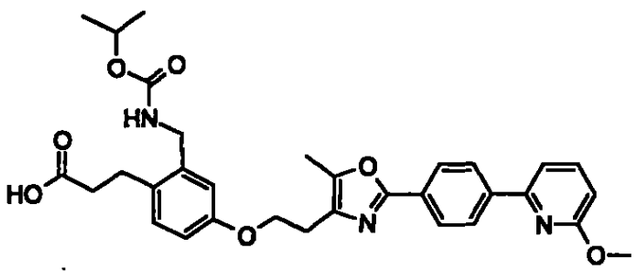
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{2-[4-(6-metoxipiridin-3-il)fenil]-5-metiloxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 574 (M+1).

Ejemplo 377

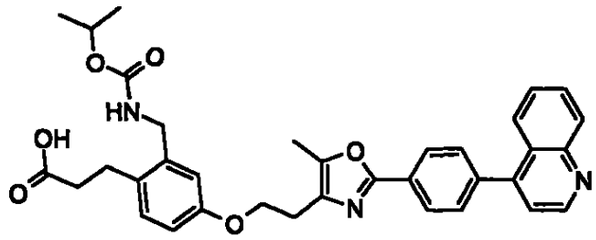
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{2-[4-(6-metoxipiridin-2-il)fenil]-5-metiloxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 574 (M+1).

Ejemplo 378

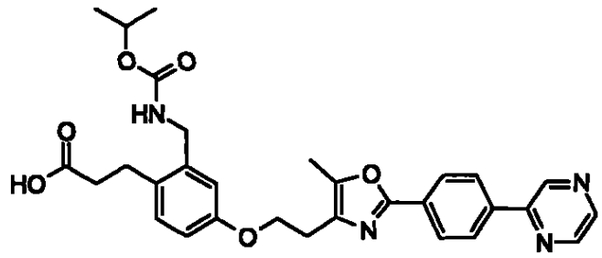
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(4-quinolin-4-ilfenil)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 594 (M+1).

Ejemplo 379

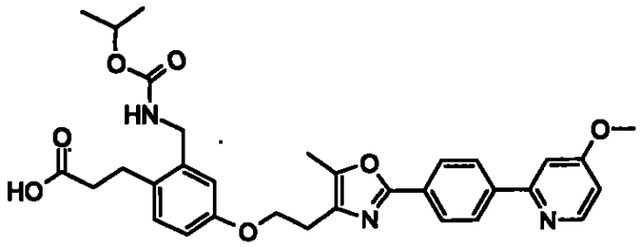
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(4-pirazin-2-ilfenil)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 545 (M+1).

Ejemplo 380

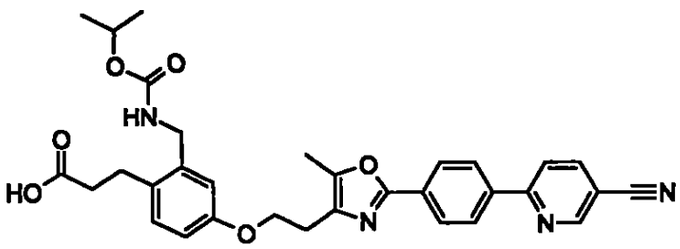
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{2-[4-(4-metoxipiridin-2-il)fenil]-5-metiloxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 574 (M+1).

Ejemplo 381

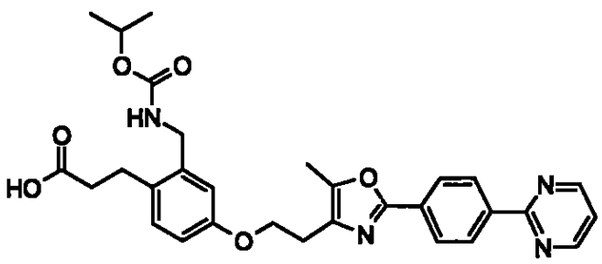
Ácido 3-[4-(2-{2-[4-(5-cianopiridin-2-il)fenil]-5-metiloxazol-4-il}etoxi)-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 569 (M+1).

Ejemplo 382

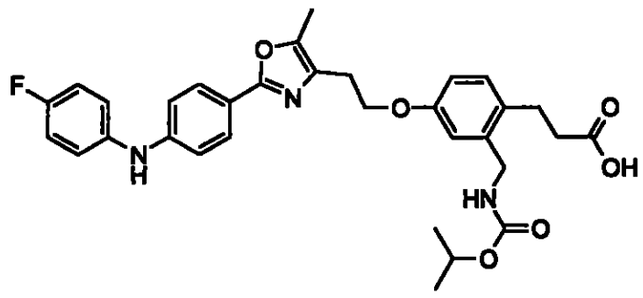
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-pirimidin-2-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico:



MS (ES) m/z 545 $(M+H)^+$. Anal. Calculado para C 66,16%, H 5,92%, N 10,29%. Encontrado C 65,87%, H 6,17%, N 10,53%.

Ejemplo 383

Ácido 3[4-(2-[2-[4-(4-fluoro-fenilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico

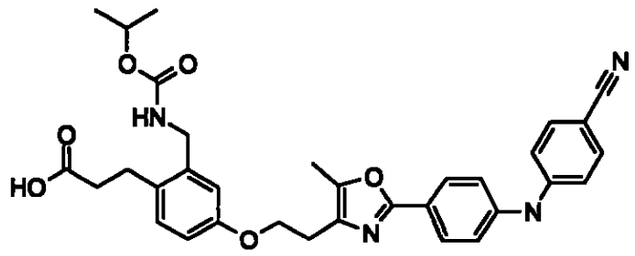


Se disolvió éster terc-butílico del ácido 3-[4-[2-[2-(4-bromo-fenil)-5-metoxi-oxazol-4-il]-etoxi]-2-(isopropoxi-carbonilamino-metil)-propiónico (0,10 g, 0,17 mmol) en DME (5 ml) en un tubo cerrado herméticamente. Se burbujeó N_2 a través de la solución, y se añadieron 4-fluoroanilina (24 mg, 0,20 mmol), 2-(di-t-butilfosfino)-bifenilo (20 mg), $Pd_2(dba)_3$ (10 mg), y K_3PO_4 (50 mg, 0,24 mmol). El tubo se cerró herméticamente y se calentó a 100 °C durante 16 h. La mezcla de reacción se enfrió, se diluyó con EtOAc, y se lavó con agua. La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró. El residuo se purificó usando cromatografía en gel de sílice (hexanos/EtOAc 2/1 a 1/1). Usando el procedimiento de Hidrólisis Convencional C, este material se convirtió en el compuesto del título en forma de un aceite (25 mg): MS (ESI) m/z 594 $(M+H)^+$.

Los siguientes Ejemplos 384 a 387 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 383.

Ejemplo 384

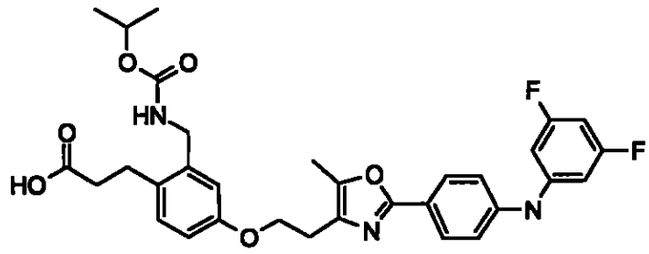
Ácido 3-[4-(2-{2-[4-(4-ciano-fenilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 583 (M+1).

Ejemplo 385

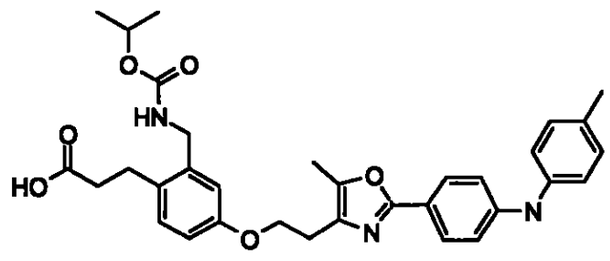
Ácido 3-[4-(2-{2-[4-(3,5-difluoro-fenilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 594 (M+1).

Ejemplo 386

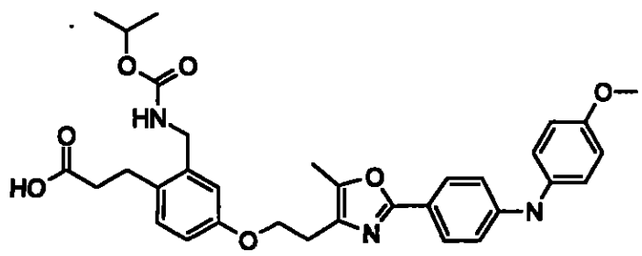
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-p-tolilamino-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ES) m/z 572 (M+1).

Ejemplo 387

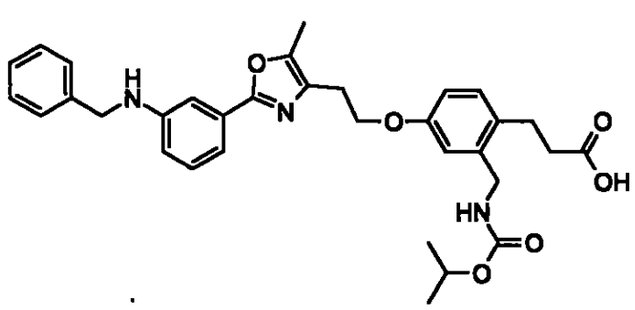
Ácido 3-[2-(isopropoxicarbonilamino-metil)-4-(2-{2-[4-(4-metoxi-fenilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-fenil]-propiónico



MS (ES) m/z 588 (M+1).

Ejemplo 390

Ácido 3[4-(2-{2-[3-bencilamino-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico

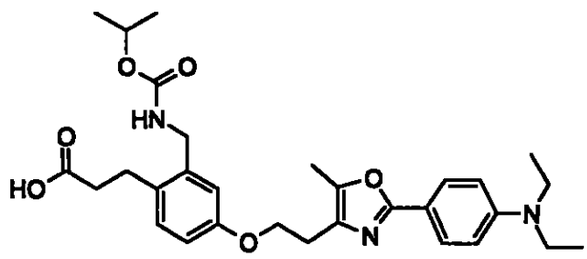


Se disolvió éster terc-butílico del ácido 3-[4-{2-[2-(3-bromo-fenil)-5-metoxi-oxazol-4-il]-etoxi}-2-(isopropoxi-carbonilamino-metil)-propiónico (0,10 g, 0,17 mmol) se disolvió en tolueno (5 ml) en un tubo cerrado herméticamente. Se burbujeó N_2 a través de la solución, y se añadieron bencilamina (46 µL, 0,42 mmol), 2-(diciclohexilfosfino)-bifenilo (12 mg), $Pd_2(dba)_3$ (16 mg) y t-BuONa (23 mg, 0,24 mmol). El tubo se cerró herméticamente y se calentó a 100 °C durante 16 h. La mezcla de reacción se enfrió, se diluyó con EtOAc, y se lavó

con agua. La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró. El residuo se purificó usando cromatografía en gel de sílice (hexanos/EtOAc 2/1 a 1/1). Usando el procedimiento de Hidrólisis Convencional C, este material se convirtió en el correspondiente ácido carboxílico; el compuesto del título se aisló como la sal HCl por tratamiento con 1M HCl en éter (15 mg). MS (ES) m/z 572 $(M+H)^+$.

Ejemplo 391

Ácido 3-[4-{2-[2-(4-dietilamino-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico

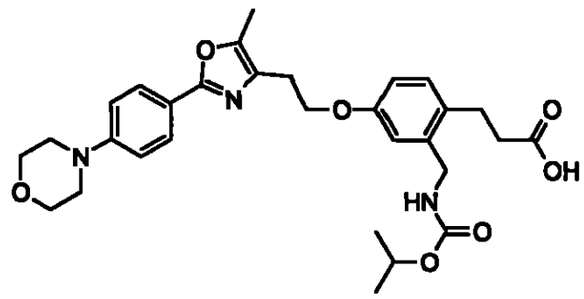


El compuesto anterior se prepara siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 390 con la excepción de que la reacción se realiza en DME a 80°C.

MS (ES) m/z 538,2 $(M+H)^+$.

Ejemplo 392

Ácido 3-(2-(Isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-morfolin-4-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico

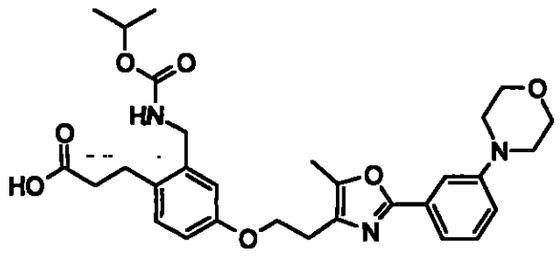


Una solución de éster terc-butílico del ácido 3-[4-{2-[2-(4-bromo-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (60 mg, 0,100 mmol) en tolueno (3,0 ml) en un tubo cerrado herméticamente en una atmósfera de N_2 se trató con $Pd(OAc)_2$ (5 mg), 2-(di-t-butilfosfino)bifenilo (10 mg), morfolina (17 mg, 0,20 mmol), y t-butóxido sódico (19 mg, 0,200 mmol). El tubo se cerró herméticamente y se calentó a 105 °C durante 14 h. La mezcla se enfrió y se purificó directamente usando cromatografía en gel de sílice (30-50% EtOAc/hexanos) para producir el éster intermedio. Una solución de éster en TFA (1,0 ml)/CH_2Cl_2 (1,5 ml)/H_2O (0,1 ml) se agitó durante 14 h y se concentró. El residuo se purificó usando cromatografía en gel de sílice (hexanos/EtOAc/HOAc, 5/5/0,02) para producir el compuesto del título (36 mg, 65%): MS (ESI) m/z 552,3 $(M+H)^+$.

Los siguientes Ejemplos 393 a 395 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 392.

Ejemplo 393

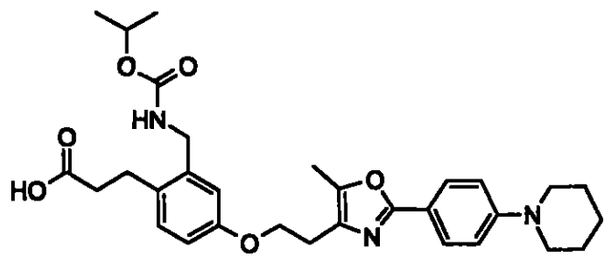
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(3-morfolin-4-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ESI) m/z 552,2 $(M+H)^+$.

Ejemplo 394

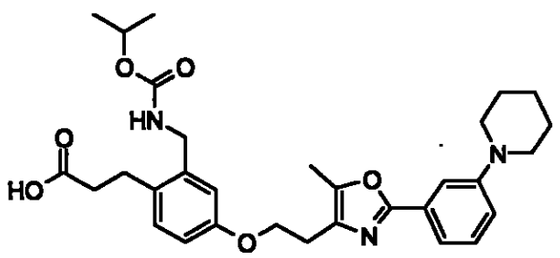
Ácido 3-(2-(Isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-piperidin-1-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ESI) m/z 550,3 $(M+H)^+$.

Ejemplo 395

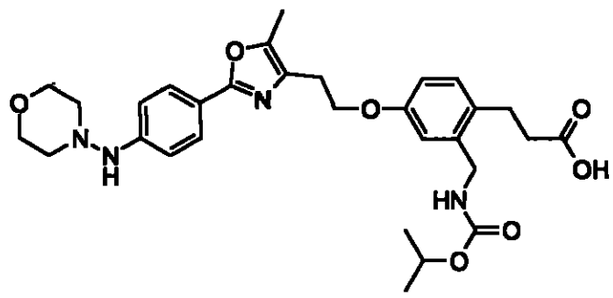
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(3-piperidin-1-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ESI) m/z 550,3 $(M+H)^+$.

Ejemplo 396

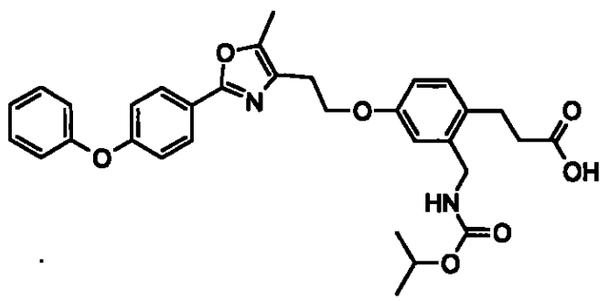
Ácido 3-[2-(Isopropoxicarbonilamino-metil)-4-(2-{5-metil-2-[4-(morfolin-4-ilamino)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico



Una solución de éster terc-butílico del ácido 3-[4-{2-[2-(4-bromo-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (120 mg, 0,200 mmol) en tolueno (2,0 ml) en un tubo cerrado herméticamente en una atmósfera de N_2 se trató con $Pd_2(dba)_3$ (10 mg), 2-(di-t-butilfosfino)bifenilo (10 mg), N-aminomorfolina (29 mg, 0,28 mmol), y t-butóxido sódico (38 mg, 0,40 mmol). El tubo se cerró herméticamente y se calentó a 100 °C durante 60 min. La mezcla se enfrió y se purificó usando cromatografía en gel de sílice (5-MeOH al 10%/EtOAc) para producir directamente el compuesto del título (22 mg, 21%): MS (ESI) m/z 567,3 $(M+H)^+$.

Ejemplo 397

Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-fenoxi-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



Una mezcla de éster terc-butílico del ácido 3-[4-[2-[2-(4-bromo-fenil)-5-metil-oxazol-4-il]-etoxi]-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (0,44 mmol, 0,24 g), fenol (0,53 mmol, 0,050 g), K_3PO_4 (0,88 mmol, 0,19g), 2-(di-t-butilfosfino)bifenilo (0,066 mmol, 0,020g), y $Pd(OAc)_2$ (0,044 mmol, 0,010g) en tolueno (7 ml) se desgasificó al vacío y se cargó de nuevo con nitrógeno (3 x) y se calentó a 110 °C durante 18 h. Se añadieron más $Pd(OAc)_2$ (10 mg) y 2-(di-t-butilfosfino)bifenilo (20 mg) para asegurar la completa reacción y la mezcla se calentó durante 5 h. Después de la refrigeración, la mezcla se puso directamente en una columna de gel de sílice y se eluyó con 30%-50% EtOAc/hexanos para dar éster terc-butílico del ácido 3-(2-(isopropoxicarbonilamino-metil)-4-[2-[5-metil-2-(4-fenoxi-fenil)-oxazol-4-il]-etoxi]-fenil)-propiónico (0,11 g).

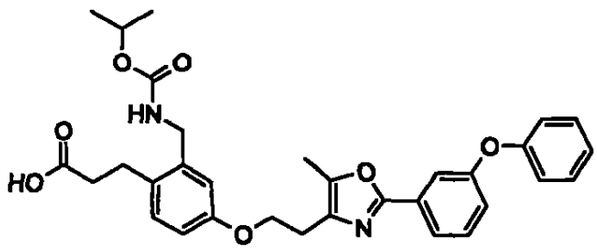
Se disolvió el éster terc-butílico (0,18 mmol, 0,11g) en CH_2Cl_2 (3 ml), y se añadió TFA al 90%/agua (5 ml). La mezcla se agitó durante 3 h y se concentró. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo al 50%/hexanos) para dar un aceite. La trituración con Et_2O dio el compuesto del título en forma de un sólido blanco (90 mg, 90%): ^1H RMN (250 MHz, $CDCl_3$) δ 8,11 (d, 2H, J = 8,8 Hz), 7,56 (t, 2H, J = 7,9 Hz), 7,37-7,20 (m, 6H), 7,0-6,93 (m, 2H), 5,11 (heptuplete, 1H, J = 6,3 Hz), 4,53 (d, 2H, J = 5,1Hz),

4,38 (t, 2H, J = 6,7 Hz), 3,12 (q, 4H, J = 7,3 Hz), 2,80 (t, 2H, J = 7,6 Hz), 2,54 (s, 3H), 1,41 (d, 6H, J = 6,3 Hz).

Los siguientes Ejemplos 398 a 405 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplos 396 y 397.

Ejemplo 398

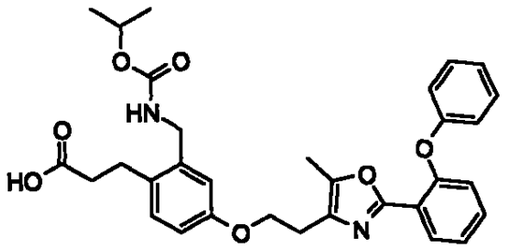
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(3-fenoxi-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ESI) m/z 559,2 $(M+H)^+$.

Ejemplo 399

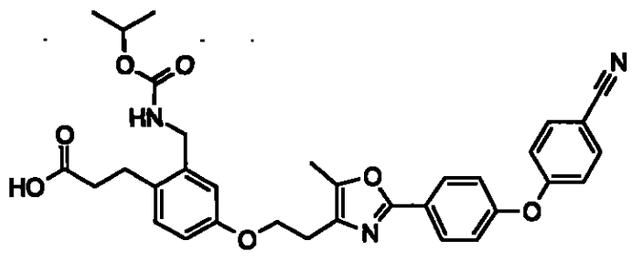
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(2-fenoxi-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ESI) 559 $(M+H)^+$. Anal Calculado para $C_{32}H_{34}N_2O_7$: C, 68,8; H, 6,1; N, 5,0. Encontrado: C, 67,9; H, 6,2; N, 5,3.

Ejemplo 400

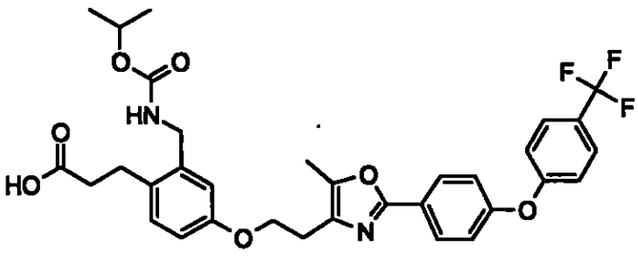
Ácido 3-[4-(2-{2-[4-(4-ciano-fenoxi)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 584.

Ejemplo 401

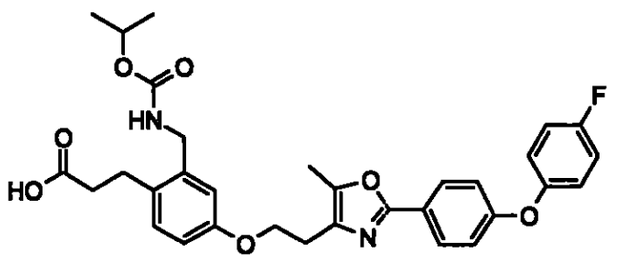
Ácido 3-[2-(Isopropoxicarbonilamino-metil)-4-(2-{5-metil-2-[4-(4-trifluorometil-fenoxi)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico



MS (ES) m/z 627 (M+1).

Ejemplo 402

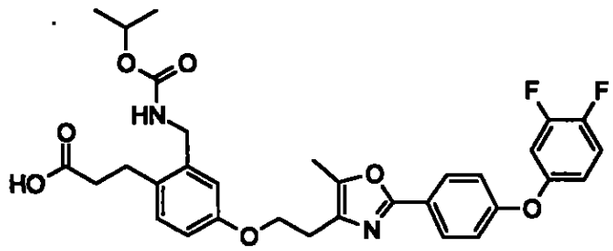
Ácido 3-[4-(2-{2-[4-(4-fluoro-fenoxi)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 577 (M+1).

Ejemplo 403

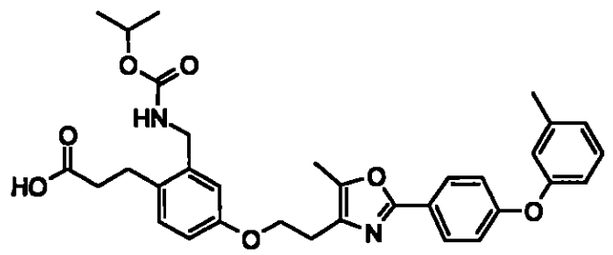
Ácido 3-[4-(2-{2-[4-(3,4-difluoro-fenoxi)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 595 (M+1).

Ejemplo 404

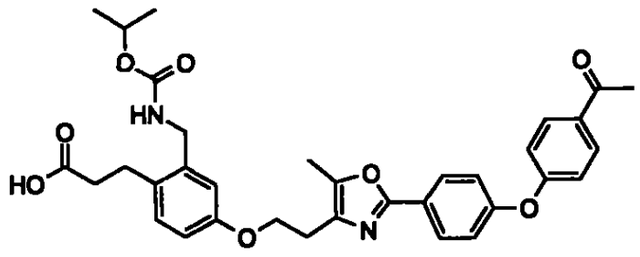
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-m-toliloxi-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ES) m/z 573 (M+1).

Ejemplo 405

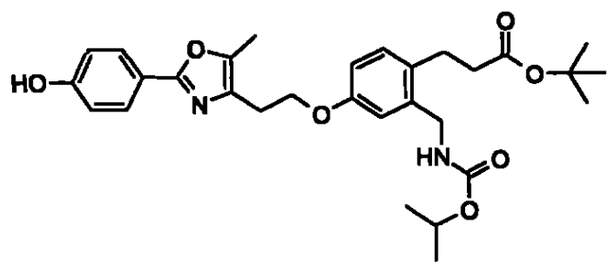
Ácido 3-[4-(2-{2-[4-(4-acetil-fenoxi)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 601 (M+1).

Ejemplo 406

Éster terc-butílico del ácido 3-[4-{2-[2-(4-Hidroxi-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico

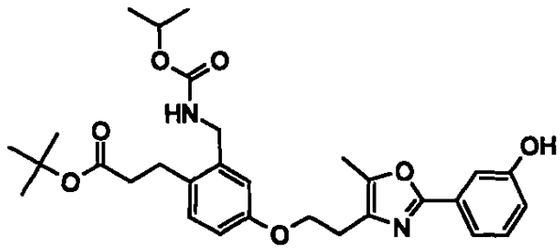


De acuerdo con el procedimiento de *Organic Synthesis*, vol. V, p. 918, una solución de éster terc-butílico del ácido 3-[2-(isopropoxicarbonilamino-metil)-4-(2-{5-metil-2-[4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico (1,4 g, 2,16 mmol, Ejemplo 368, Etapa A) en THF (8 ml) se trató con ácido acético glacial (194 mg, 3,24 mmol) a 0°C. Una solución de H_2O_2 al 30% en agua (4,75 ml) se diluyó con H_2O (1 ml) y se añadió a la mezcla de reacción. La mezcla se calentó a temperatura ambiente y se trató con una solución acuosa 1 M de $Na_2S_2O_3$ (50 ml). El THF se retiró al vacío y la fase acuosa se extrajo con acetato de etilo. La capa orgánica se lavó con $Na_2S_2O_3$ 1 M (2 x 50ml), se secó ($MgSO_4$), se filtró, y se concentró hasta un aceite (1,21 g). La purificación usando cromatografía en gel de sílice (1:1

acetato) produjo el compuesto del título en forma de un sólido blanco (1,10 g, 95%). ^{1}H RMN (300MHz $CDCl_3$) δ 1,15 (d, 6H), 1,19 (s, 9H), 2,26 (s, 3H), 2,39 (t, 2H), 2,75 (t, 2H), 2,85 (t, 2H), 4,10 (t, 2H), 4,28 (d, 2H), 4,85 (m, 1H), 5,01 (d a, 1H), 6,63 (dd, 1H), 6,74 (m, 3H), 6,96 (d, 1h), 7,70 (d, 2H); MS [EI+] m/z 539 (M+H).

Ejemplo 407

Éster terc-butílico del ácido 3-[4-{2-[2-(3-hidroxi-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico:

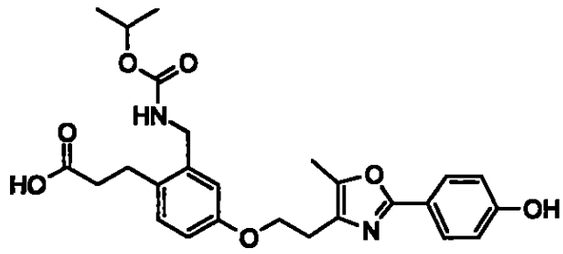


El compuesto anterior se prepara siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 406, MS [EI+] m/z 539 (M+H).

Los siguientes Ejemplos 408 a 409 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 406 y los correspondientes ácidos carboxílicos se obtuvieron mediante el procedimiento de Hidrólisis Convencional C:

Ejemplo 408

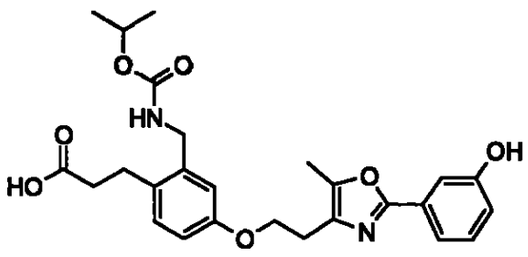
Ácido 3-[4-{2-[2-(4-hidroxifenil)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 483 (M+1).

Ejemplo 409

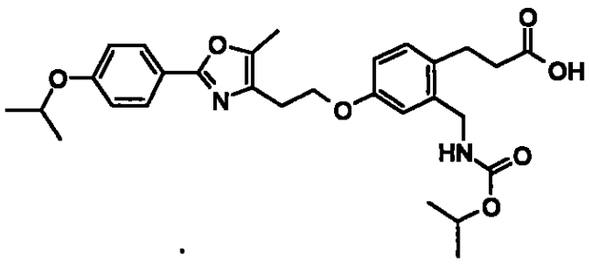
Ácido 3-[4-{2-[2-(3-hidroxifenil)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)fenil] propiónico:



MS (ES) m/z 483 (M+1).

Ejemplo 410

Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[2-(4-isopropoxi-fenil)-5-metil-oxazol-4-il]-etoxi}-fenil)-propiónico



Una solución de éster terc-butílico del ácido 3-[4-{2-[2-(4-hidroxi-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (300

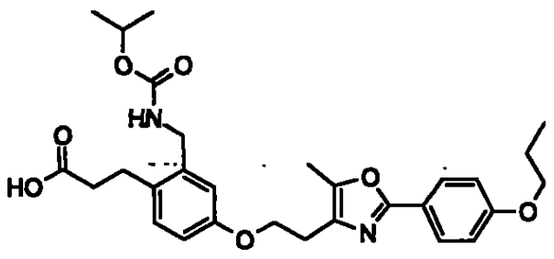
mg, 0,557 mmol, Ejemplo 406) en etanol (20 ml) se trató con 2-yodopropano (473 mg, 2,78mmol) y K_2CO_3 (231 mg, 1,67 mmol) y se calentó a reflujo durante una noche. La mezcla de reacción se enfrió y se concentró. El residuo se diluyó con H_2O y acetato de etilo. Las capas se separaron, y la capa acuosa se extrajo con acetato de etilo (2 x). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, y se concentraron para producir un aceite. La purificación usando cromatografía en gel de sílice (3:1 de hexano:acetato de etilo) produjo éster terc-butílico del ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[2-(4-isopropoxi-fenil)-5-metil-oxazol-4-il]-etoxi}-fenil)-propiónico en forma de un aceite amarillo (210 mg). ^{1}H RMN (300MHz $CDCl_3$) δ 1,28 (d, 6H), 1,40 (d, 6H), 1,45 (s, 9H), 2,38 (s, 3H), 2,53 (t, 2H), 2,91 (t, 2H), 2,99 (t, 2H), 4,25 (t, 2H), 4,39 (d, 2H), 4,66 (m, 1H), 5,00 (m a, 2H), 6,80 (dd, 1H), 6,87 (d, 1H), 6,95 (d, 2H), 7,13 (d, 1H), 7,95 (d, 2H) MS [ES] 581 (M+H).

Este éster se convirtió en el compuesto del título de acuerdo con Procedimiento Convencional C; un sólido blanco (134 mg). ^{1}H RMN (300MHz $CDCl_3$) δ 1,15 (d, 6H), 1,29 (d, 6H), 2,31 (s, 3H), 2,53 (t, 2H), 2,82 (t, 2H), 2,97 (t, 2H), 4,15 (t, 2H), 4,26 (d, 2H), 4,55 (m, 1H), 4,84 (m, 1H), 4,99 (s a, 1H), 6,68 (dd, 1H), 6,73 (d, 1H), 6,87 (d, 2H), 7,00 (d, 1H), 7,90 (d, 2H) MS [ES] m/z 525 (M+H).

Los siguientes Ejemplos 411 a 422 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 410.

Ejemplo 411

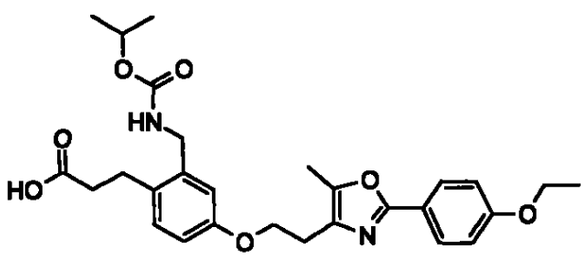
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(4-propoxifenil)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 525 (M+1).

Ejemplo 412

Ácido 3-[4-[2-[2-(4-etoxifenil)-5-metiloxazol-4-il]etoxi]-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 511 (M+1).

Ejemplo 413

Ácido 3-(2-(isopropoxicarbonilaminometil)-4-[2-[2-(4-metoxifenil)-5-metoxazol-4-il]etoxi]fenil) propiónico

MS (ES) m/z 497 (M+1).

Ejemplo 414

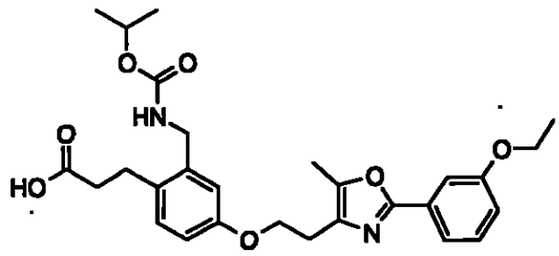
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-[2-[2-(3-metoxifenil)-5-metoxazol-4-il]etoxi]fenil) propiónico

MS (ES) m/z 497 (M+1)

Ejemplo 415

Ácido 3-[4-[2-[2-(3-etoxifenil)-5-metiloxazol-4-il]-etoxi]-2-

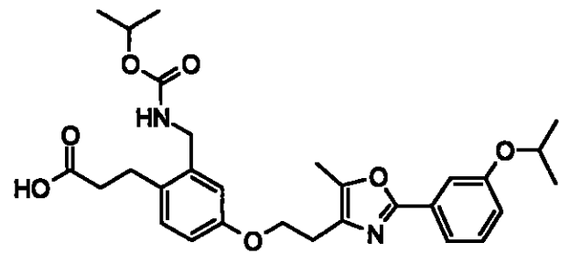
(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 511 (M+1).

Ejemplo 416

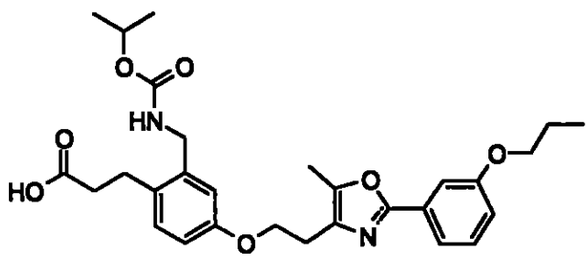
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[2-(3-isopropoxifenil)-5-metiloxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 525 (M+1).

Ejemplo 417

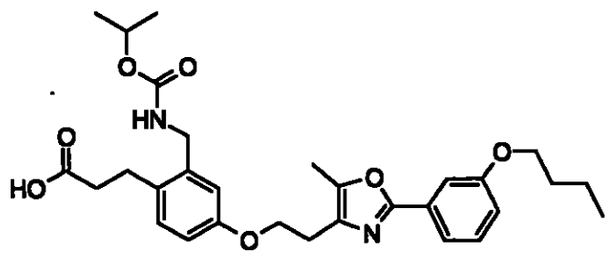
Ácido 3-(2-(isopropoxicarbonilaminometil)-4-{2-[5-metil-2-(3-propoxifenil)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 525 (M+1).

Ejemplo 418

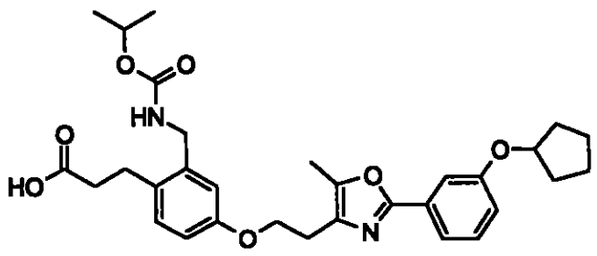
Ácido 3-[4-{2-[2-(3-butoxifenil)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 539 (M+1).

Ejemplo 419

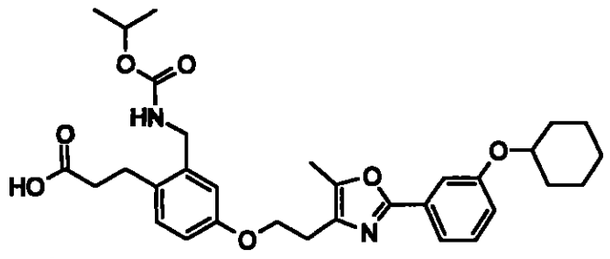
Ácido 3-[4-{2-[2-(3-ciclopentiloxifenil)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 551 (M+1).

Ejemplo 420

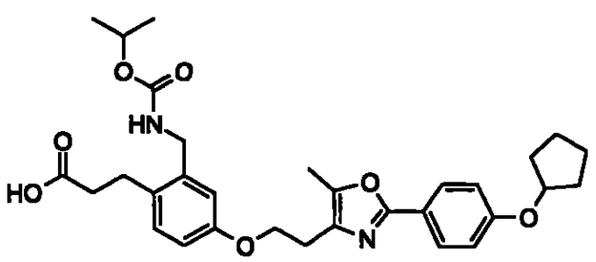
Ácido 3-[4-{2-[2-(3-ciclohexiloxifenil)-5-metiloxazol-4-il] etoxi}-2-(isopropoxicarbonilaminometil)-fenil] propiónico



MS (ES) m/z 565 (M+1).

Ejemplo 421

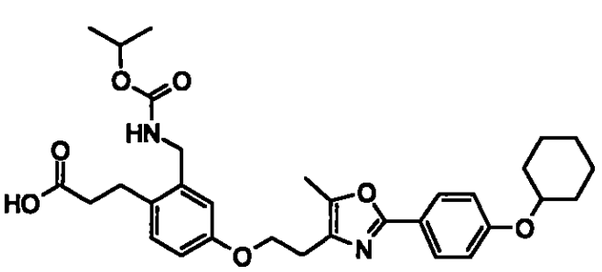
Ácido 3-[4-{2-[2-(4-ciclopentiloxifenil)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 551 (M+1).

Ejemplo 422

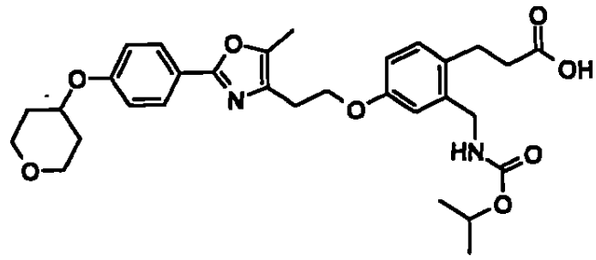
Ácido 3-[4-{2-[2-(4-ciclohexiloxifenil)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 565 (M+1).

Ejemplo 423

Ácido 3-[2-(isopropoxicarbonilamino-metil)-4-(2-{5-metil-2-[4-(tetrahidro-piran-4-iloxi)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico

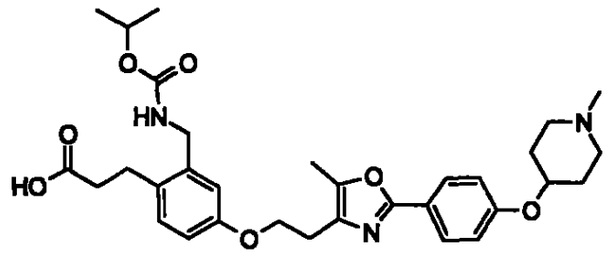


Una mezcla de éster terc-butílico del ácido 3-[4-{2-[2-(4-hidroxi-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (120 mg, 0,223 mmol, Ejemplo 406), tetrahidro-piran-4-ol (22,7 mg, 0,223 mmol), trifenilfosfina (58,4 mg, 0,223 mmol) y tolueno (10 ml) se trató gota a gota con DIAD (45 mg, 0,223 mmol). La mezcla se agitó en una atmósfera de N_2 a temperatura ambiente durante 16 h y se concentró. El producto bruto se purificó por cromatografía radial (EtOAc al 10-70%/hexanos) para dar éster terc-butílico del ácido 3-[2-(isopropoxicarbonilamino-metil)-4-(2-{5-metil-2-[4-(tetrahidro-piran-4-iloxi)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico. El producto de éster se disolvió HCl 4 M/dioxano (5 ml), se agitó durante 16 h y se concentró para dar el compuesto del título: MS [ES] m/z 525 (M+H).

Los siguientes Ejemplos 424 a 431 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 423.

Ejemplo 424

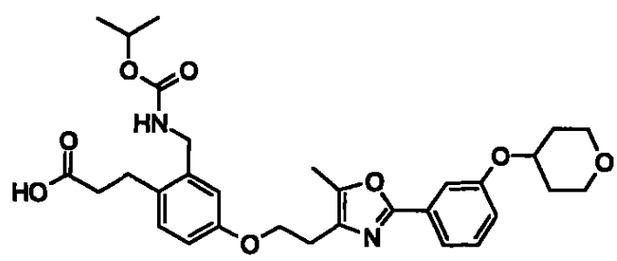
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(1-metilpiperidin-4-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 580 (M+1).

Ejemplo 425

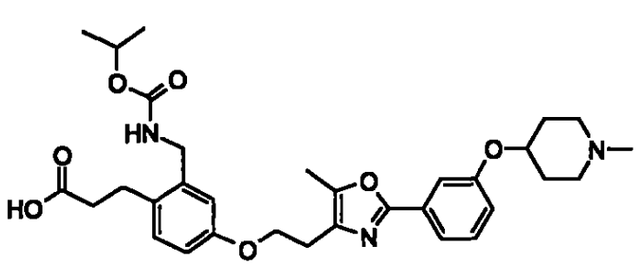
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[3-(tetrahidropiran-4-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 567 (M+1).

Ejemplo 426

Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[3-(1-metilpiperidin-4-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico

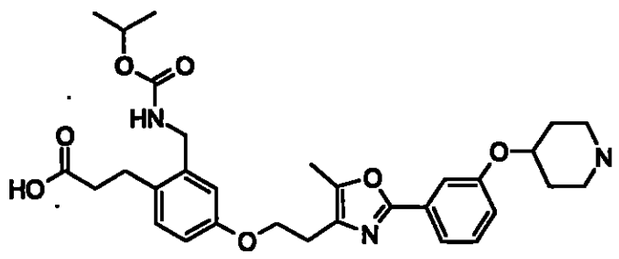


MS (ES) m/z 580 (M+1).

Ejemplo 427

Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[3-(piperidin-4-

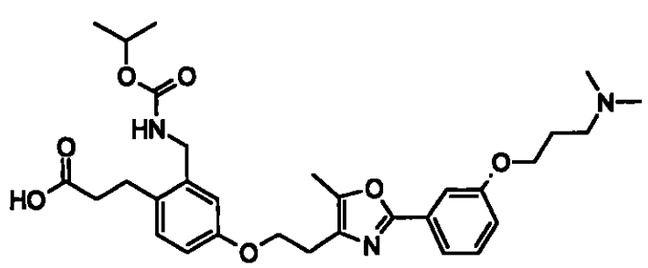
iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 566 (M+1).

Ejemplo 428

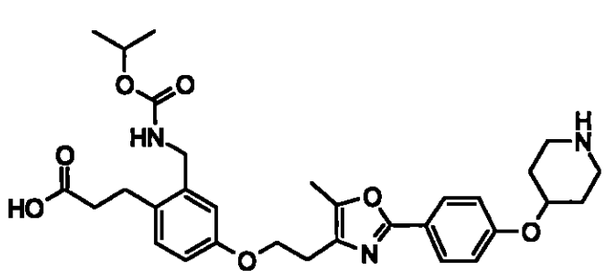
Ácido 3-[4-(2-{2-[3-(3-dimetilaminopropoxi)fenil]-5-metiloxazol-4-il}etoxi)-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 568 (M+1).

Ejemplo 429

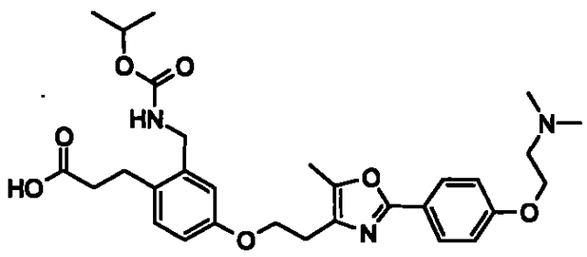
Ácido 3-[2-(Isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(piperidin-4-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 566 (M+1).

Ejemplo 430

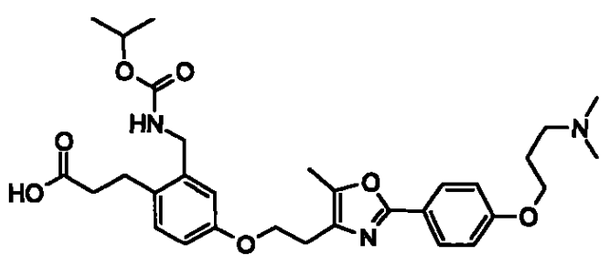
Ácido 3-[4-(2-{2-[4-(2-dimetilaminoetoxi)fenil]-5-metiloxazol-4-il}etoxi)-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 554 (M+1).

Ejemplo 431

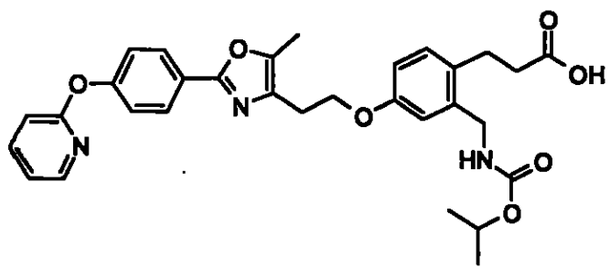
Ácido 3-[4-(2-{2-[4-(3-dimetilaminopropoxi)fenil]-5-metiloxazol-4-il}etoxi)-2-(isopropoxicarbonilaminometil)fenil] propiónico



MS (ES) m/z 568 (M+1).

Ejemplo 432

Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(piridin-2-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico

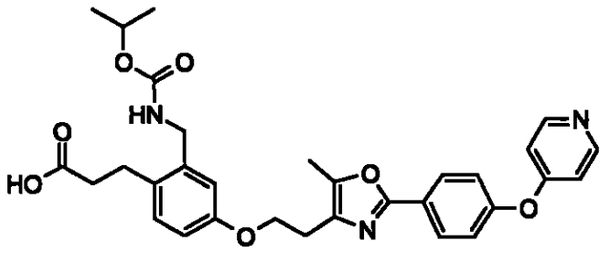


Se hizo reaccionar éster terc-butílico del ácido 3-[4-{2-[2-(4-hidroxi-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxi-carbonilamino-metil)-fenil]-propiónico (Ejemplo 406) con 2-bromopiridina por el procedimiento del Ejemplo 397 para dar el compuesto del título. MS (ES) m/z 560 (M+1).

Los siguientes Ejemplos 433 a 435 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 432.

Ejemplo 433

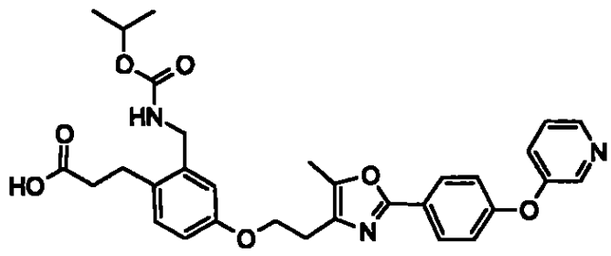
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(piridin-4-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 560 (M+1).

Ejemplo 434

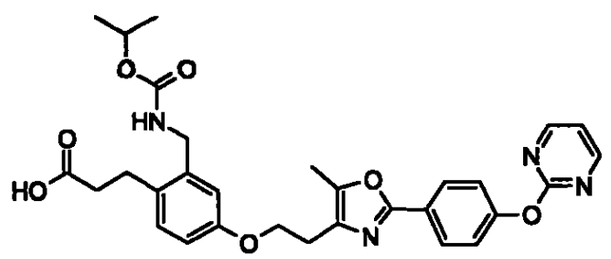
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(piridin-3-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico



MS (ES) m/z 560 (M+1).

Ejemplo 435

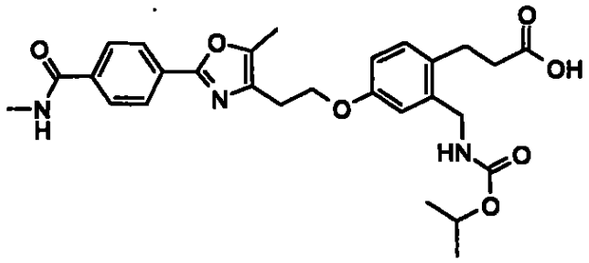
Ácido 3-[2-(isopropoxicarbonilaminometil)-4-(2-{5-metil-2-[4-(pirimidin-2-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico



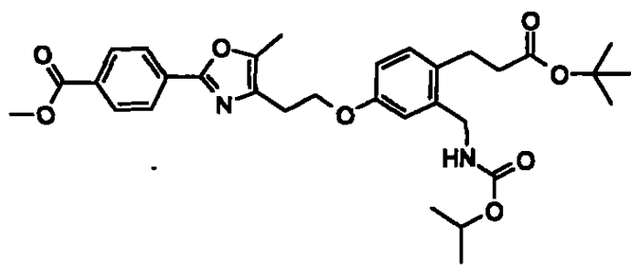
MS (ES) m/z 561 (M+1).

Ejemplo 436

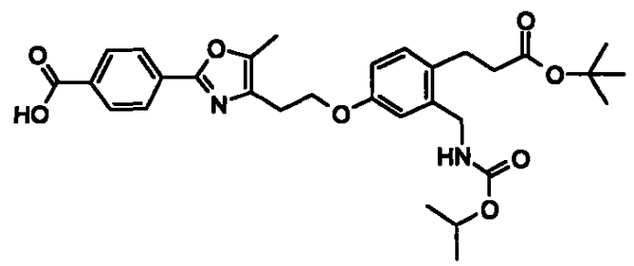
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-carbamoil-fenil)-oxazol-4il]-etoxi}-fenil)-propiónico



Etapa A: Éster metílico del ácido 4-(4-{2-[4-(2-terc-butoxicarbonil-etil)-3-(isopropoxicarbonilamino-metil)-fenoxi]-etil}-5-metil-oxazol-2-il)-benzoico



Una mezcla de éster terc-butílico del ácido 3-[4-{2-[2-(4-bromo-fenil)-5-metoxi-oxazol-4-il]-etoxi}-2-(isopropoxi-carbonilamino-metil-fenil)-propiónico (0,25 g, 0,42 mmol), cloruro de 1,1'-bis(difenilfosfino)-ferroceno paladio (II) (50 mg), MeOH (0,1 ml) y trietilamina (0,12 ml, 0,66 mmol) en acetonitrilo (2 ml) se agitó y se calentó a 70°C en una atmósfera de gas CO (globo) durante 16 h. La mezcla de reacción se enfrió y se concentró. El residuo se purificó por cromatografía en gel de sílice (hexanos/EtOAc, 5/1 a 1/1) para producir el compuesto del título en forma de un sólido blanco (0,12 g, 50%): MS (ESI) m/z 581 $(M+H)^+$.



Una solución de éster metílico del ácido 4-(4-{2-[4-(2-terc-Butoxicarbonil-etil)-3-(isopropoxicarbonil-amino-metil)-fenoxi]-etil}-5-metil-oxazol-2-il)-benzoico (100 mg, 0,17 mmol) en metanol (2 ml) se trató con LiOH acuoso 1,5 N (1,0 ml) y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se acidificó con HCl 1 N y se extrajo con CH_2Cl_2. La capa orgánica se secó ($MgSO_4$), se concentró, y se purificó por cromatografía en gel de sílice

(hexanos/EtOAc, 1/1 a 0/1) para producir el compuesto del título (55 mg, 57%). MS (ESI) m/z 567 $(M+H)^+$.

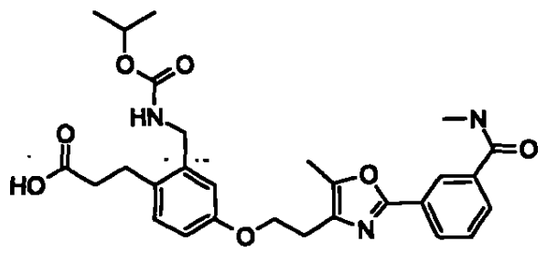
Etapa C: Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-carbamoil-fenil)-oxazol-4il]-etoxi}-fenil)-propiónico

Una solución de ácido 4-(4-{2-[4-(2-terc-butoxicarbonil-etil)-3-(isopropoxicarbonil-amino-metil)-fenoxi]-etil}-5-metil-oxazol-2-il)-benzoico (40 mg, 0,07 mmol) en CH_2Cl_2 (2 ml) se trató con cloruro de oxalilo (1,0 □L, 0,12 mmol) y una gota de DMF. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, se concentró, y se co-evaporó con tolueno. El residuo se disolvió en CH_2Cl_2 (2 ml) y se añadió a un matraz cargado con metilamina 2,0 M en THF (2M, 0,04 ml) y trietilamina (20 µL, 0,12 mmol). La mezcla se agitó a temperatura ambiente durante 16 h, se diluyó con CH_2Cl_2 (10 ml), y se lavó con H_2O. La capa orgánica se secó ($MgSO_4$), se concentró, y se purificó por cromatografía en gel de sílice (hexanos/EtOAc, 3:1 a 0:1) para producir éster *terc*-butílico intermedio. El éster se convirtió en el ácido por el Procedimiento Convencional C; la purificación por HPLC dirigida de masas produjo el compuesto del título. MS (ESI) m/z 524 $(M+H)^+$.

Los siguientes Ejemplos 437 a 448 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 436.

Ejemplo 437

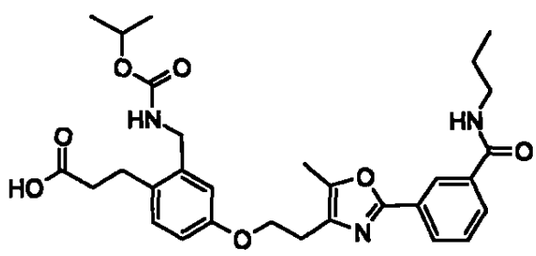
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(3-metilcarbamoil-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ES) m/z 524 (M+1).

Ejemplo 438

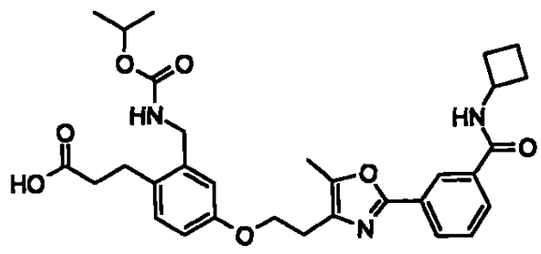
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(3-propilcarbamoil-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ES) m/z 552 (M+1).

Ejemplo 439

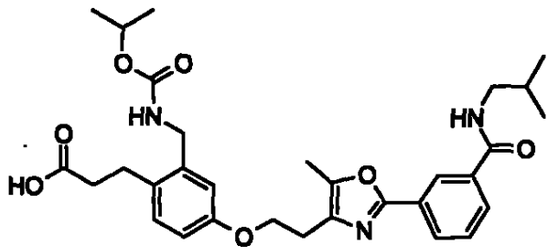
Ácido 3-[4-{2-[2-(3-ciclobutilcarbamoil-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 564 (M+1).

Ejemplo 440

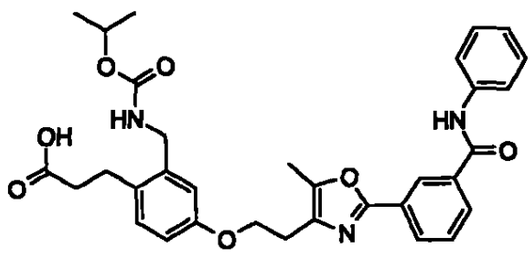
Ácido 3-[4-{2-[2-(3-isobutilcarbamoil-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 566 (M+1).

Ejemplo 441

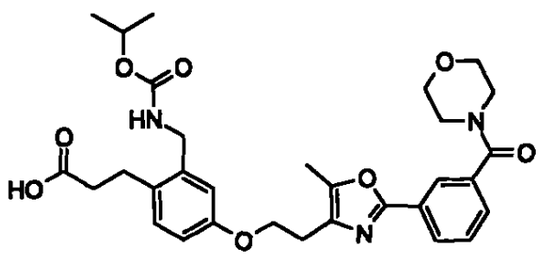
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(3-fenilcarbamoil-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ES) m/z 586 (M+1).

Ejemplo 442

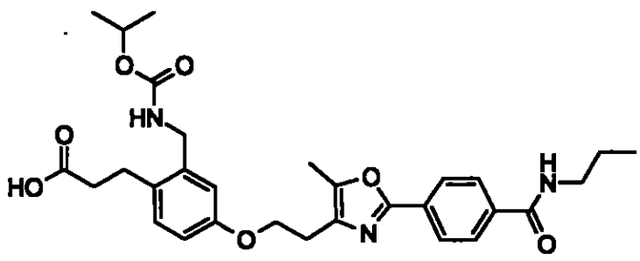
Ácido 3-[2-(isopropoxicarbonilamino-metil)-4-(2-{5-metil-2-[3-(morfolina-4-carbonil)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico



MS (ES) m/z 580 (M+1).

Ejemplo 443

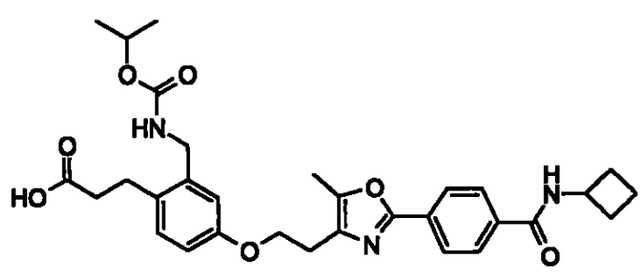
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-propilcarbamoil-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ES) m/z 552 (M+1).

Ejemplo 444

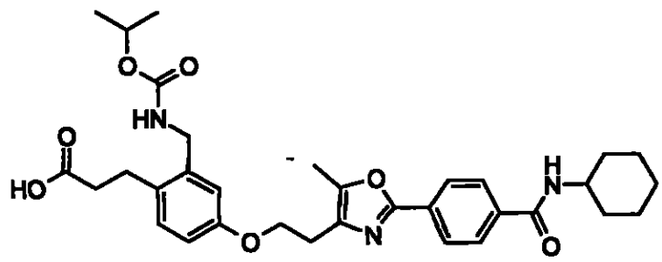
Ácido 3-[4-{2-[2-(4-ciclobutilcarbamoil-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 564 (M+1).

Ejemplo 445

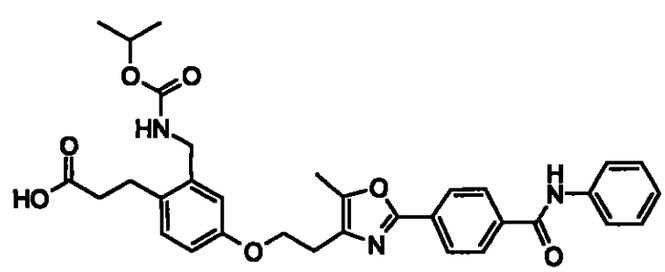
Ácido 3-[4-{2-[2-(4-ciclohexilcarbamoil-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 592 (M+1).

Ejemplo 446

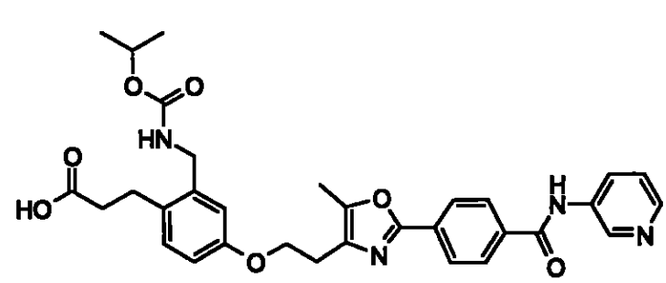
Ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-fenilcarbamoil-fenil)-oxazol-4-il]-etoxi)-fenil)-propiónico



MS (ES) m/z 586 (M+1).

Ejemplo 447

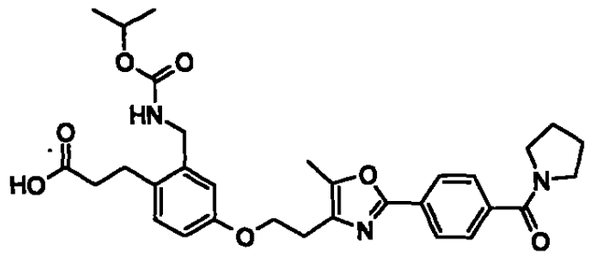
Ácido 3-[2-(isopropoxicarbonilamino-metil)-4-(2-{5-metil-2-[4-(piridin-3-ilcarbamoil)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico



MS (ES) m/z 587 (M+1).

Ejemplo 448

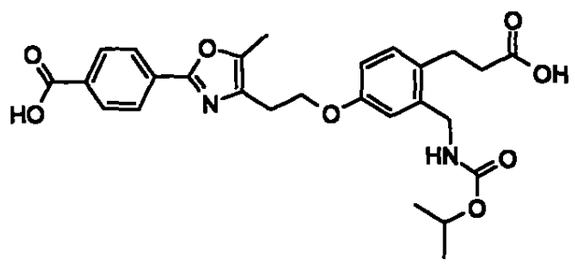
Ácido 3-[2-(isopropoxicarbonilamino-metil)-4-(2-{5-metil-2-[4-(pirrolidina-1-carbonil)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico



MS (ES) m/z 564 (M+1).

Ejemplo 449

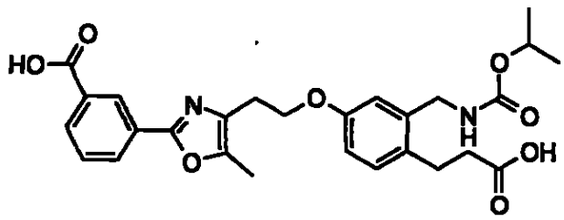
Ácido 4-(4-{2-[4-(2-carboxi-etil)-3-(isopropoxicarbonilamino-metil)-fenoxi]-etil}-5-metil-oxazol-2-il)-benzoico



Se convirtió el ácido 4-(4-{2-[4-(2-terc-butoxicarbonil-etil)-3-(isopropoxicarbonilamino-metil)-fenoxi]-etil}-5-metil-oxazol-2-il)-benzoico (50 mg, 0,09 mmol, Ejemplo 436, Etapa B) en el compuesto del título usando el Procedimiento Convencional C (40 mg, 95%): MS (ESI) m/z 525 $(M+H)^+$.

Ejemplo 450

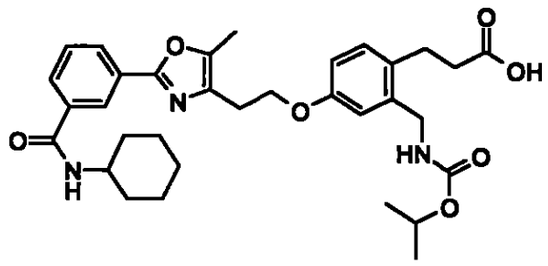
Ácido 3-(4-{2-[4-(2-carboxi-etil)-3-(isopropoxicarbonilamino-metil)-fenoxi]-etil}-5-metil-oxazol-2-il)-benzoico:



El compuesto anterior se prepara siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 449, MS (ESI) m/z 525 $(M+H)^+$.

Ejemplo 451

Ácido 3-[4-{2-[2-(3-ciclohexilcarbamoil-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico

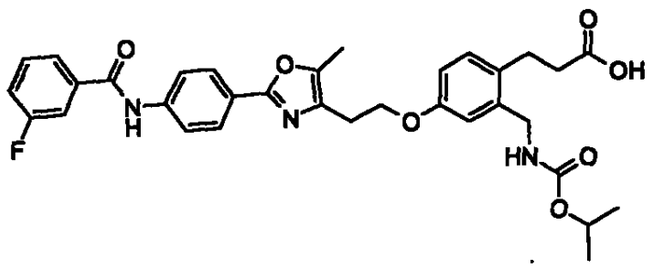


Una solución de éster terc-butílico del ácido 3-[4-{2-[2-(4-bromo-fenil)-5-metoxi-oxazol-4-il]-etoxi}-2-(isopropoxi-carbonilamino-metil)-propiónico (230 mg, 0,38 mmol) en acetonitrilo (20 ml) en un matraz de 3 bocas seco se trató con 2-hidroxipiridina (44 mg, 0,46 mmol) y cloruro de 1,1'-bis(difenilfosfino)-ferroceno paladio (II) (47 mg, 0,057 mmol). La mezcla se agitó durante aproximadamente 5 minutos en una atmósfera de N_2, y se añadió gota a gota trietilamina (58 mg, 0,57 mmol). Se burbujeó gas CO a través de la mezcla, y la reacción se calentó a 70°C durante 4 h. El gas de burbujeo CO se remplazó con un globo cargado con CO, y la reacción se agitó durante 16 h más. La mezcla se enfrió y se repartió en dos partes iguales en dos matraces. Una

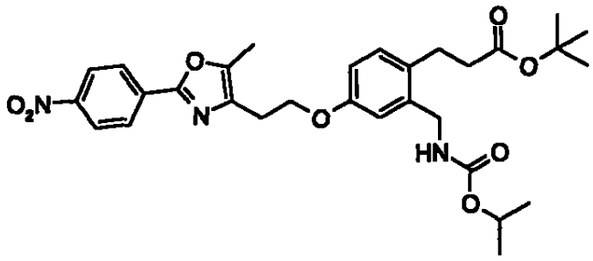
porción se trató con ciclohexilamina (46 mg, 0,46 mmol) y trietilamina (58 mg, 0,57 mmol). La mezcla se agitó a 70°C durante 16 h, se enfrió, se filtró a través de Celite, y se concentró hasta un sólido pardo (196 mg). El sólido se purificó por cromatografía radial (10-70% EtOAc/hexanos) para dar el penúltimo éster *terc*-butílico (78 mg; MS (ESI) m/z 648,6 $(M+H)^+$). El éster se convirtió en el compuesto del título por el Procedimiento Convencional D (72 mg, 64%). MS (ESI) m/z 592,0 $(M+H)^+$.

Ejemplo 452

Ácido 3-[4-(2-{2-[4-(3-Fluoro-benzoilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



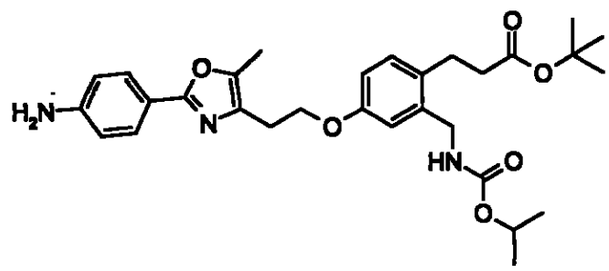
Etapa A: Éster terc-butílico del ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-nitro-fenil)-oxazol-4-il]-etoxi}-fenil) -propiónico



Se acoplaron 2-[5-metil-2-(4-nitro-fenil)-oxazol-4-il]-etil éster del ácido 4-metil-3-nitro-bencenosulfónico (Preparación 7) y éster terc-butílico del ácido 3-[4-hidroxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico por el

Procedimiento Convencional A para dar el compuesto del título.

Etapa B: Éster terc-butílico del ácido 3-[4-{2-[2-(4-amino-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil] -propiónico



Una mezcla de éster terc-butílico del ácido 3-(2-(isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(4-nitro-fenil)-oxazol-4-il]-etoxi}-fenil) -propiónico (207 mg, 0,365 mmol) y Pd al 10%-C (27 mg) en EtOAc (20 ml) se agitó en una atmósfera de H_2 (1 atm) durante 18 h. La mezcla de reacción se filtró a través de Celite y se concentró (75°C) para dar el compuesto del título en forma de un aceite incoloro (196 mg, 100%): MS (ESI) m/z 538 $(M+H)^+$.

Etapa C: Ácido 3-[4-(2-{2-[4-(3-Fluoro-benzoilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico

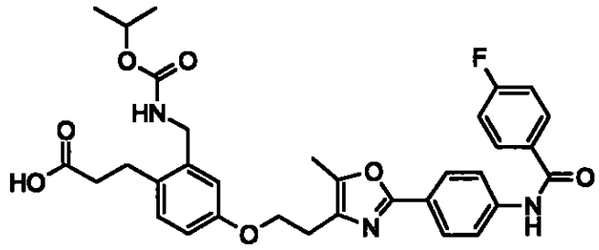
Se añadió 3-fluorocloruro de benzoílo (31 mg, 0,20 mmol, 1,8 equiv) a una solución de éster terc-butílico del ácido 3-[4-{2-[2-(4-amino-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonil-amino-metil)-fenil]-propiónico (58 mg, 0,11 mmol, 1 equiv) y trietilamina (30 µL, 22 mg, 0,22 mmol, 2,0 equiv) en CH_2Cl_2 (5 ml). Después de 16 h, la solución de reacción se lavó con HCl acuoso 1 M (5 ml) y $NaHCO_3$ acuoso saturado (5 ml). La capa orgánica se secó ($MgSO_4$) y se concentró (75 °C) para dar el éster intermedio en forma de un aceite amarillo claro. El aceite se diluyó con HCl 4 M en 1,4-dioxano (5 ml),

se agitó durante 64 h, y se concentró para dar el compuesto del título (73 mg, 110%). HRMS Calculado para $C_{33}H_{35}FN_3O_7$: m/z 604,2459. Encontrado: 604,2453.

Los siguientes Ejemplos 453 a 475 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplos 451 y 452.

Ejemplo 453

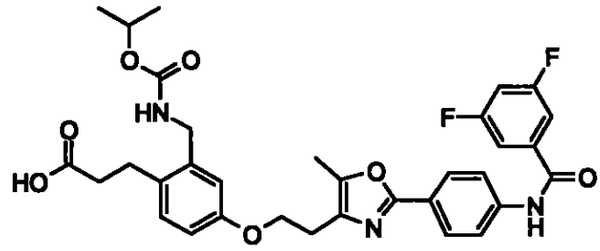
Ácido 3-[4-(2-{2-[4-(4-Fluoro-benzoilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



HRMS Calculado para $C_{33}H_{35}FN_3O_7$: m/z 604,2459. Encontrado: 604,2454.

Ejemplo 454

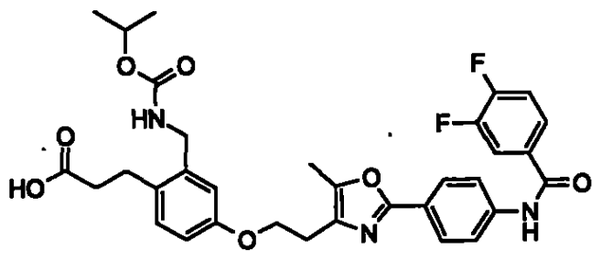
Ácido 3-[4-(2-{2-[4-(3,5-Difluoro-benzoilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



HRMS Calculado para $C_{33}H_{34}F_2N_3O_7$: m/z 622,2365. Encontrado: 622,2352.

Ejemplo 455

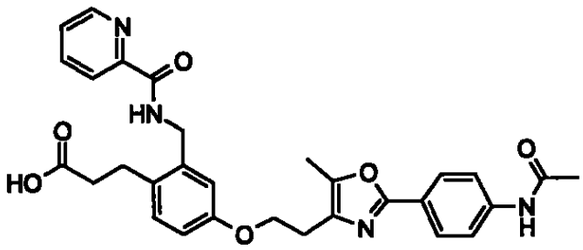
Ácido 3-[4-(2-{2-[4-(3,4-difluoro-benzoilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



HRMS Calculado para $C_{33}H_{34}F_2N_3O_7$: m/z 622,2365. Encontrado: 622,2382.

Ejemplo 456

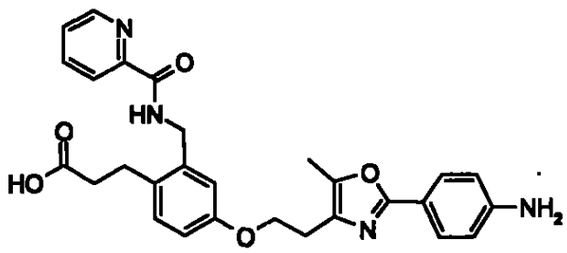
Ácido 3-(4-{2-[2-(4-acetilamino-fenil)-5-metil-oxazol-4-il]-etoxi}-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



MS (ES) m/z 543 (M+1).

Ejemplo 457

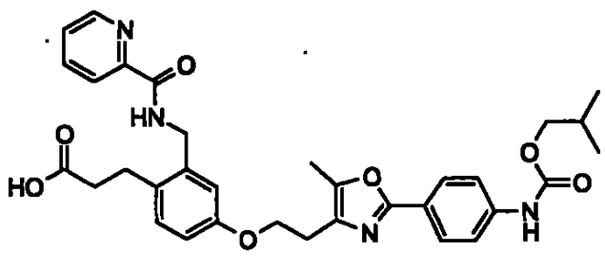
Ácido 3-(4-{2-[2-(4-Amino-fenil)-5-metil-oxazol-4-il]-etoxi}-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



MS (ES) m/z 501 (M+1).

Ejemplo 458

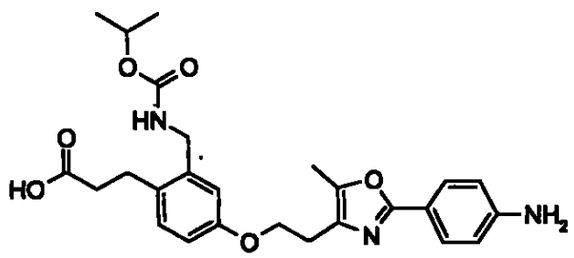
Ácido 3-(4-{2-[2-(4-Isobutoxicarbonilamino-fenil)-5-metil-oxazol-4-il]-etoxi}-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



MS (ES) m/z 601 (M+1).

Ejemplo 459

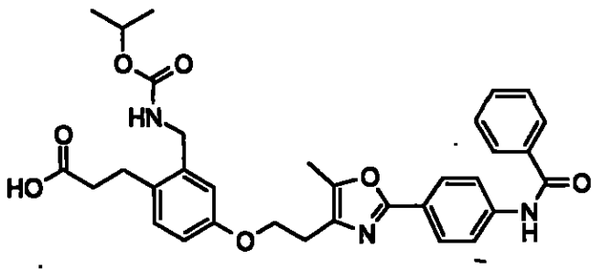
Ácido 3-[4-{2-[2-(4-amino-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil] -propiónico



MS (ES) m/z 482 (M+1).

Ejemplo 460

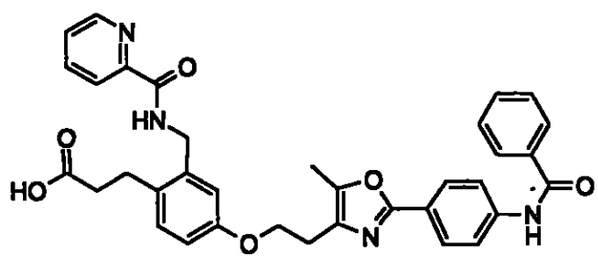
Ácido 3-[4-{2-[2-(4-benzoilamino-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 586 (M+1).

Ejemplo 461

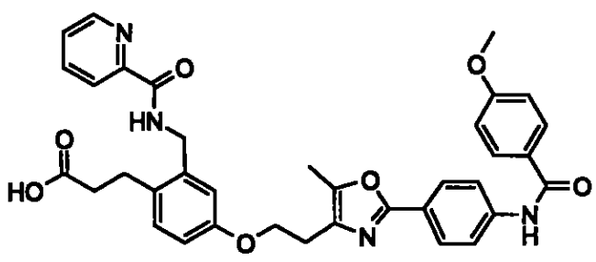
Ácido 3-(4-{2-[2-(4-benzoilamino-fenil)-5-metil-oxazol-4-il]-etoxi}-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



MS (ES) m/z 661 (M+1).

Ejemplo 462

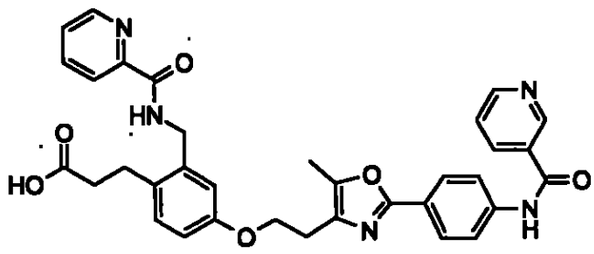
Ácido 3-(4-(2-{2-[4-(4-metoxi-benzoilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



MS (ES) m/z 635 (M+1).

Ejemplo 463

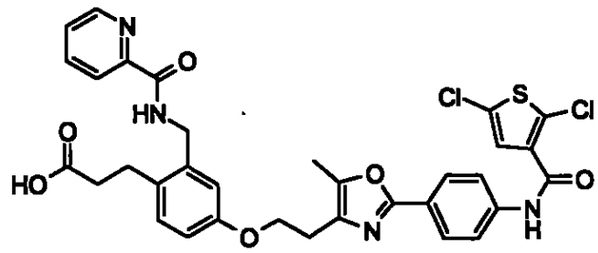
Ácido 3-(4-[2-(5-metil-2-{4-[(piridina-3-carbonil)-amino]-fenil}-oxazol-4-il)-etoxi]-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



MS (ES) m/z 606 (M+1).

Ejemplo 464

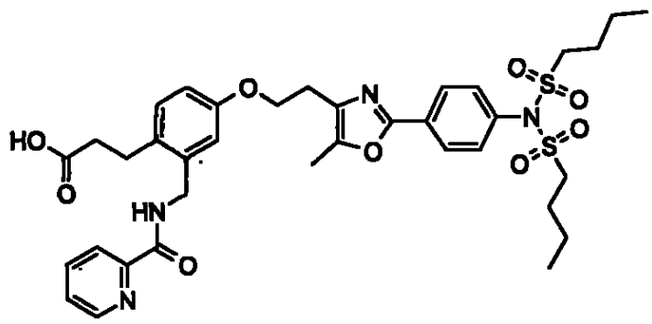
Ácido 3-(4-[2-(2-{4-[(2,5-dicloro-tiofeno-3-carbonil)-amino]-fenil}-5-metil-oxazol-4-il)-etoxi]-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



MS (ES) m/z 680 (M+1).

Ejemplo 465

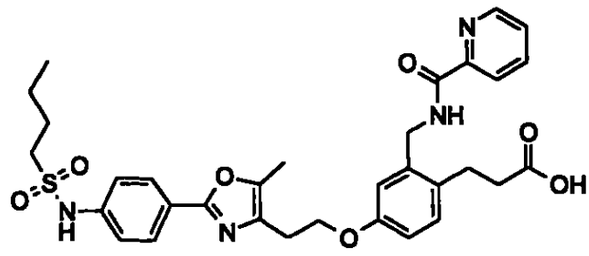
Ácido 3-(4-(2-{2-[4-(*N*,*N*-di-(butano-1-sulfonil)amino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



MS (ES) m/z 741 (M+1).

Ejemplo 466

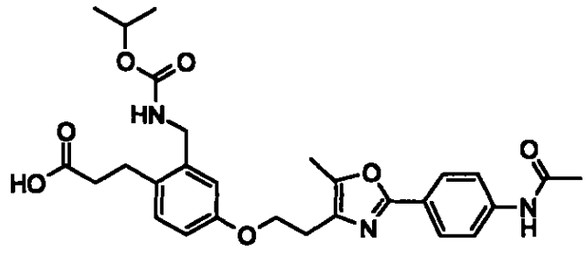
Ácido 3-(4-(2-[2-[4-(butano-1-sulfonilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico



MS (ES) m/z 621 (M+1).

Ejemplo 467

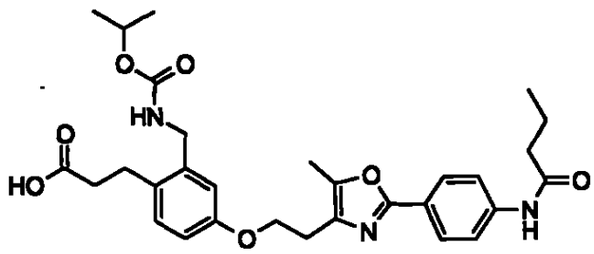
Ácido 3-[4-{2-[2-(4-acetilamino-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 524 (M+1).

Ejemplo 468

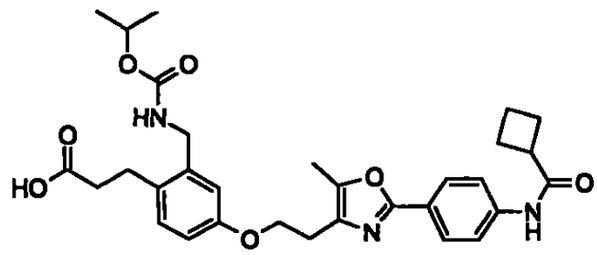
Ácido 3-[4-{2-[2-(4-butirilamino-fenil)-5-metil-oxazol-4-il]-etoxi}-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 552 (M+1).

Ejemplo 469

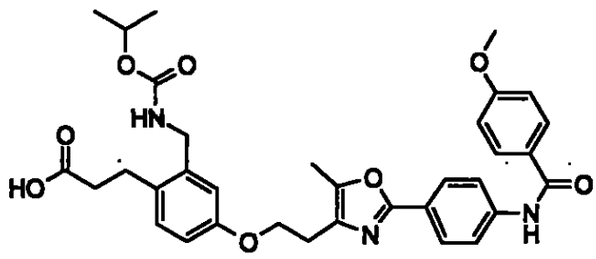
Ácido 3-[4-(2-{2-[4-(ciclobutanocarbonil-amino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 564 (M+1).

Ejemplo 470

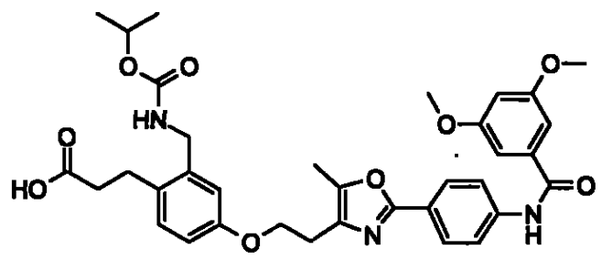
Ácido 3-[2-(isopropoxicarbonilamino-metil)-4-(2-{2-[4-(4-metoxi-benzoilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-fenil]-propiónico



MS (ES) m/z 616 (M+1).

Ejemplo 471

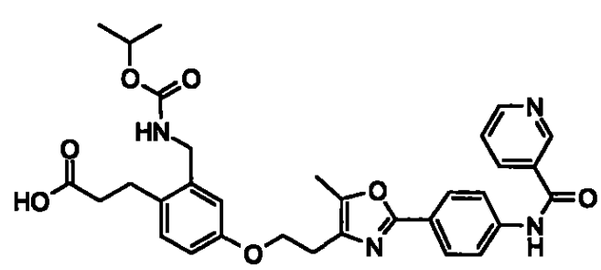
Ácido 3-[4-(2-{2-[4-(3,5-dimetoxi-benzoilamino)-fenil]-5-metil-oxazol-4-il}-etoxi)-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 646 (M+1).

Ejemplo 472

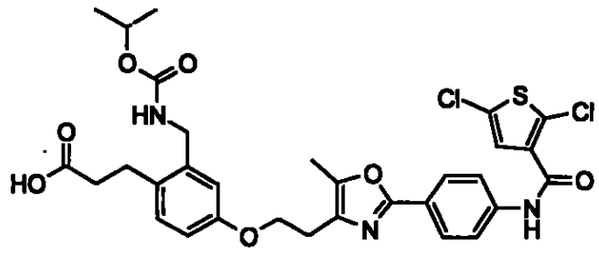
Ácido 3-{2-(Isopropoxicarbonilamino-metil)-4-[2-(5-metil-2-{4-[(piridina-3-carbonil)-amino]-fenil}-oxazol-4-il)-etoxi]-fenil}-propiónico



MS (ES) m/z 587 (M+1).

Ejemplo 473

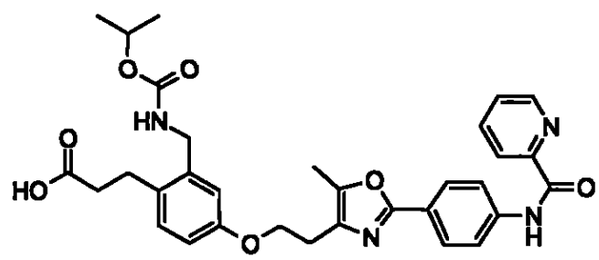
Ácido 3-[4-[2-(2-{4-[(2,5-dicloro-tiofeno-3-carbonil)-amino]-fenil}-5-metil-oxazol-4-il)-etoxi]-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 661 (M+1).

Ejemplo 474

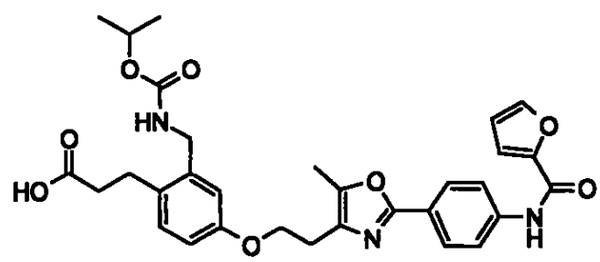
Ácido 3-{2-(isopropoxicarbonilamino-metil)-4-[2-(5-metil-2-{4-[(piridina-2-carbonil)-amino]-fenil}-oxazol-4-il)-etoxi]-fenil}-propiónico



MS (ES) m/z 587 (M+1).

Ejemplo 475

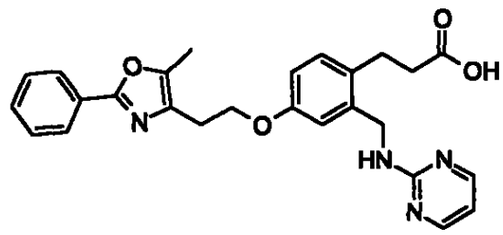
Ácido 3-[4-[2-(2-{4-[(furano-2-carbonil)-amino]-fenil}-5-metil-oxazol-4-il)-etoxi]-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



MS (ES) m/z 576 (M+1).

Ejemplo 476

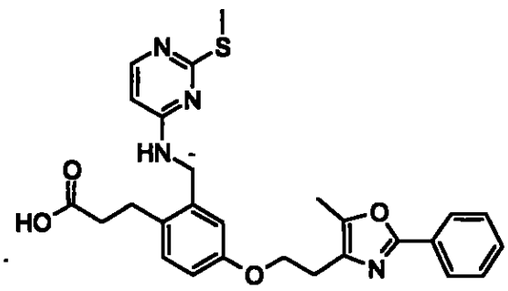
Ácido 3-[4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-(pirimidin-2-ilaminometil)-fenil]-propiónico



Una solución de éster terc-butílico del ácido 3-{2-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico: sal del ácido acético (0,40 mmol, 0,20 g, Ejemplo 1 Etapa B) en DMF (2 ml) se trató con K_2CO_3 (1,0 mmol, 0,14 g) y 2-cloropirimidina (1,2 mmol, 0,14 g). La mezcla se calentó a 60 °C durante 18 h, se enfrió, se diluyó con agua (50 ml), y se extrajo con EtOAc (3 x 15 ml). Las capas orgánicas combinadas se secaron (Na_2SO_4), se concentraron y se purificaron por cromatografía en gel de sílice para dar el éster terc-butílico intermedio. Este material se convirtió en el compuesto del título (80 mg) usando el Procedimiento Convencional C. MS (ESI) m/z 459,2 $(M+H)^+$.

Ejemplo 477

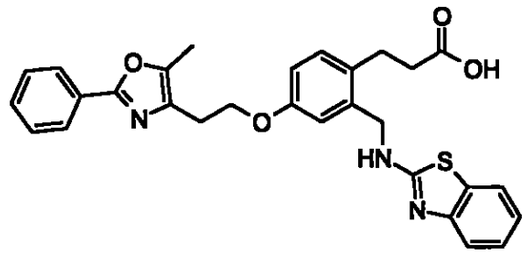
Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(2-metilsulfanil-pirimidin-4-ilamino)-metil]-fenil}-propiónico



El compuesto anterior se prepara siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 476, MS (ESI) m/z 505,1 $(M+H)^+$.

Ejemplo 478

Ácido 3-{2-(benzotiazol-2-ilaminometil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

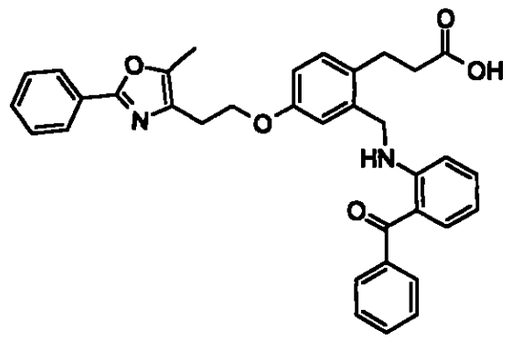


Una solución de éster terc-butílico del ácido 3-{2-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico: sal del ácido acético (150 mg, 0,302 mmol; Ejemplo 1 Etapa B) y 2-cloro-benzotiazol (154 mg, 0,907 mmol) en tolueno (5 ml) se trató con K_2CO_3 (42 mg). La suspension se calentó a 110°C durante 48 h y se concentró. El residuo se purificó por cromatografía en gel de sílice (25-50% EtOAc/hexanos) para producir el éster *terc*-butílico intermedio (15 mg). Este material se convirtió en el compuesto del título (80 mg) usando el Procedimiento Convencional C. El intermedio se trató con TFA (0,25 ml)/CH_2Cl_2 (1,0 ml)/H_2O (0,1 ml), se agitó durante 3 h, y se concentró. El

residuo se disolvió en CH_2Cl_2 (10 ml), se lavó con tampón acuoso (pH = 7), se secó (Na_2SO_4), y se concentró para producir el compuesto del título (12 mg, 8%). MS (ESI) m/z 514,3 $(M+H)^+$.

Ejemplo 479

Ácido 3-{2-[(2-benzoil-fenilamino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

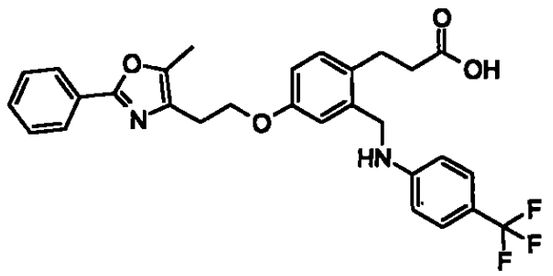


Una solución de éster terc-butílico del ácido 3-{2-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico:sal del ácido acético (290 mg, 0,665 mmol, Ejemplo 1, Etapa B) y 2-benzoil-ciclohexanona (161 mg, 0,797 mmol) en anisol (20 ml) se trató con una suspensión de Pd/C (60 mg) en anisol (2 ml). La mezcla se calentó a reflujo a 200°C con destilación azeotrópica de agua durante 2 h y se enfrió a temperatura ambiente. El catalizador se filtró y se añadió una suspensión reciente de Pd/C (60 mg) en anisol. La mezcla se calentó a 110°C durante 72 h y se filtró a través de una capa de celite. El filtrado se concentró, se purificó por cromatografía en gel de sílice (25% EtOAc/hexanos) para producir una mezcla de material de partida y éster terc-butílico intermedio. La mezcla se trató con TFA (1,0 ml)/CH_2Cl_2 (1,0 ml)/H_2O (0,1 ml), se agitó durante 3 h, y se concentró. El residuo se purificó usando

cromatografía en gel de sílice (MeOH/EtOAc 1/9) para dar el compuesto del título (38 mg, 10%). MS (ESI) m/z 561,3 $(M+H)^+$.

Ejemplo 480

Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(4-trifluorometil-fenilamino)-metil]-fenil}-propiónico

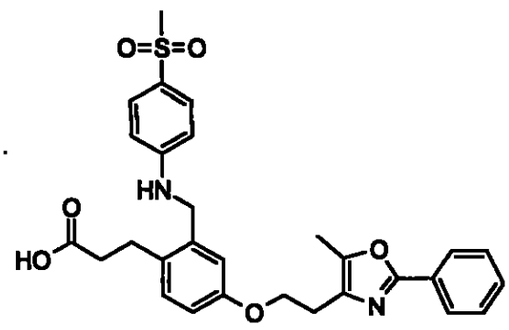


Una solución de éster terc-butílico del ácido 3-{2-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (174 mg, 0,40 mmol, Ejemplo 1 y Procedimiento I) en tolueno (5,0 ml) en un tubo cerrado herméticamente en una atmósfera de N_2 se le añadió $Pd(OAc)_2$ (15 mg), 2-(di-t-butilfosfino)bifenilo (10 mg), t-butóxido sódico (54 mg, 0,56 mmol) y 4-trifluorometilclorobenceno (29 mg, 0,16 mmol). El tubo se cerró herméticamente y se calentó a 110 °C durante 14 h. La mezcla de reacción se enfrió, se inactivó con agua (1,0 ml), y se extrajo con EtOAc (2 x 15 ml). Los extractos orgánicos combinados se concentraron y se purificaron usando cromatografía en columna de gel de sílice (10-50% EtOAc/hexanos) para producir el éster *terc*-butílico intermedio (80 mg). Este material se convirtió en el compuesto del título (40 mg, 48%) usando el Procedimiento Convencional C. MS (ESI) m/z 525,4 $(M+H)^+$.

Los siguientes Ejemplos 481 a 484 se prepararon siguiendo un procedimeinto sustancialmente similar al descrito en el Ejemplos 478 a 480.

Ejemplo 481

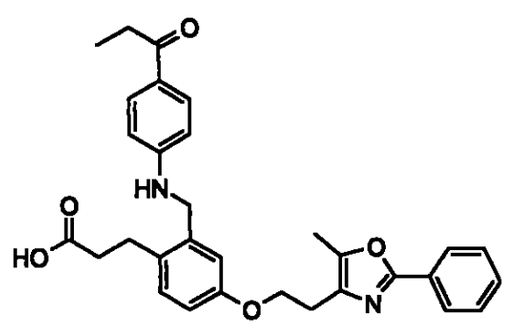
Ácido 3-{2-[(4-metanosulfonil-fenilamino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



MS (ESI) m/z 535,1 $(M+H)^+$.

Ejemplo 482

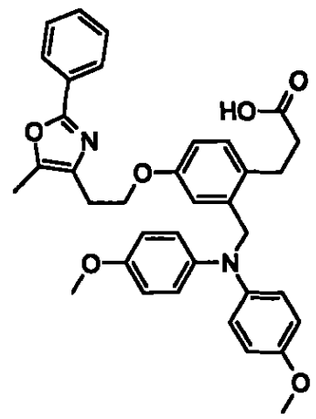
Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(4-propionil-fenilamino)-metil]-fenil}-propiónico



MS (ESI) m/z 513,2 $(M+H)^+$.

Ejemplo 483

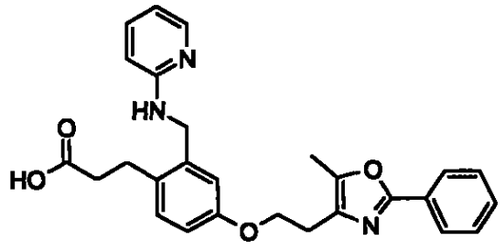
Ácido 3-{2-{[bis-(4-metoxi-fenil)-amino]-metil}-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



MS (ESI) m/z 593,3 $(M+H)^+$.

Ejemplo 484

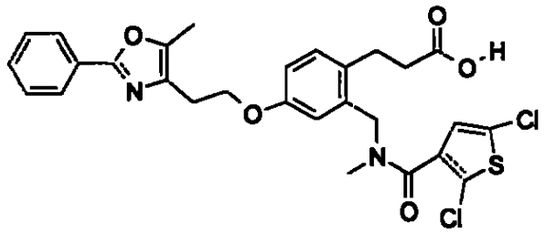
Ácido 3-[4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-(piridin-2-ilaminometil)-fenil]-propiónico



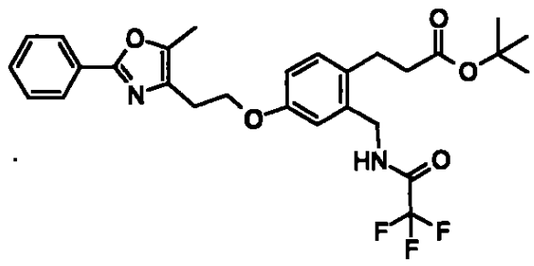
MS (ESI) m/z 458,2 $(M+H)^+$.

Ejemplo 485

Ácido 3-{2-[[(2,5-dicloro-tiofeno-3-carbonil)-metil-amino]-metil}-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

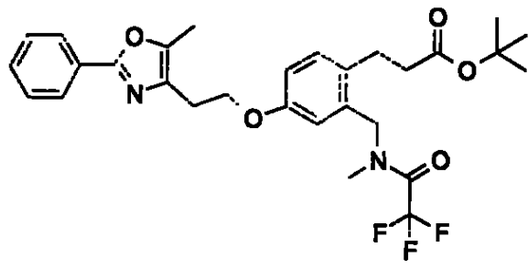


Etapa A: Éster terc-butílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(2,2,2-trifluoro-acetilamino)-metil]-fenil}-propiónico



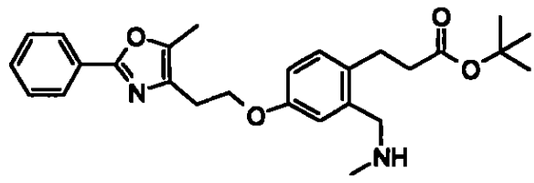
Se disolvió éster terc-butílico del ácido 3-{2-Aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico: sal del ácido acético (894 mg, 1,80 mmol) en CH_2Cl_2 (25 ml) y se lavó con una solución saturada de $NaHCO_3$ (15 ml). La capa orgánica se secó ($NaSO_4$), se filtró, y se concentró para dar un aceite amarillo (681 mg). La amina bruta se disolvió en CH_2Cl_2 (25 ml) y se trató con trifluoroanhídrido acético (0,66 ml, 4,7 mmol) y después con piridina (0,37 ml, 4,6 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 h y se concentró. El residuo se repartió entre EtOAc y HCl 1 N, y la capa orgánica se lavó con una solución saturada de $NaHCO_3$ y después con salmuera. La capa orgánica se secó (Na_2SO_4) y se concentró para dar un sólido amarillo pálido (839 mg, 88%).

Etapa B: Éster terc-butílico del ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{[metil-(2,2,2-trifluoro-acetil)-amino]-metil}-fenil)-propiónico



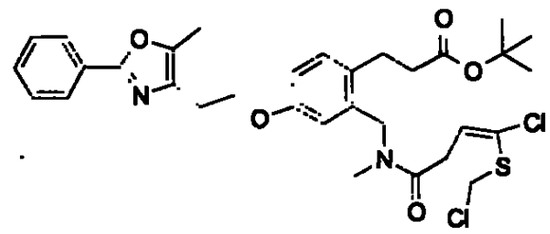
Una solución de éster terc-butílico del ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(2,2,2-trifluoro-acetilamino)-metil]-fenil}-propiónico (151 mg, 0,28 mmol) en DMF seca (10 ml) se enfrió en un baño de hielo y se trató con NaH (22 mg, 0,55 mmol, dispersión en aceite al 60%). Después la mezcla de reacción se agitó durante 25 min, se le añadió yodometano (0,15 ml, 3,0 mmol), y la reacción se dejó calentar gradualmente a temperatura ambiente. Después de 4 h, se añadió más yodometano (0,10 ml, 2 mmol). La mezcla se agitó durante una noche y se repartió entre EtOAc y una solución acuosa de LiCl. La capa orgánica se lavó con salmuera, se secó (Na_2SO_4), y se concentró. El residuo se purificó por cromatografía radial en gel de sílice (CH_2Cl_2/EtOAc 100/0 a 95/5) para dar el compuesto del título (111 mg, 73%).

Etapa C: Éster terc-butílico del ácido 3-{2-metilaminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



Una solución de éster terc-butílico del ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{[metil-(2,2,2-trifluoro-acetil)-amino]-metil}-fenil)-propiónico (111 mg, 0,20 mmol) en metanol (5 ml) y THF (5 ml) se trató con NaOH 2 N (1,0 ml, 2,0 mmol) y se calentó a 55°C durante 1 h. La mezcla de reacción se enfrió, se concentró, se neutralizó con HCl 1 N y se extrajo en EtOAc. La capa orgánica se lavó con una solución saturada de $NaHCO_3$ y salmuera, se secó (Na_2SO_4), y se concentró. El residuo se purificó por cromatografía radial en gel de sílice (CH_2Cl_2/metanol 95/5 a 90/10) para dar el compuesto del título (37 mg, 42%). MS (ES) m/z 451,3 [M+1].

Etapa D: Éster terc-butílico del ácido 3-{2-{[(2,5-dicloro-tiofeno-3-carbonil)-metil-amino]-metil}-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



Una solución de éster terc-butílico del ácido 3-{2-metilaminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (37 mg, 0,083 mmol) en CH_2Cl_2 (5 ml) se trató con trietilamina (0,035 ml, 0,25 mmol) y después con cloruro de 2,5-dicloro-tiofeno-3-carbonilo (0,054 ml, 0,25 mmol) y se agitó a temperatura ambiente durante una noche. La mezcla se diluyó con EtOAc (25 ml) y se lavó con salmuera (3 x 10 ml). La capa orgánica se secó (Na_2SO_4) y se concentró para dar el compuesto del título (50 mg, 96%). MS (ES) m/z 629, 631 [M+1].

Etapa E: Ácido 3-{2-{[(2,5-dicloro-tiofeno-3-carbonil)-metil-amino]-metil}-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

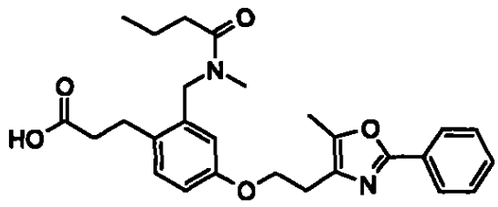
Una solución de 3-{2-{[(2,5-dicloro-tiofeno-3-carbonil)-metil-amino]-metil}-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico éster terc-butílico del ácido (50 mg, 0,079 mmol) en CH_2Cl_2 (2 ml) se trató con anisol (1,0 ml) y después con TFA (0,6 ml). La solución se agitó a temperatura ambiente 2 h, y se añadió más TFA (1,0 ml). Después de 15 min, la reacción se concentró y co-evaporó con CCl_4 (3 x). El residuo se trituró con hexanos para producir una espuma (43 mg, 95%). ^1H RMN (400 MHz, $CDCl_3$) δ 2,36 (s, 3H), 2,48 (t, 0,6H, J = 7,8 Hz), 2,58 (t, 1,4H, J = 7,8 Hz), 2,72 (t, 0,6H, J = 7,8 Hz), 2,84 (s, 2H), 2,90 (t, 1,4H, J = 7,8 Hz), 2,93 (s, 1H), 2,98 (s a, 2H), 4,17 (t, 2H, J = 6,4 Hz), 4,47 (s, 0,6H), 4,71 (s, 1,4H), 6,61 (s a, 0,3H), 6,71-6,76 (m, 2H), 6,79 (s, 0,7H),

7,04 (d, 0,3H, *J* = 8,3 Hz), 7,08 (d, 0,7H, *J* = 8,3 Hz), 7,41-7,43 (m, 3H), 7,94 (s a, 2H).

Los siguientes Ejemplos 486 a 488 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 485.

Ejemplo 486

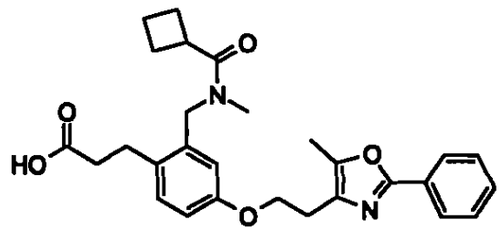
Ácido 3-{2-[(butiril-metil-amino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



MS (ES) m/z 465 (M+1).

Ejemplo 487

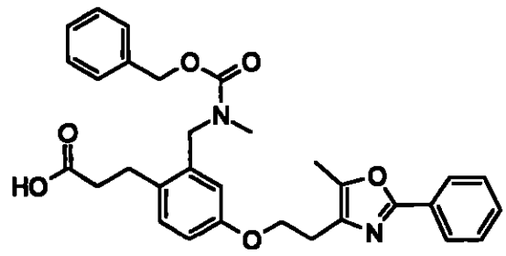
Ácido 3-{2-[(ciclobutanocarbonil-metil-amino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



MS (ES) m/z 477 (M+1).

Ejemplo 488

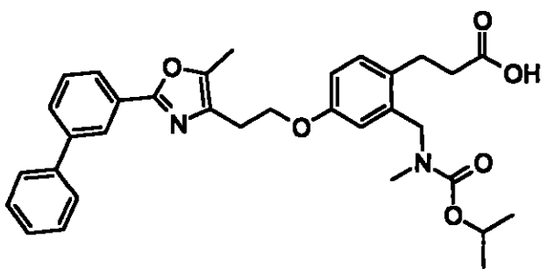
Ácido 3-{2-[(benciloxicarbonil-metil-amino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



MS (ES) m/z 529 (M+1).

Ejemplo 489

Ácido 3-{4-[2-(2-Bifenil-3-il-5-metil-oxazol-4-il)-etoxi]-2-[(isopropoxicarbonil-metil-amino)-metil]-fenil}-propiónico

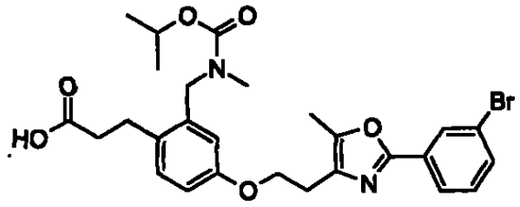


Se acoplaron éster terc-butílico del ácido 3-{4-Hidroxi-2-[(isopropoxicarbonil-metil-amino)-metil]-fenil}-propiónico (500 mg, 1,4 mmol; Preparación 22) y 2-(2-bifenil-3-il-5-metil-oxazol-4-il)etil éster del ácido tolueno-4-sulfónico (617 mg, 1,4 mmol; Preparación1/2) usando el Procedimiento Convencional A para dar el penúltimo éster *terc*-butílico. Este éster se convirtió en el compuesto del título usando el Procedimiento Convencional D (326 mg): MS (ESI) m/z 557 $(M+H)^+$.

Los siguientes Ejemplos 490 a 501 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 489.

Ejemplo 490

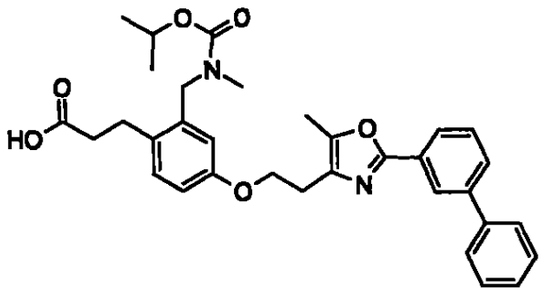
Ácido 3-{4-[2-[2-(3-bromofenil)-5-metiloxazol-4-il]etoxi}-2-[(isopropoxi-carbonilmetilamino)metil]fenil} propiónico



MS (ES) m/z 560 (M+1).

Ejemplo 491

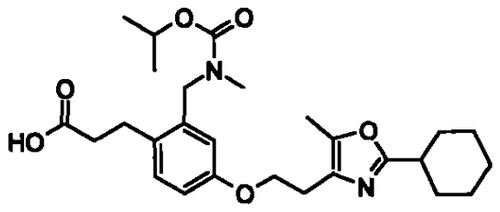
Ácido 3-{4-[2-(2-bifenil-3-il-5-metiloxazol-4-il)etoxi]-2-[(isopropoxi-carbonilmetilamino)metil]fenil} propiónico



MS (ES) m/z 577 (M+1).

Ejemplo 492

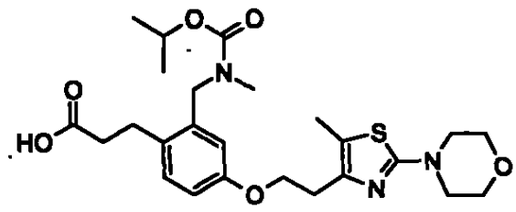
Ácido 3-{4-[2-(2-ciclohexil-5-metiloxazol-4-il)etoxi]-2-[(isopropoxi-carbonilmetilamino)metil]fenil} propiónico



MS (ES) m/z 487 (M+1).

Ejemplo 493

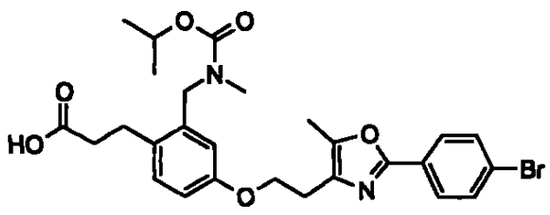
Ácido 3-{2-[(isopropoxicarbonilmetilamino)metil]-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil} propiónico



MS (ES) m/z 506 (M+1).

Ejemplo 494

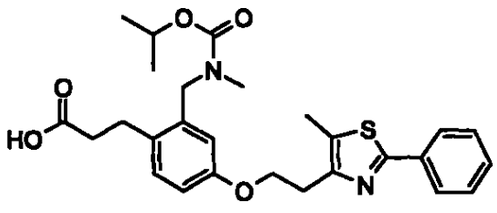
Ácido 3-{4-{2-[2-(4-bromofenil)-5-metiloxazol-4-il]etoxi}-2-[(isopropoxi-carbonilmetilamino)metil]fenil} propiónico



MS (ES) m/z 560 (M+1).

Ejemplo 495

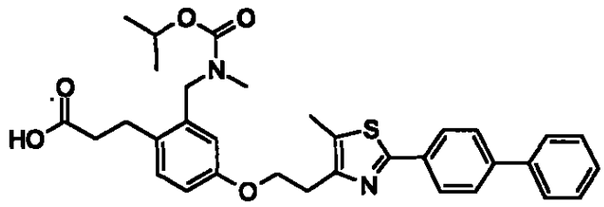
Ácido 3-{2-[(isopropoxicarbonilmetilamino)metil]-4-[2-(5-metil-2-feniltiazol4-il)etoxi]fenil} propiónico



MS (ES) m/z 497 (M+1).

Ejemplo 496

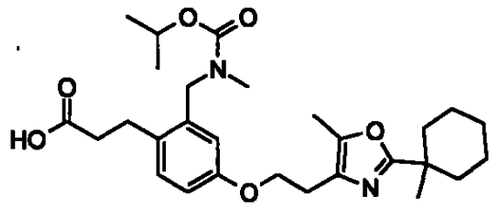
Ácido 3-{4-[2-(2-bifenil-4-il-5-metiltiazol-4-il)etoxi]-2-[(isopropoxi-carbonilmetilamino)metil]fenil} propiónico



MS (ES) m/z 573 (M+1).

Ejemplo 497

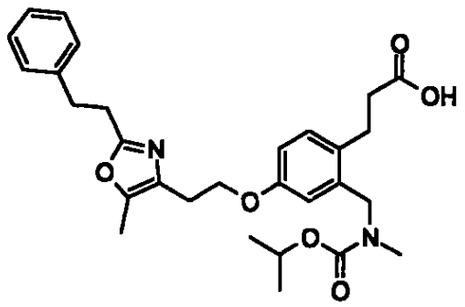
Ácido 3-(2-[(isopropoxicarbonilmetilamino)metil]-4-{2-[5-metil-2-(1-metil-ciclohexil)oxazol-4-il]etoxi}fenil) propiónico



MS (ES) m/z 501 (M+1).

Ejemplo 498

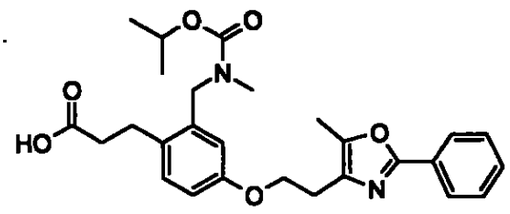
Ácido 3-{2-[(isopropoxicarbonilmetilamino)metil]-4-[2-(5-metil-2-fenetil-oxazol-4-il)etoxi]fenil} propiónico



MS (ES) m/z 509 (M+1).

Ejemplo 499

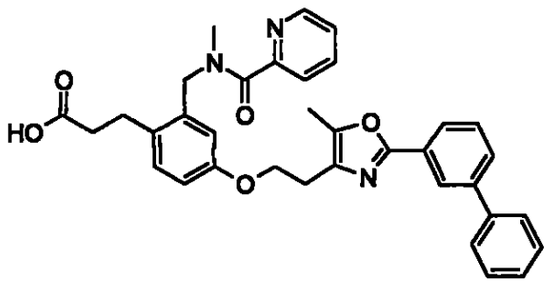
Ácido 3-{2-[(isopropoxicarbonilmetilamino)metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)etoxi]fenil} propiónico



MS (ES) m/z 481 (M+1).

Ejemplo 500

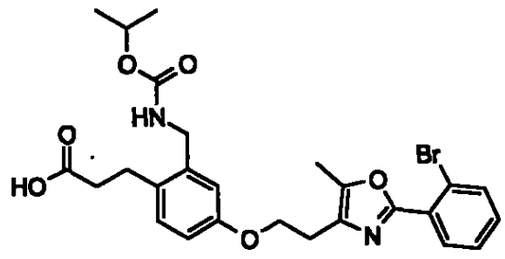
Ácido 3-(4-[2-(2-bifenil-3-il-5-metiloxazol-4-il)etoxi]-2-{[metil(piridina-2-carbonil)amino]metil}fenil) propiónico



MS (ES) m/z 576 (M+1).

Ejemplo 501

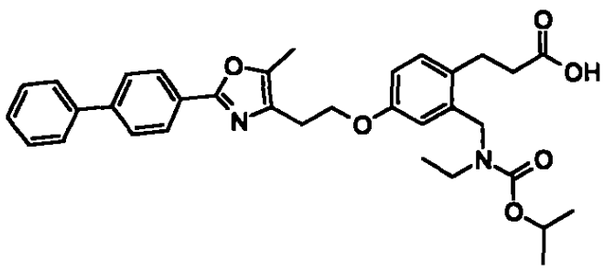
Ácido 3-[4-{2-[2-(2-bromofenil)-5-metiloxazol-4-il]etoxi}-2-(isopropoxi-carbonilaminometil)fenil] propiónico



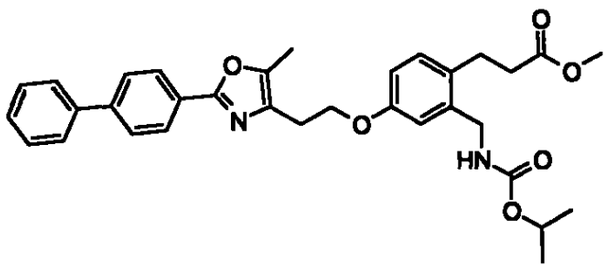
MS (ES) m/z 546 (M+1).

Ejemplo 502

Ácido 3-{4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-[(etil-isopropoxicarbonil-amino)-metil]-fenil}-propiónico



Etapa A: Éster metílico del ácido 3-[4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico



Se combinaron éster metílico del ácido 3-[4-Hidroxi-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (Preparación 17) y 2-(2-bifenil-4-il-5-metil-oxazol-4-il)etil éster del ácido tolueno-4-sulfónico (Preparación 1) de acuerdo con Procedimiento Convencional A para dar el compuesto del título.

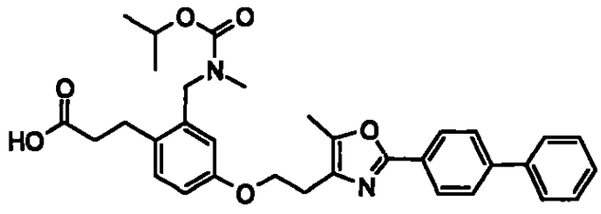
Etapa B: Ácido 3-{4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-[(etil-isopropoxicarbonil-amino)-metil]-fenil}-propiónico

Una solución de éster metílico del ácido 3-[4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-(isopropoxicarbonilamino-metil)-fenil]-propiónico (200 mg, 0,36 mmol) en DMF (15 ml) se trató con sodio bis(trimetilsilil)amida (132 mg, 0,719 mmol). Se le añadió yoduro de etilo (112 mg, 0,719 mmol), y la mezcla de reacción se agitó durante una noche a temperatura ambiente en una atmósfera de N_2. La mezcla se diluyó con EtOAc (100 ml) y se lavó con salmuera (100ml), después con agua (100 ml). La capa orgánica se secó ($MgSO_4$) y se concentró para dar el penúltimo éster en forma de un sólido blanco (179 mg). El material se disolvió en EtOH (20 ml), se trató con NaOH 5 N (20 ml), y se agitó a temperatura ambiente durante una noche. La mezcla se acidificó con HCl 1 N(10ml) y se extrajo con EtOAc (50ml). Los extractos orgánicos se secaron ($MgSO_4$) y se concentraron para dar un sólido blanco (201mg). MS [EI+] m/z 571 $(M+H)^+$. Anal. Calculado para $C_{34}H_{38}N_2O_6$: C, 71,6; H, 6,7; N, 4,9. Encontrado: C, 70,8; H, 6,8; N, 5,0,

Los siguientes Ejemplos 503 a 504 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 502,

Ejemplo 503

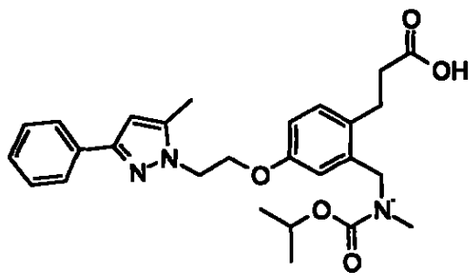
Ácido 3-{4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-[(isopropoxicarbonil-metil-amino)-metil]-fenil}-propiónico



MS [EI+] m/z 557 $(M+H)^+$. Anal. Calculado para $C_{33}H_{36}N_2O_6$: C, 71,2; H, 6,5; N, 5,0. Encontrado: C, 70,6; H, 6,6; N, 5,1,

Ejemplo 504

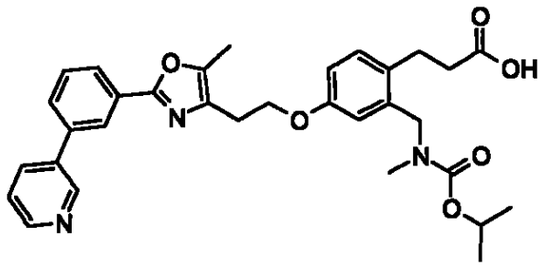
Ácido 3-{2-[(isopropoxicarbonil-metil-amino)-metil]-4-[2-(5-metil-3-fenil-pirazol-1-il)-etoxi]-fenil}-propiónico



MS [EI+] m/z 480,1 $(M+H)^+$.

Ejemplo 505

Ácido 3-(2-[(isopropoxicarbonil-metil-amino)-metil)-4-{2-[5-metil-2-(3-piridin-3-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



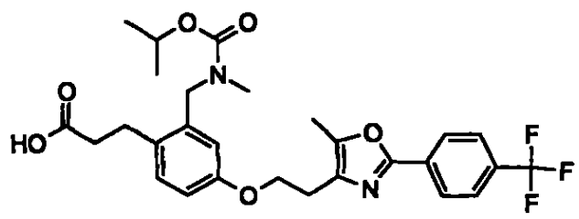
N-Metilación de carbamatos: en un vial de tapa a rosca se puso éster terc-butílico del ácido 3-(2 (isopropoxicarbonilamino-metil)-4-{2-[5-metil-2-(3-piridin-3-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico (0,5 mmol). A 1/1 mezcla de $CHCl_3$/TFA (1,6 ml) se le añadió seguido de 37% HCHO (50 ml). La mezcla de reacción se agitó a temperatura ambiente durante 0,5 h y se añadió trietilsilano (110 ml, 0,7 mmol). La mezcla se agitó durante otra 0,5 h y se concentró. La

mezcla del producto se purificó usando HPLC de fase inversa guiada de masas para producir el compuesto del título (85%). MS [EI+] m/z 571 $(M+H)^+$.

Los siguientes Ejemplos 506 a 509 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 505,

Ejemplo 506

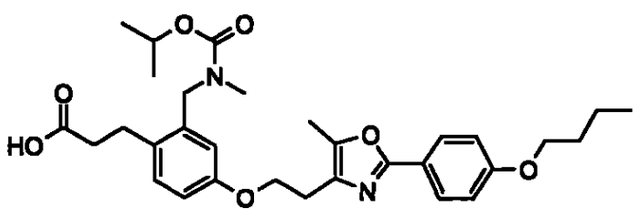
Ácido 3-(2-[(isopropoxicarbonil-metil-amino)-metil]-4-{2-[5-metil-2-(4-trifluorometil-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ES) m/z 549 $(M+H)^+$.

Ejemplo 507

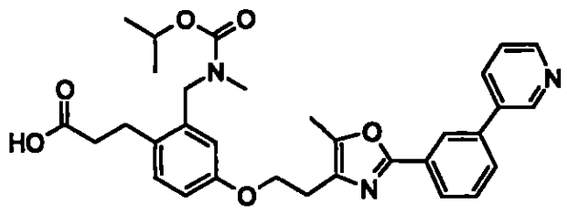
Ácido 3-{4-{2-[2-(4-butoxi-fenil)-5-metil-oxazol-4-il]-etoxi}-2-[(isopropoxicarbonil-metil-amino)-metil]-fenil}-propiónico



MS (ES) m/z 553 $(M+H)^+$.

Ejemplo 508

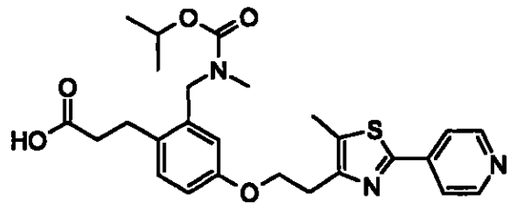
Ácido 3-(2-[(isopropoxicarbonil-metil-amino)-metil]-4-{2-[5-metil-2-(3-piridin-3-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS (ES) m/z 558 $(M+H)^+$.

Ejemplo 509

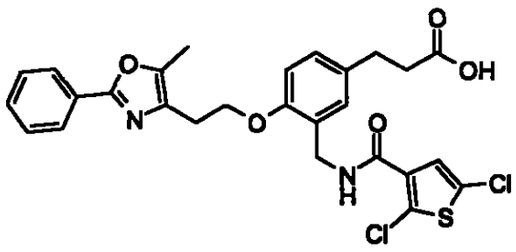
Ácido 3-{2-[(isopropoxicarbonil-metil-amino)-metil]-4-[2-(5-metil-2-piridin-4-il-tiazol-4-il)-etoxi]-fenil}-propiónico



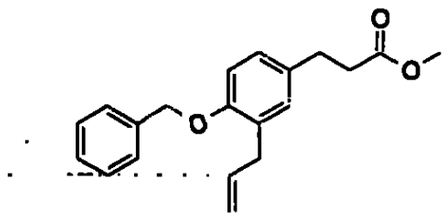
MS (ES) m/z 498 $(M+H)^+$.

Ejemplo 510

Ácido 3-{3-{[(2,5-dicloro-tiofeno-3-carbonil)-amino]-metil}-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

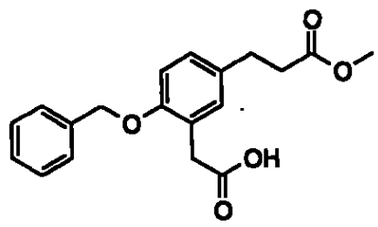


Etapa A: Éster metílico del ácido 3-(3-alil-4-benciloxi-fenil)-propiónico

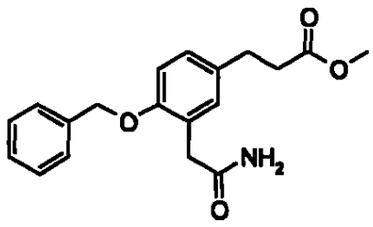


Una solución de éster metílico del ácido 3-(3-alil-4-hidroxi-fenil)-propiónico (20,5 g, 93,0 mmol; Brown GR, et al. *Bioorg. y Med. Chem. Lett.* 1997, 7, 597) en DMF (50 ml) se trató con Cs_2CO_3 (32,6 g, 100 mmol) después con bromuro de bencilo (12,8 ml, 108 mmol) y se calentó a 55 °C durante 16 h. Cs_2CO_3 (16,3 g, 50 mmol) y se le añadió bromuro de bencilo (6,4 ml, 54 mmol). La mezcla se agitó a 55°C durante 23 h, se enfrió, y se repartió entre EtOAc (250 ml) y agua (100 ml). La capa orgánica se lavó con salmuera (75 ml). Las capas acuosas combinadas se extrajeron con EtOAc (100 ml). Las capas orgánicas combinadas se secaron (Na_2SO_4), y se concentraron. El residuo se purificó por cromatografía en columna de gel de sílice (CH_2Cl_2/hexanos 1/1 a 100/0) para dar el compuesto del título (27,0 g, 93%).

Etapa B: Éster metílico del ácido 3-(4-benciloxi-3-carboximetil-fenil)-propiónico

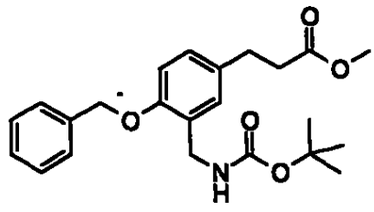


Una solución de éster metílico del ácido 3-(3-alil-4-benciloxi-fenil)-propiónico (25,0 g, 80,5 mmol) en acetona (300 ml) y agua (30 ml) se trató con 4-metil-morfolina 4-óxido (12,96 g, 95,8 mmol) después con óxido de osmio (IV) (5 trozos). El matraz se cubrió con una lámina y se agitó durante 20 h. La solución se diluyó con EtOAc (1 l) y se lavó con $Na_2S_2O_3$ 1N (2 x 150 ml) y con salmuera (125 ml). La capa orgánica se concentró para dar un aceite amarillo (28,9 g). El aceite se disolvió en THF (190 ml) y agua (125 ml), y se añadió peryodato de sodio (49,0 g, 229 mmol). Se añadieron THF (190 ml) y agua (125 ml). La suspensión blanca espesa se agitó durante 2 h y se filtró. El filtrado se extrajo con EtOAc (1 l). La capa orgánica se lavó sucesivamente con salmuera, $Na_2S_2O_3$ 1N, y con salmuera (cada 150 ml) y se concentró hasta un aceite naranja (25,3 g). El aceite se diluyó con *terc*-butanol (400 ml) y 2-metil-2-butano (100 ml) y se enfrió en un baño de hielo. La mezcla se trató con cloruro de sodio (68 g, 0,76 mol), y se añadió una solución de NaH_2PO_4 (68 g, 0,49 mol) en agua (250 ml) durante 5 min. Después de 15 min, el baño de hielo se retiró. La mezcla se agitó durante 2 h y se repartió entre EtOAc (1 l) y agua (125 ml). La capa orgánica se lavó con $Na_2S_2O_3$ 1N (125 ml) y con salmuera (125 ml), se secó (NaSO4), y se concentró para dar el compuesto del título en forma de un sólido castaño (31,4 g, 119%). Este material se usó en reacciones posteriores sin purificación adicional.



Se combinaron éster metílico del ácido 3-(4-benciloxi-3-carboximetil-fenil)-propiónico (80,5 mmol), cloruro de amonio (7,75 g, 145 mmol), EDC (27,7 g, 144 mmol), y *N*-hidroxibenzotriazol hidrato (19,6 g, 145 mmol) en un matraz y se diluyó con DMF (320 ml). Se añadió etil-diisopropil-amina (51 ml, 293 mmol). La solución se agitó durante 20 h y se repartió entre EtOAc (1,2 l) y HCl 1 N (250 ml). La capa orgánica se lavó con una solución saturada de $NaHCO_3$ (200 ml) y con salmuera (200 ml), se secó (NaSO4), y se concentró. El producto bruto se suspendió con etil éter y se filtró para dar el compuesto del título (15,9 g, 60%).

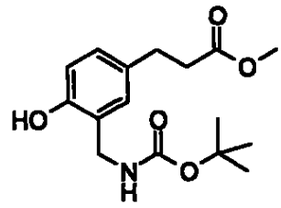
Etapa C: Ester metílico del ácido 3-[4-benciloxi-3-(terc-butoxicarbonilamino-metil)-fenil]-propiónico



Se disolvió éster metílico del ácido 3-(4-benciloxi-3-carbamoilmetil-fenil)-propiónico (15,9 g, 48,6 mmol) en CH_3CN (850 ml) y DMF (8 ml) con

calentamiento. Se añadió agua, la solución se enfrió a temperatura ambiente, y se añadió [bis(trifluoroacetoxi)yodo]benceno (31,32 g, 72,8 mmol). Después de 30 min, se añadió piridina (8,2 ml), y la solución se agitó durante 17 h. Se añadieron trietilamina (28 ml, 200 mmol) y di-terc-butilo dicarbonato (16,0 g, 73,3 mmol). La mezcla se agitó durante 2,5 h y se concentró. El residuo se repartió entre EtOAc (1 l) y salmuera (150 ml). La capa orgánica se lavó con HCl 1N enfriado con hielo (150 ml), con una solución saturada de $NaHCO_3$ (150 ml) y con salmuera (100 ml); se secó ($NaSO_4$); y se concentró. El residuo se purificó por cromatografía en columna de gel de sílice (CH_2Cl_2/EtOAc 100/0 a 95/5) para dar un aceite amarillo (11,0 g, 57%).

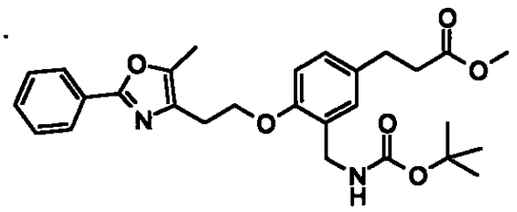
Etapa D: Éster metílico del ácido 3-[3-(terc-butoxicarbonilamino-metil)-4-hidroxi-fenil]-propiónico



Una solución de éster metílico del ácido 3-[4-benciloxi-3-(terc-butoxicarbonilamino-metil)-fenil]-propiónico (8,50 g, 21,3 mmol) en THF (100 ml) se trató con Pd-sobre-carbono al 5% (1,1 g) y agitando en una atmósfera de hidrógeno (60 psi) a temperatura ambiente durante 6 h. La mezcla se filtró a

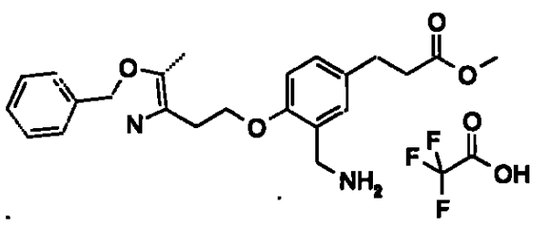
través de Celite y se concentró en forma de un sólido amarillo pálido (5,63 g, 85%).

Etapa E: Éster metílico del ácido 3-{3-(terc-butoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



Se suspendieron éster metílico del ácido 3-[3-(terc-Butoxicarbonilamino-metil)-4-hidroxi-fenil]-propiónico (5,50 g, 17,8 mmol), 2-(5-metil-2-fenil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (7,93 g, 22,2 mmol) y Cs_2CO_3 (7,23 g, 22,2 mmol) en DMF (40 ml) y se agitaron a 55°C durante 18 h. Adicionalmente se añadieron 2-(5-metil-2-fenil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (3,00 g, 8,39 mmol) y Cs_2CO_3 (2,73 g, 8,39 mmol) y se continuaron agitando durante 22 h. La mezcla de reacción se enfrió y se repartió entre EtOAc (125 ml) y agua (50 ml). La capa orgánica se lavó con salmuera (50 ml), se secó ($NaSO_4$), y se concentró. El residuo se purificó por cromatografía en columna de gel de sílice (CH_2Cl_2/EtOAc 97/3 a 80/20) para dar un producto puro (3,33 g, 38%) y un producto ligeramente impuro (7,08g).

Etapa F: Éster metílico del ácido 3-{3-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico: Sal del ácido trifluoroacético



Una solución de éster metílico del ácido 3-{3-(terc-butoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (3,33 g, 6,73 mmol) en CH_2Cl_2 (24 ml) se trató a temperatura ambiente con TFA (10 ml) y se agitó durante 3 h. La solución se concentró y co-evaporó con CCl_4 (3x) para producir el compuesto del título en forma de una espuma (4,13 g, cuantitativo)

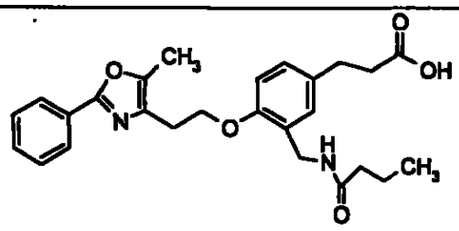
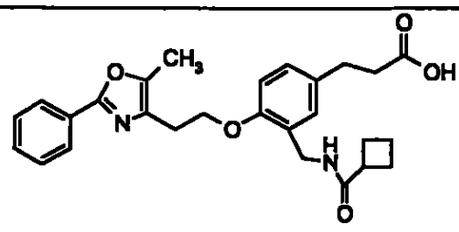
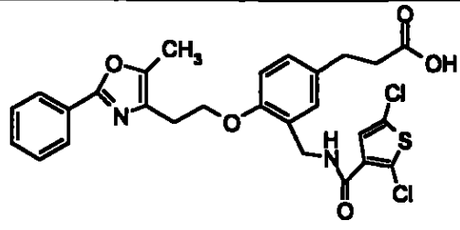
Etapa G: Ácido 3-{3-[[(2,5-dicloro-tiofeno-3-carbonil)-amino]-metil}-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

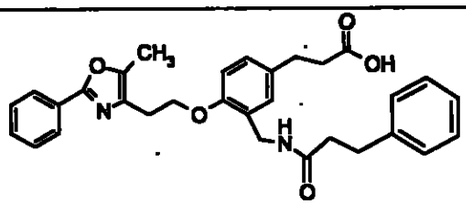
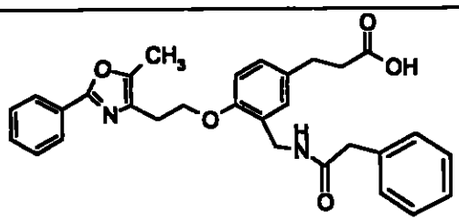
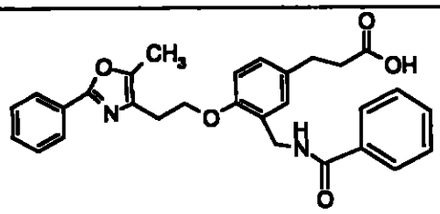
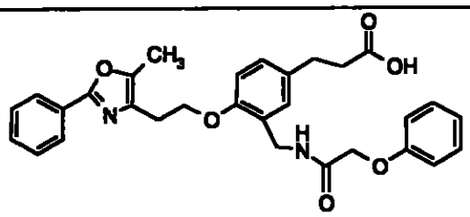
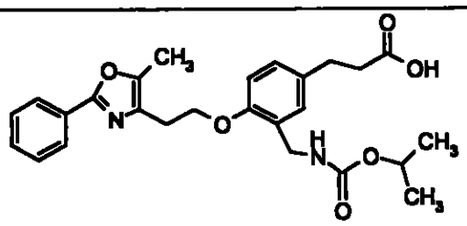
Procedimiento general de síntesis: Se disolvió éster metílico del ácido 3-{3-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico: sal del ácido trifluoroacético (565 mg, 1,1 mmol) en CH_2Cl_2 (25 ml) y se lavó con una solución saturada de $NaHCO_3$ (15 ml). La capa orgánica se secó ($NaSO_4$), se filtró, y se concentró a éster metílico del ácido 3-{3-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (368 mg, 0,93 mmol, 84%). Una porción de esta base libre (26 mg, 0,071 mmol) en CH_2Cl_2 (0,5 ml) se trató con trietilamina (0,075 ml, 0,54 mmol) después con cloruro de 2,5-dicloro-tiofeno-3-carbonilo (0,049 ml, 0,22 mmol). La mezcla de reacción se agitó durante una noche y se añadió *dimetiletilenodiamina* (0,15 ml, 1,4 mmol). La mezcla de reacción se agitó durante 2 h y se pasó a través de una columna SCX (1g, equilibrado con 2 ml MeOH después 2 ml MeOH/CH_2Cl_2 1/1). El producto de metil éster-amida se eluyó con MeOH/CH_2Cl_2 (1:1, 10 ml) y se concentró. El residuo se disolvió en THF (2 ml) y MeOH (2 ml) y se trató con NaOH 5 N (1 ml). La solución se calentó a 55°C durante 2,5 h, se enfrió, y se acidificó con HCl 5 N (1,5 ml). La mezcla se transfirió a un cartucho ChemElute y se eluyó con CH_2Cl_2. El disolvente se retiró en una atmósfera de N_2. El producto bruto

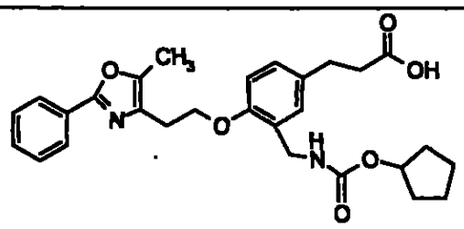
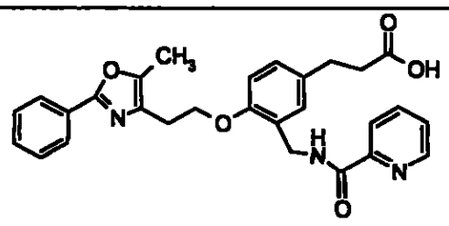
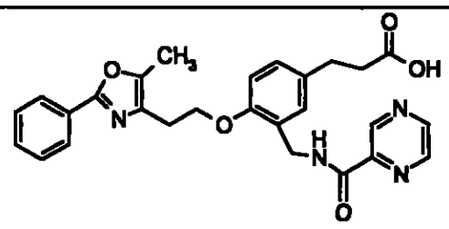
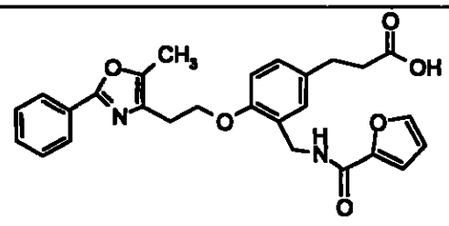
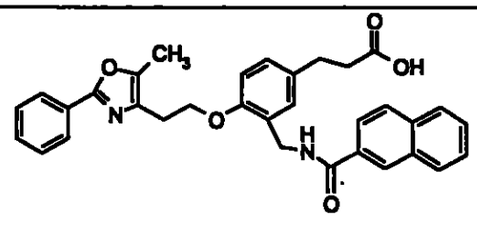
se secó al vacío y se purificó por HPLC de masa dirigida para dar el compuesto del título en forma de una espuma (9,9 mg, 26%). MS (ESI) m/z 559,1 $(M+H)^+$.

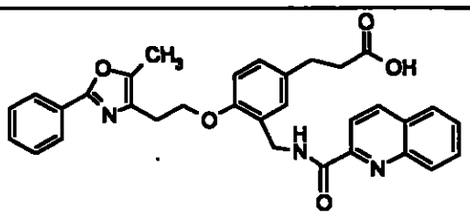
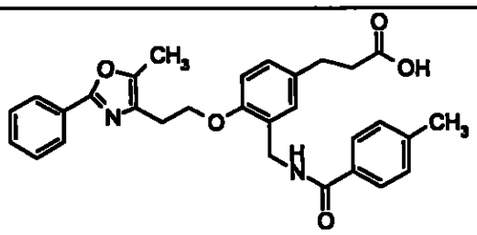
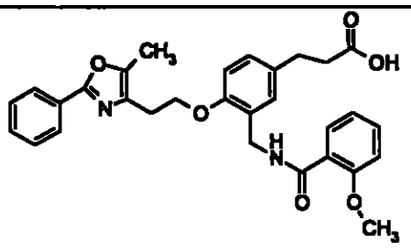
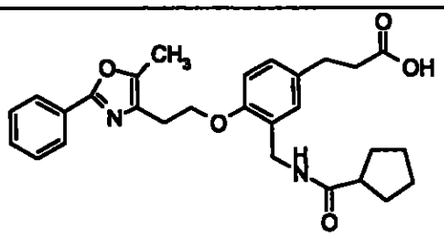
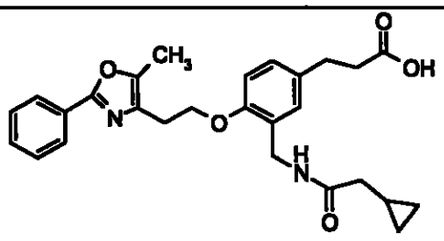
Ejemplos 511-543

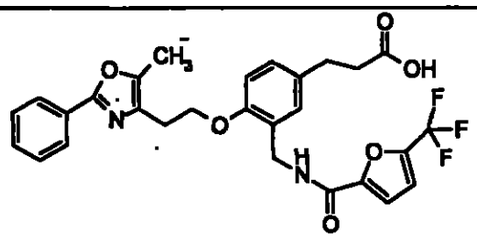
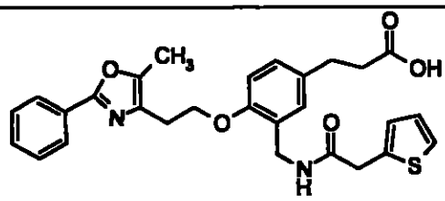
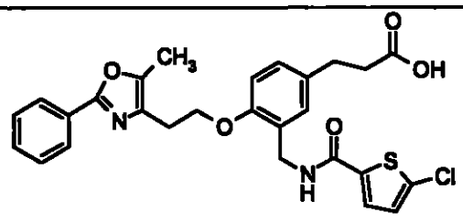
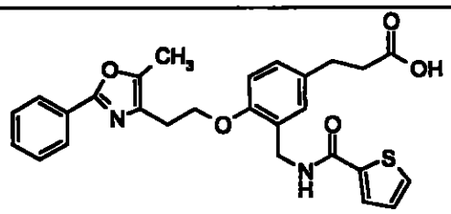
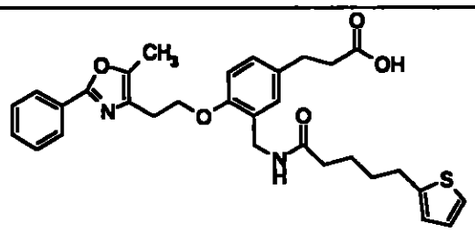
Ejemplos 511 a 543 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 510.

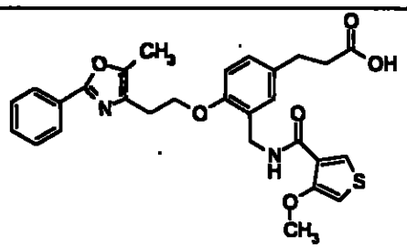
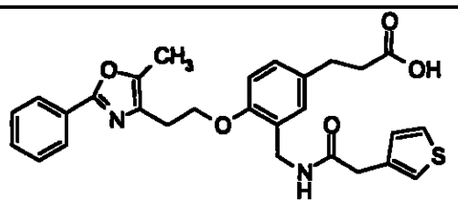
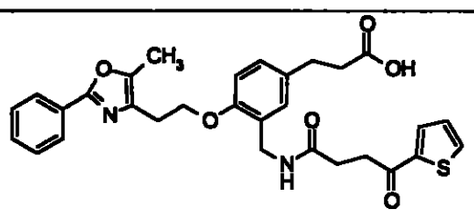
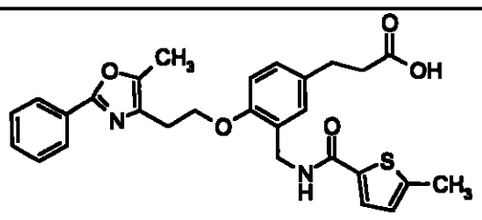
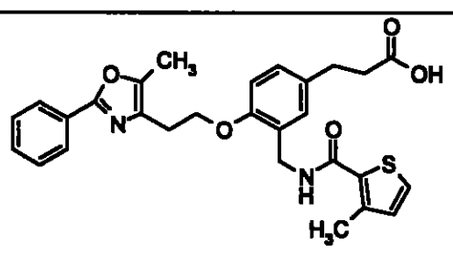
No.	Compuestos	MS (ES+)
511		541,3
512		463,3
513		559,1

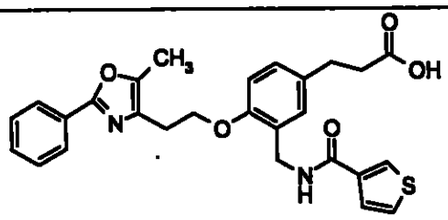
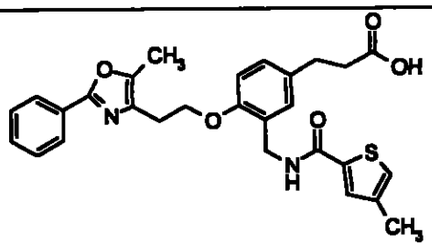
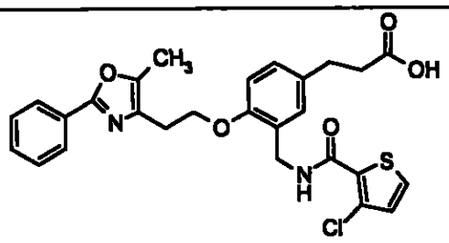
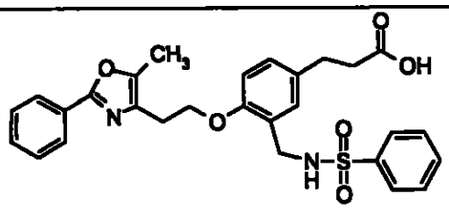
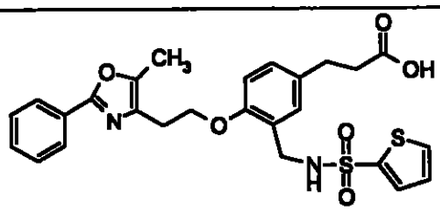
No.	Compuestos	MS (ES+)
514		513,3
515		499,3
516		485,3
517		515,3
518		481,3

No.	Compuestos	MS (ES+)
519		493,3
520		486,2
521		487,2
522		475,2
523		535,2

No.	Compuestos	MS (ES+)
524		536,2
525		499,2
526		515,2
527		477,3
528		463,3

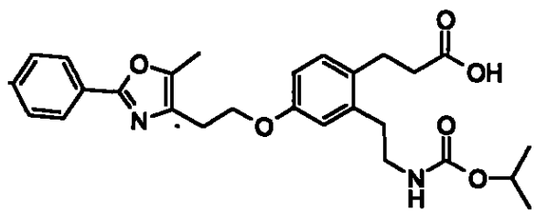
No.	Compuestos	MS (ES+)
529		543,2
530		505,3
531		525,2
532		491,2
533		547,3

No.	Compuestos	MS (ES+)
534		521,3
535		505,3
536		547,3
537		505,3
538		505,3

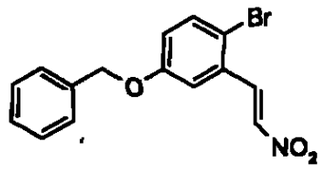
No.	Compuestos	MS (ES+)
539		491,3
540		505,3
541		525,2
542		521,2
543		527,1

Ejemplo 544

Ácido 3-{2-(2-isopropoxicarbonilamino-etil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



Etapa A: 5-Benciloxi-2-bromo-(2-nitrovinil)benceno



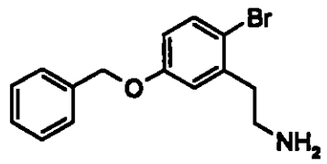
Una solución de 2-bromo-5-hidroxi-benzaldehído (5,99 g, 29,8 mmol, Preparación 13 Etapa A) en DMF (50 ml) se trató con bromuro de bencilo (7,65 g, 44,7 mmol) y Cs_2CO_3 (15,1 g, 44,7 mmol). La mezcla resultante se calentó a 80°C durante 60 min y se inactivó con agua (200 ml). La mezcla se extrajo con EtOAc (2 x 100 ml), se secó (Na_2SO_4), y se concentró para dar un residuo, que se purificó por cromatografía en gel de sílice (hexanos/EtOAc 9/1) para producir 5-benciloxi-2-bromo-benzaldehído en forma de un sólido blanco con un rendimiento cuantitativo.

Una solución de nitrometano (2,02 ml, 37,3 mmol) en etanol (10 ml) se trató con NaOH 10N (3,0 ml) a temperatura ambiente. Se precipitó inmediatamente un sólido blanco, y se añadió una solución de 5-benciloxi-2-bromo-benzaldehído (8,67 g, 29,8 mmol) en CH_2Cl_2 (50 ml). La mezcla de reacción se agitó durante 18 h y se inactivó con agua (100 ml). La mezcla se extrajo con CH_2Cl_2 (2 x 50 ml), se secó (Na_2SO_4), y se concentró para dar un

residuo, que después se purificó por cromatografía en gel de sílice (hexanos/EtOAc 8/2) para producir 1-(5-benciloxi-2-bromo-fenil)-2-nitro-etanol en forma de un aceite amarillo.

Este intermedio se disolvió en CH_2Cl_2 (150 ml) y se enfrió a 0°C. Se añadió cloruro de metanosulfonilo (2,55 ml, 60,0 mmol), y la mezcla se agitó durante 15 min. Se añadió trietilamina (8,41 ml), y la mezcla se agitó durante 60 min. La reacción se interrumpió con agua (200 ml) y se extrajo con CH_2Cl_2 (150 ml). La capa orgánica se secó (Na_2SO_4) y se concentró. El residuo se purificó por cromatografía en gel de sílice (hexanos/EtOAc 8/2) para producir el compuesto del título (8,60 g, 86%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 5,04 (s, 2 H), 6,93 (dd, 1H, *J* = 2,7 Hz, 9,0 Hz), 7,11 (d, 1H, *J* = 3,2 Hz), 7,34-7,37 (m, 5H), 7,48 (d, 1H, *J* = 13,7 Hz), 7,51 (d, 1H, *J* = 9,0 Hz), 8,28 (d, 1H, *J* = 13,7 Hz).

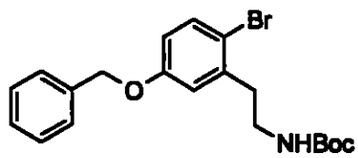
Etapa B: 2-(5-Benciloxi-2-bromo-fenil)-etilamina



A una solución de 5-benciloxi-2-bromo-(2-nitrovinil)benceno (8,60 g, 25,6 mmol) en THF (100 ml) a -78°C se le añadió LAH (4,1 g, 102 mmol) por porciones durante 30 min. La mezcla de reacción se dejó calentar gradualmente a temperatura ambiente. Después de 18 h, la mezcla se inactivó cuidadosamente con agua (4 ml), NaOH 2 N (4 ml), y agua (12 ml) sucesivamente. La suspensión se filtró y se precipitó, se lavó con CH_2Cl_2 (3 x 150 ml), se secó (Na_2SO_4), y se concentró. El residuo se purificó por cromatografía en gel de sílice (EtOAc, después CH_2Cl_2/MeOH/NH_4OH 10/1/0,01) para producir el compuesto del título en forma de un aceite (3,36 g,

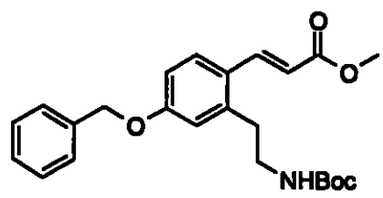
43%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 2,84 (t, 2H, *J* = 6,7 Hz), 2,96 (t, 2H, *J* = 6,7 Hz), 5,03 (s, 2 H), 6,71 (dd, 1H, *J* = 2,7 Hz, 8,6 Hz), 6,86 (d, 1H, *J* = 2,4 Hz), 7,33-7,43 (m, 6H).

Etapa C: Éster terc-butílico del ácido 2-(5-benciloxi-2-bromo-fenil)-etil]-carbámico



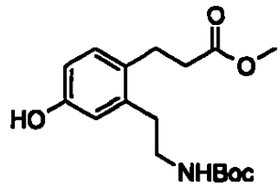
Una solución de 2-(5-benciloxi-2-bromo-fenil)-etilamina (3,36 g, 10,97 mmol) en CH_2Cl_2 (50ml) a 0°C se trató con Et_3N (3,08 ml, 21,9 mmol) y dicarbonato de di-*terc*-butilo (2,87 g, 13,2 mmol). La mezcla se agitó durante 2 h, mientras se dejaba calentar gradualmente a temperatura ambiente y se concentró. El residuo se purificó por cromatografía en gel de sílice (EtOAc/hexanos, 65:35) para producir el compuesto del título en forma de un aceite (4,45 g, 100%). ^{1}H RMN (400 MHz, $CDCl_3$): δ 1,44 (s, 9H), 2,90 (t, 2H, *J* = 6,7 Hz), 3,39 (dt, 2H, *J* = 6,3 Hz, 6,7 Hz), 5,02 (s, 2 H), 6,72 (dd, 1H, *J* = 3,1 Hz, 8,6 Hz), 6,87 (s a, 1H), 7,33-7,43 (m, 6H).

Etapa D: Éster metílico del ácido 3-[4-benciloxi-2-(2-terc-butoxicarbonilamino-etil)-fenil]-acrílico



Una solución de éster terc-butílico del ácido 2-(5-benciloxi-2-bromo-fenil)-etil]-carbámico (4,40 g, 10,8 mmol) en propionitrilo (100 ml) se desgasificó (vacío/ purga con Ar, 3x). Se añadieron *tri-orto*-tolilfosfina (0,660 g, 2,17 mmol), acrilato de metilo (2,93 ml, 32,5 mmol), y diisopropiletil amina (3,76 ml, 21,6 mmol). La mezcla se desgasificó (vacío/ purga con Ar, 3x). Se añadió $Pd(OAc)_2$ (242 mg, 1,08 mmol), y la mezcla de reacción se desgasificó de nuevo. La mezcla se agitó a 95 °C durante 18 h y se concentró para dar un residuo, que se purificó por cromatografía en gel de sílice (EtOAc/hexanos, 7/3) para producir el compuesto del título (4,15 g, 93%). ^{1}H RMN (400 MHz, $CDCl_3$) (isómero principal): δ 1,43 (s, 9H), 2,94 (t, 2H, *J* = 6,8 Hz), 3,33 (dt, 2H, *J* = 6,3 Hz, 6,8 Hz), 3,79 (s, 3 H), 5,08 (s, 2 H), 6,28 (d, 1H, *J* = 15,6 Hz), 6,84 (s a, 1 H), 6,86 (d, 1H, *J* = 8,3 Hz), 7,34-7,43 (m, 5 H), 7,55 (d, 1H, *J* = 8,3 Hz), 7,91 (d, 1H, *J* = 15,6 Hz).

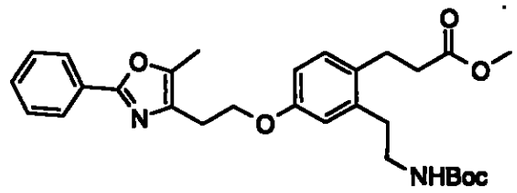
Etapa E: Éster metílico del ácido 3-[2-(2-terc-butoxicarbonilamino-etil)-4-hidroxi-fenil]-propiónico



A una solución de éster metílico del ácido 3-[4-benciloxi-2-(2-terc-butoxicarbonilamino-etil)-fenil]-acrílico (4,15 g, 10,1 mmol) en THF (100 ml) y MeOH (10 ml) se le añadió Pd-C al 5% (200 mg) en THF (10 ml). La suspensión resultante se trató con hidrógeno en una presión de globo durante 18 h. La mezcla se filtró a través de una capa de celite y se concentró. El residuo se purificó por cromatografía en gel de sílice (EtOAc/hexanos, 6/4) para producir el compuesto del título (1,20 g, 34%). ^{1}H RMN (400 MHz, $CDCl_3$): δ

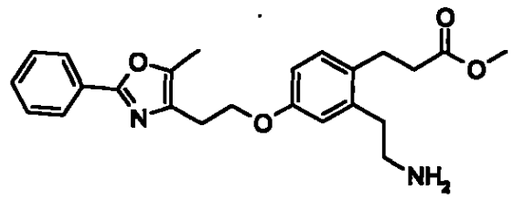
1,44 (s, 9H), 2,57 (t, 2H, *J* = 7,8 Hz), 2,77 (t, 2H, *J* = 7,3 Hz), 2,88 (t, 2H, *J* = 7,8 Hz), 3,33 (s a, 2H), 3,68 (s, 3 H), 6,65 (s a, 1 H), 6,67 (d, 1H, *J* = 8,3 Hz), 7,02 (d, 1H, *J* = 8,3 Hz). MS (ES^+) m/z 324,1 $[M+H]^+$.

Etapa F: Éster metílico del ácido 3-{2-(2-terc-butoxicarbonilamino-etil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



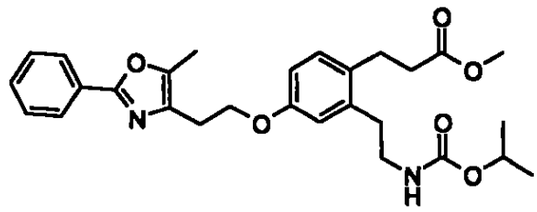
A una solución de éster metílico del ácido 3-[2-(2-terc-butoxicarbonilamino-etil)-4-hidroxi-fenil]-propiónico (0,807 g, 2,50 mmol) y 2-(5-metil-2-fenil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (1,34 g, 3,74 mmol) en DMF (5 ml) se le añadió Cs_2CO_3 (1,22 g, 3,74 mmol). La suspension se agitó a 65°C durante 48 h, se inactivó con H_2O (200 ml), y se extrajo con EtOAc (3 x 100 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentró para dar un residuo, que se purificó por cromatografía en gel de sílice (hexanos/EtOAc 9/1 a 8/2 a 6/4) para producir el compuesto del título en forma de un aceite incoloro (0,90 g, 71%). ^1H RMN (400 MHz, $CDCl_3$): d1,42 (s, 9H), 2,37 (s, 3H), 2,54 (t, 2H, *J* = 7,8 Hz), 2,77 (t, 2H, *J* = 7,8 Hz), 2,88 (t, 2H, *J* = 6,8 Hz), 2,96 (t, 2H, *J* = 6,8 Hz), 3,33 (~dt, 2H, *J* = 6,8 Hz), 3,65 (s, 3 H), 4,20 (t, 2H, *J* = 6,8 Hz), 6,70 (s a, 1 H), 6,72 (d, 1H, *J* = 8,3 Hz), 7,05 (d, 1H, *J* = 8,3 Hz), 7,39-7,44 (m, 3H), 7,95-7,98 (m, 2H). MS (ES^+) m/z $[M+H]^+$.

Etapa G: Éster metílico del ácido 3-{2-(2-Amino-etil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



Una solución de éster metílico del ácido 3-{2-(2-terc-butoxicarbonilamino-etil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico (0,90 g, 1,77 mmol) en CH_2Cl_2 (10ml) a 0°C se trató con TFA (5,0 ml) y agua (0,2 ml). La solución resultante se dejó calentar gradualmente a temperatura ambiente. Después de 18 h, la mezcla se concentró. El residuo se repartió entre CH_2Cl_2 (30ml) y NaOH 5 N (2 ml), y la capa acuosa se extrajo con CH_2Cl_2 (3 x 30ml). Los extractos orgánicos combinados se secaron (K_2CO_3) y se concentró para dar un residuo, que se purificó por cromatografía en gel de sílice (CH_2Cl_2 /MeOH/NH_4OH, 8/2/0,05) para producir el compuesto del título en forma de un aceite incoloro (0,42 g, 58%). ^1H RMN (400 MHz, $CDCl_3$): d2,34 (s, 3H), 2,52 (t, 2H, *J* = 7,8 Hz), 2,81 (t, 2H, *J* = 7,8 Hz), 2,91 (t, 4H, *J* = 6,4 Hz), 3,06 (t, 2H, *J* = 7,3 Hz), 3,60 (s, 3 H), 4,20 (t, 2H, *J* = 6,8 Hz), 6,68 (s a, 1 H), 6,71 (d, 1H, *J* = 8,3 Hz), 7,01 (d, 1H, *J* = 8,3 Hz), 7,37-7,39 (m, 3H), 7,89-7,92 (m, 2H).

Etapa H: Ácido 3-{2-(2-isopropoxicarbonilamino-etil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



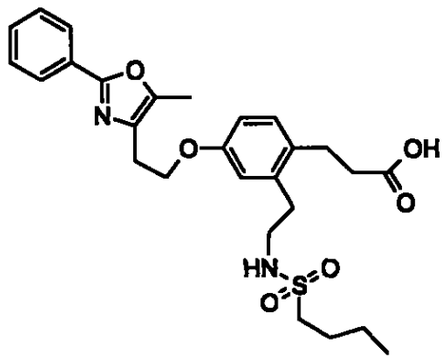
Una solución de éster metílico del ácido 3-[2-(2-amino-etil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil]-propiónico (26 mg, 0,064 mmol) en CH_2Cl_2 (2 ml) a 0 °C se trató con TEA (0,2 ml) y cloroformiato de isopropilo (0,13 ml, 1,0 M en éter). La mezcla resultante se dejó calentar gradualmente a temperatura ambiente. Después de 2 h, la mezcla se concentró para dar un residuo, que se purificó por cromatografía en gel de sílice (hexanos/EtOAc 7/3) para producir el isopropilo carbamato en forma de un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$): d1,19 (d, 6H, *J* = 5,9 Hz), 2,42 (s, 3H), 2,54 (t, 2H, *J* = 7,8 Hz), 2,79 (t, 2H, *J* = 6,8 Hz), 2,89 (t, 2H, *J* = 7,8 Hz), 3,05 (s a, 2H), 3,38 (s a, 2H), 3,60 (s, 3 H), 4,26 (t, 2H, *J* = 6,8 Hz), 4,68 (s a, 1H), 4,89 (q, 1H, *J* = 6,4 Hz), 6,70 (s a, 1 H), 6,71 (d, 1H, *J* = 8,3 Hz), 7,05 (d, 1H, *J* = 8,3 Hz), 7,47 (m, 3H), 8,10 (m, 2H).

Este compuesto se disolvió en THF (1,0 ml) y MeOH (0,5 ml). La solución se trató con NaOH 2 N (0,32 ml) y se calentó a 60 °C durante 60 min. La mezcla de reacción se concentró, se neutralizó con 2N HCl (0,40 ml), y se extrajo con EtOAc (3 x 5 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentró para dar un residuo, que se purificó por cromatografía en gel de sílice (hexanos/EtOAc 9/1, después EtOAc/MeOH 95/5) para producir el compuesto del título en forma de un sólido blanco (12 mg, 32% en dos etapas). ^{1}H RMN (400 MHz, $CDCl_3$): d1,17 (d, 6H, *J* = 5,9 Hz), 2,36 (s, 3H), 2,52 (s a, 2H), 2,79 (t, 2H, *J* = 6,8 Hz), 2,89 (t, 2H, *J* = 7,8 Hz), 2,93 (t, 2H, *J* = 6,8 Hz), 3,31 (s a, 2H), 4,16 (t, 2H, *J* = 6,8 Hz), 4,68 (s a, 1H), 4,89 (q, 1H, *J* = 6,4 Hz), 6,67 (s a, 1 H), 6,71 (d, 1H, *J* = 8,3 Hz), 7,05 (d, 1H, *J* = 8,3 Hz), 7,47 (m, 3H), 8,10 (m, 2H). MS [ES] m/z 481,4 (M+1).

Los siguientes Ejemplos 545 a 552 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 544.

Ejemplo 545

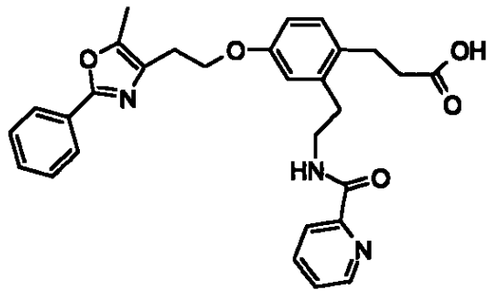
Ácido 3-{2-[2-(butano-1-sulfonilamino)-etil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



MS [ES] m/z 515,3 (M+1).

Ejemplo 546

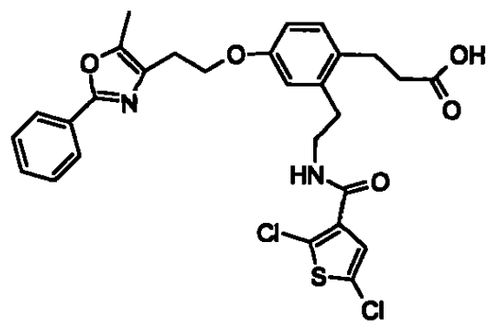
Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{2-[(piridina-2-carbonil)-amino]-etil}-fenil)-propiónico



MS [ES] m/z 500,3 (M+1).

Ejemplo 547

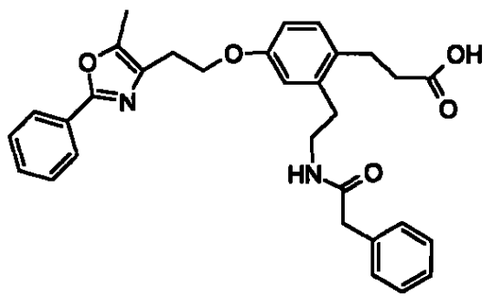
Ácido 3-{2-{2-[(2,5-dicloro-tiofeno-3-carbonil)-amino]-etil}-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



MS [ES-] m/z 573,0(M-1).

Ejemplo 548

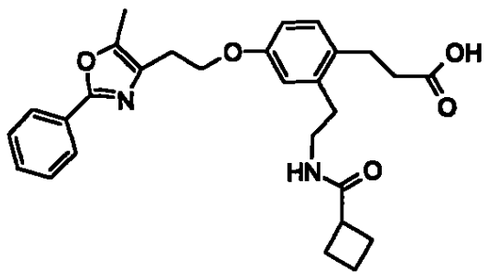
Ácido 3-[4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-(2-fenilacetilamino-etil)-fenil]-propiónico



MS [ES] m/z 513,2 (M+1).

Ejemplo 549

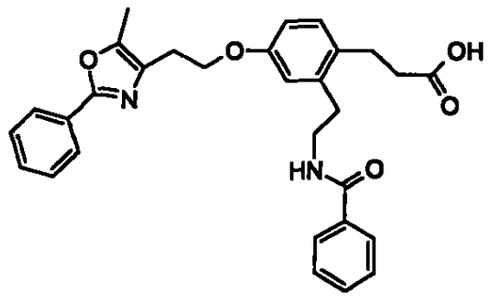
Ácido 3-{2-[2-(ciclobutanocarbonil-amino)-etil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



MS [ES] m/z 477,1 (M+1).

Ejemplo 550

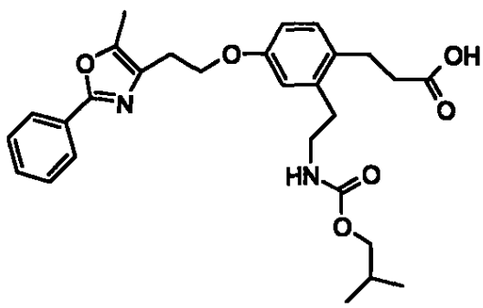
Ácido 3-{2-(2-benzoilamino-etil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



MS [ES] m/z 499,3 (M+1).

Ejemplo 551

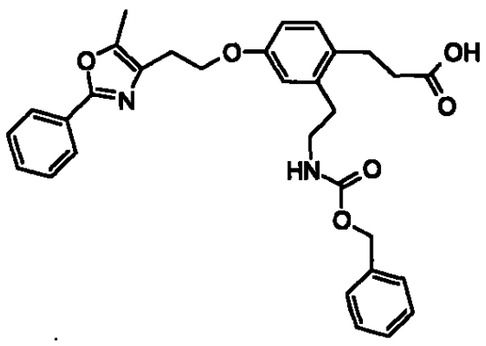
Ácido 3-{2-(2-isobutoxicarbonilamino-etil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



MS [ES] m/z 495,3 (M+1).

Ejemplo 552

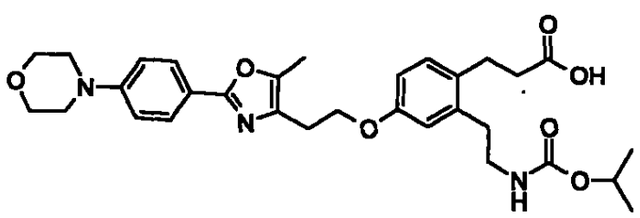
Ácido 3-{2-(2-benciloxicarbonilamino-etil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico



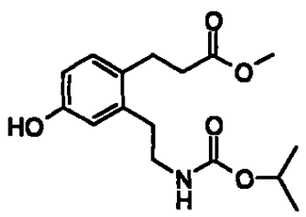
MS [ES] m/z 529,0 (M+1).

Ejemplo 553

Ácido 3-(2-(2-isopropoxicarbonilamino-etil)-4-{2-[5-metil-2-(4-morfolin-4-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



Etapa A: Éster metílico del ácido 3-[4-Hidroxi-2-(2-isopropoxicarbonilamino-etil)-fenil]-propiónico



Una solución de éster metílico del ácido 3-[2-(2-terc-butoxicarbonilamino-etil)-4-hidroxi-fenil]-propiónico (282 mg, 0,876 mmol; Ejemplo 544, Etapa E) en CH_2Cl_2 (10 ml) a temperatura ambiente se trató con TFA (5,0 ml), se agitó durante 60 min, y se concentró. El residuo en CH_2Cl_2 (10 ml) se trató con trietilamina (2,0 ml) y cloroformiato de iso-propilo (0,97 ml, 1,0 M en tolueno). La mezcla de reacción se agitó a temperatura ambiente durante 16 h y se concentró. El material bruto se purificó usando cromatografía en gel de sílice (50% EtOAc/hexanos) para producir el compuesto del título (180 mg, 67%).

Etapa B: Ácido 3-(2-(2-Isopropoxicarbonilamino-etil)-4-{2-[5-metil-2-(4-morfolin-4-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico

Una solución de 2-[5-metil-2-(4-morfolin-4-il-fenil)-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico (44 mg, 0,10 mmol; Preparación 5) y éster metílico del ácido 3-[4-hidroxi-2-(2-isopropoxicarbonilamino-etil)-fenil]-propiónico (31 mg, 0,10 mmol) en DMF (1,0 ml) se trató con K_2CO_3 (30 mg). La suspensión resultante se agitó a 65 °C durante 16 h y se diluyó con agua (10 ml). La mezcla se extrajo con EtOAc (3 x 10 ml). Las capas orgánicas combinadas se secaron (Na_2SO_4), se concentró, y se purificó usando cromatografía en gel de sílice (50% EtOAc/hexanos para producir éster metílico del ácido 3-(2-(2-isopropoxicarbonilamino-etil)-4-{2-[5-metil-2-(4-morfolin-4-il-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico.

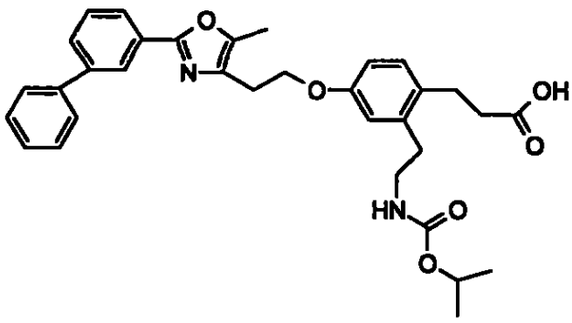
Este éster intermedio se disolvió en THF (0,6 ml) y MeOH (0,4 ml) y se trató con LiOH 2 M acuoso (1,0 ml, 2,0 mmol). La mezcla se agitó durante 16 h a temperatura ambiente, se neutralizó con HCl (1,0 ml, 2,0 M), y se concentró. El residuo se extrajo con EtOAc (3 x 5 ml). Las capas orgánicas combinadas se secaron (Na_2SO_4), se concentraron, y se purificaron usando cromatografía

en columna de gel de sílice (hexanos/EtOAc/HOAc, 5/5/0,02) para producir el compuesto del título (10 mg, 18%). MS (ES+) m/z 566,2 $(M+H)^+$.

Los siguientes Ejemplos 554 a 560 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 553.

Ejemplo 554

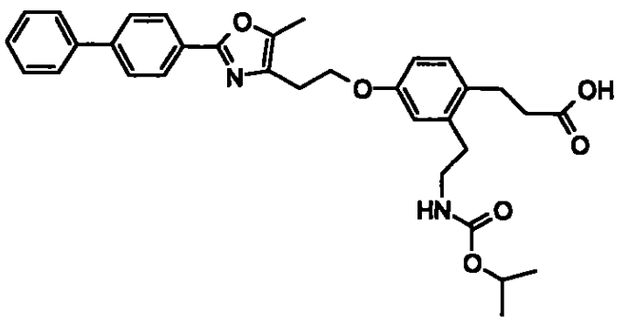
Ácido 3-[4-[2-(2-bifenil-3-il-5-metil-oxazol-4-il)-etoxi]-2-(2-isopropoxicarbonil-amino-etil)-fenil]-propiónico



MS [ES] m/z 557,5 (M+1).

Ejemplo 555

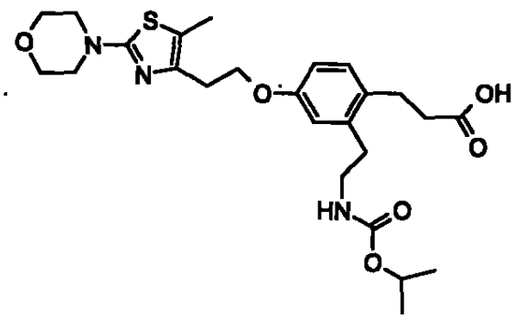
Ácido 3-[4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-(2-isopropoxicarbonil-amino-etil)-fenil]-propiónico



MS [ES] m/z 557,2 (M+1).

Ejemplo 556

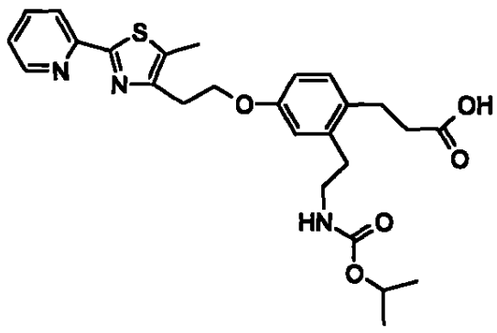
Ácido 3-{2-(2-isopropoxicarbonil-amino-etil)-4-[2-(5-metil-2-morfolin-4-il-tiazol-4-il)-etoxi]-fenil}-propiónico



MS [ES] m/z 506,2 (M+1).

Ejemplo 557

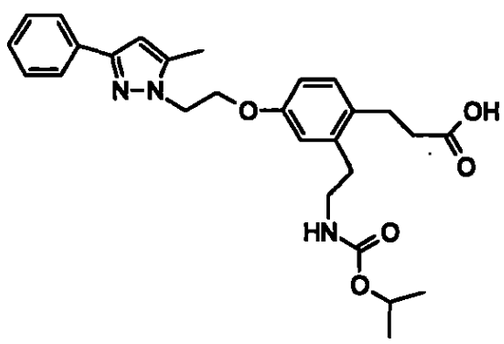
Ácido 3-{2-(2-isopropoxicarbonilamino-etil)-4-[2-(5-metil-2-piridin-2-il-tiazol-4-il)-etoxi]-fenil}-propiónico



MS [ES] m/z 498,3 (M+1).

Ejemplo 558

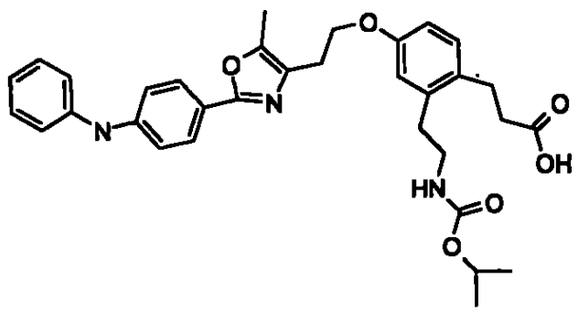
Ácido 3-{2-(2-isopropoxicarbonilamino-etil)-4-[2-(5-metil-3-fenil-pirazol-1-il)-etoxi]-fenil}-propiónico



MS [ES] m/z 480,3 (M+1).

Ejemplo 559

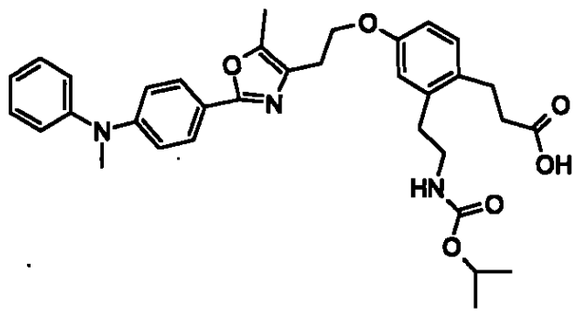
Ácido 3-(2-(2-isopropoxicarbonilamino-etil)-4-{2-[5-metil-2-(4-fenilamino-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico



MS [ES] m/z 572,2 (M+1).

Ejemplo 560

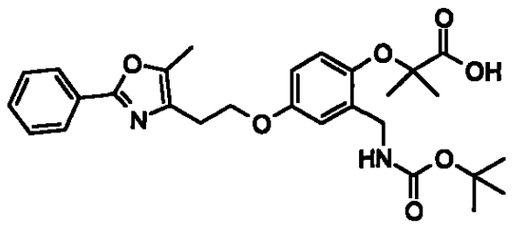
Ácido 3-[2-(2-isopropoxicarbonilamino-etil)-4-(2-{5-metil-2-[4-(metil-fenil-amino)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico



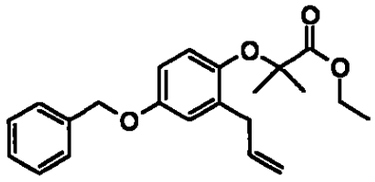
MS [ES] m/z 586,2 (M+1).

Ejemplo 561

Ácido 2-{2-(terc-butoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico



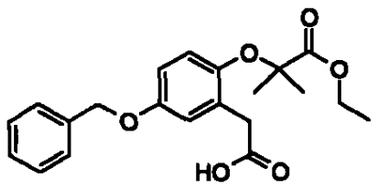
Etapa A: Etil éster del ácido 2-(2-alil-4-benciloxi-fenoxi)-2-metil-propiónico



Se enfrió 2-alil-4-benciloxi-fenol (WO 9728137 A1 19970807, Adams et al.) (6,04 g, 25,1 mmol) en DMF seca (75 ml) en un baño de hielo y se trató con NaH (1,78 g, 44,5 mmol, dispersión en aceite al 60%). Después de 30 min, la mezcla de reacción se trató durante 5 min con bromoisobutirato de etilo (7,4 ml, 50 mmol). El baño frío se retiró después de 5 min. La reacción se agitó 20 min y se puso un baño de aceite (T=85°C). Después de 18 h, la mezcla se enfrió y

se repartió entre salmuera (75 ml) y éter (200 ml). La capa orgánica se lavó con salmuera (50 ml), se secó (Na_2SO_4), y se concentró hasta un aceite pardo (12g). El *producto* bruto se purificó por cromatografía rápida usando hexanos:acetato de etilo (100:0 a 5:1) para dar el producto deseado (8,47 g, 95%).

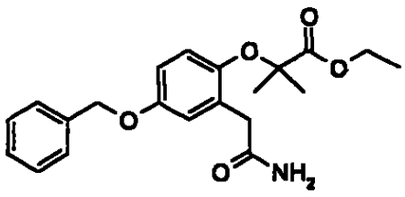
Etapa B: Etil éster del ácido 2-(4-benciloxi-2-carboximetil-fenoxi)-2-metil-propiónico



Una solución de etil éster del ácido 2-(2-alil-4-benciloxi-fenoxi)-2-metil-propiónico (8,07 g, 22,8 mmol) en acetona (85 ml) y agua (8,5 ml) se trató con 4-metil-morfolina 4-óxido (3,68 g, 27,2 mmol) después óxido de osmio (IV) (2 trozos). El matraz se cubrió con una lámina y se agitó 5 h. La solución se diluyó con EtOAc (600 ml) y se lavó con 1N $Na_2S_2O_3$ (2 x 75 ml) y salmuera (75 ml). La capa orgánica se concentró para dar un aceite (8,74 g). El aceite se disolvió en THF (54 ml) y agua (36 ml), y se añadió peryodato de sodio (15,4 g, 72,0 mmol). Se añadió THF (54 ml) y agua (36 ml). La suspensión blanca espesa se agitó durante 3 h y se filtró. El filtrado se extrajo con EtOAc (500 ml). La capa orgánica se lavó sucesivamente con salmuera, 1N $Na_2S_2O_3$, y salmuera (75 ml cada) y se concentró hasta un aceite naranja (7,65 g). El aceite se diluyó con *terc*-butanol (180 ml) y 2-metil-2-butano (60 ml) y se enfrió en un baño de hielo. La mezcla se trató con cloruro de sodio (19 g, 0,21 mol), y se añadió una solución de NaH_2PO_4 (19 g, 0,14 mol) en agua (120 ml) durante 5 min. Después de 15 min, el baño de hielo se retiró. La mezcla se agitó

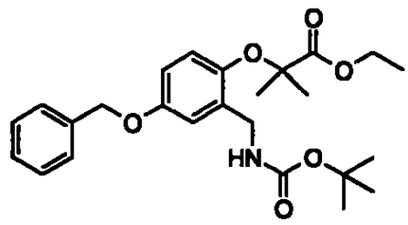
durante 2 h y se repartió entre EtOAc (500 ml) y agua (50 ml). La capa orgánica se lavó con $Na_2S_2O_3$ 1N (75 ml) y salmuera (75 ml), se secó (NaSO4), y se concentró para dar el compuesto del título en forma de un sólido amarillo pálido (6,52 g, 77%). Este material se usó en reacciones posteriores sin purificación adicional.

Etapa C: Etil éster del ácido 2-(4-benciloxi-2-carbamoilmetil-fenoxi)-2-metil-propiónico



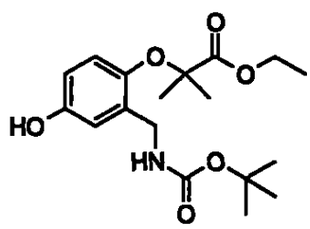
Se combinaron etil éster del ácido 2-(4-benciloxi-2-carboximetil-fenoxi)-2-metil-propiónico (500 mg, 1,34 mmol), cloruro de amonio (108 mg, 2,02 mmol), EDC (3,86 mg, 2,01 mmol), e hidrato de *N*-hidroxibenzotriazol (272 mg, 2,01 mmol) en un matraz y se diluyeron con DMF (5 ml). Se añadió etil diisopropil amina (0,70 ml, 4,0 mmol). La solución se agitó durante 18 h y se repartió entre EtOAc (25 ml) y HCl 1 N (10 ml). La capa orgánica se lavó con una solución saturada de $NaHCO_3$ (10 ml) después con salmuera (10 ml), se secó (Na_2SO_4), y se concentró. El producto bruto se purificó por cromatografía radial (hexanos/EtOAc 1/2 a 1/4) para dar el compuesto del título (430 mg, 86%).

Etapa D: Etil éster del ácido 2-[4-Benciloxi-2-(terc-butoxicarbonilamino-metil)-fenoxi]-2-metil-propiónico



Se disolvió etil éster del ácido 2-(4-benciloxi-2-carbamoilmetil-fenoxi)-2-metil-propiónico (430 mg, 1,16 mmol) en CH_3CN (4,5 ml) y agua (4,5 ml), y se añadió [bis(trifluoroacetoxi)yodo]benceno (745 mg, 1,73 mmol). Después de 10 min, se añadió piridina (0,19 ml, 2,3 mmol), y la solución se agitó durante 17 h. Se añadió trietilamina (0,60 ml, 4,3 mmol) y dicarbonato de di-terc-butilo (506 mg, 2,32 mmol). La mezcla se agitó durante 1 h y se concentró. El residuo se repartió entre éter (50 ml) y salmuera (15 ml). La capa orgánica se lavó con HCl 1 N enfriado con hielo, con una solución saturada de $NaHCO_3$, y salmuera (15 ml cada); se secó ($NaSO_4$); y se concentró. El residuo se purificó por cromatografía en columna de gel de sílice (hexanos/EtOAc 4/1 a 3/2) para dar un aceite amarillo (345 g, 67%).

Etapa E: Etil éster del ácido 2-[2-(terc-butoxicarbonilamino-metil)-4-hidroxi-fenoxi]-2-metil-propiónico



Una solución de etil éster del ácido 2-[4-benciloxi-2-(terc-butoxicarbonilamino-metil)-fenoxi]-2-metil-propiónico (0,38 g, 0,86 mmol) en

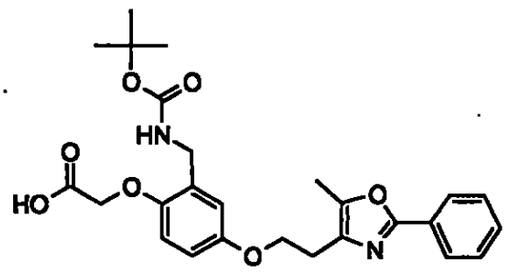
THF (15 ml) se trató con Pd-sobre-carbono al 5% (47 mg) y agitando en una atmósfera de hidrógeno (60 psi) a temperatura ambiente durante 18 h. La mezcla se filtró a través de Celite y se concentró. El producto bruto se purificó por cromatografía radial (hexanos/EtOAc 2,5/1) para dar el compuesto del título (208 mg g, 69%).

Etapa F: Ácido 2-{2-(terc-butoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico

Se suspendieron etil éster del ácido 2-[2-(terc-butoxicarbonilamino-metil)-4-hidroxi-fenoxi]-2-metil-propiónico (200 mg, 0,566 mmol), 2-(5-metil-2-fenil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (245 mg, 686 mmol) y Cs_2CO_3 (185 mg, 0,567 mmol) en DMF (5 ml) y se agitaron a 55°C durante 39 h. La mezcla de reacción se enfrió y se repartió entre Et_2O (50 ml) y agua (10 ml). La capa orgánica se lavó con salmuera (10 ml), se secó ($NaSO_4$), y se concentró. El residuo se purificó por cromatografía radial (hexanos/EtOAc 4/1) para dar un aceite (280 mg). Una solución del producto en MeOH (6 ml) y THF (3 ml) se trató con una solución acuosa de NaOH 2,5 N (2 ml) y se calentó a 55 °C durante 2 h. La mezcla se enfrió y se concentró. Se añadieron trozos de hielo (~5) y la mezcla se acidificó usando una solución acuosa de HCL 5N (2 ml). La mezcla de reacción se repartió entre EtOAc (30 ml) y salmuera (15 ml). La capa orgánica se lavó con salmuera (2 x 10 ml), se secó ($NaSO_4$), y se concentró. El residuo se purificó por cromatografía en columna de gel de sílice (hexanos/EtOAc/HOAc 3/2/0 a 3/2/0,05) para dar el compuesto del título en forma de una espuma blanca (156 mg, 54%). MS (ES^-) m/z 509,1 $[M-H]^-$. Anal. Calcd. durante $C_{28}H_{34}N_2O_7$: C: 65,88; H: 6,71; N: 5,49. Encontrado: C: 65,67; H: 6,79; N: 5,52.

Ejemplo 562

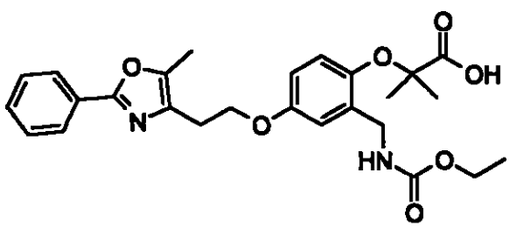
Ácido {2-(terc-butoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-acético



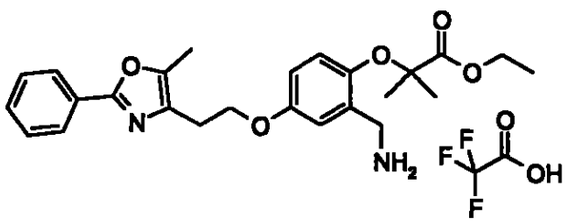
El compuesto anterior se prepara siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 561. MS [ES] m/z 483,2 (M+1).

Ejemplo 563

Ácido 2-{2-(etoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico



Etapa A: Etil éster del ácido 2-(2-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico: sal del ácido trifluoroacético



Una solución de etil éster del ácido 2-{2-(terc-butoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico (350 mg, 0,650 mmol) en CH_2Cl_2 (10 ml) se trató a temperatura ambiente con TFA (4 ml) y se agitó durante 2,5 h. La solución se concentró y co-evaporó con CCl_4 (3x) para producir el compuesto del título en forma de una espuma (381 mg, cuantitativo).

Etapa B: Ácido 2-{2-(etoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico

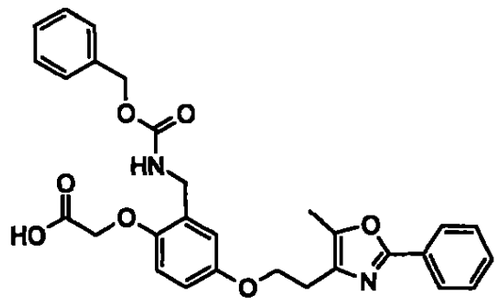
Procedimiento general de síntesis: Se disolvió etil éster del ácido 2-{2-Aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico: sal del ácido trifluoroacético (381 mg, 0,650 mmol max.) en CH_2Cl_2 (25 ml) y se lavó con una solución saturada de $NaHCO_3$ (15 ml). La capa orgánica se secó ($NaSO_4$), se filtró, y se concentró a etil éster del ácido 2-{2-aminometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico (245 mg, 0,59 mmol, 86%). Se trató una porción de esta base libre (13 mg, 0,030 mmol) en CH_2Cl_2 (0,8 ml) con trietilamina (0,050 ml, 0,36 mmol) después con cloroformitao de etilo (0,020 ml, 0,21 mmol). La mezcla de reacción se agitó durante una noche y se añadió dimetiletilenodiamina (0,050 ml, 0,47 mmol). La mezcla de reacción se agitó durante 2 h, se diluyó con MeOH (0,5 ml), y se pasó a través de una columna SCX (1g, equilibrada con 4 ml MeOH/CH_2Cl_2 1/1). El producto de metil éster-amida se eluyó con MeOH/CH_2Cl_2 (1:1, 8 ml) y se concentró. El residuo se disolvió en THF (1 ml) y EtOH (1 ml) y se trató con NaOH 2 N (0,5 ml). La solución se calentó a 45°C durante 45 min, se enfrió, se concentró, y se acidificó con HCl 1 N (2,5 ml). La mezcla se diluyó con CH_2Cl_2 (0,5 ml), se transfirió a un cartucho ChemElute 3-ml, y se eluyó con CH_2Cl_2 (8 ml). El

disolvente se retiró en una atmósfera de N_2. El producto bruto se secó al vacío y se purificó por HPLC de masa dirigida para dar una espuma (2,7 mg, 19%). %). MS (ES+) m/z 483,5 $[M+H]^+$.

Los siguientes Ejemplos 564 a 570 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 563.

Ejemplo 564

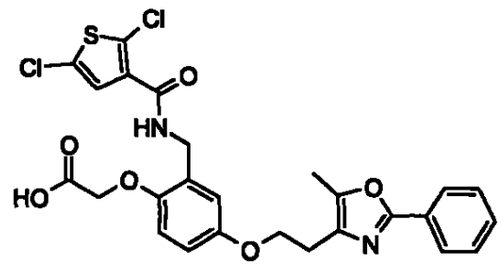
Ácido {2-(benciloxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-acético



MS [ES] m/z 517,2 (M+1).

Ejemplo 565

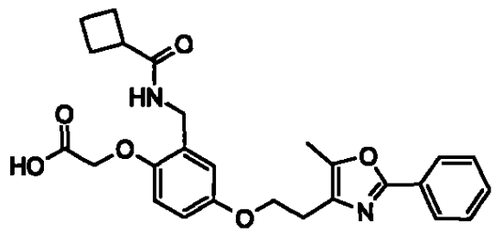
Ácido {2-{[(2,5-dicloro-tiofeno-3-carbonil)-amino]-metil}-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-acético



MS [ES] m/z 561,1 (M+1).

Ejemplo 566

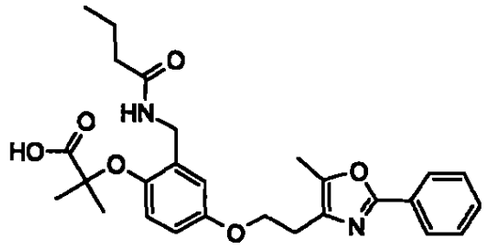
Ácido {2-[(ciclobutanocarbonil-amino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-acético



MS [ES] m/z 465,2 (M+1).

Ejemplo 567

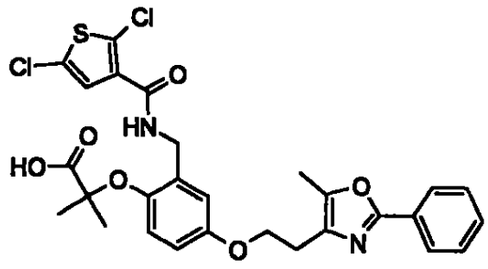
Ácido 2-{2-(butirilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico



MS [ES] 481 m/z (M+1).

Ejemplo 568

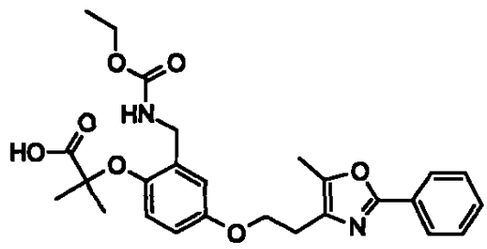
Ácido 2-{2-{[(2,5-dicloro-tiofeno-3-carbonil)-amino]-metil}-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico



MS [ES] m/z 481 (M+1).

Ejemplo 569

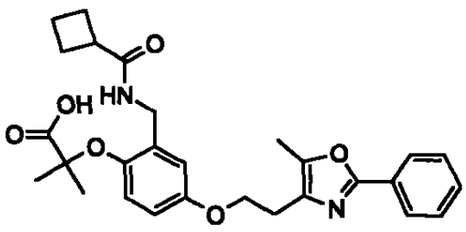
Ácido 2-{2-(etoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico



MS [ES] m/z 483 (M+1).

Ejemplo 570

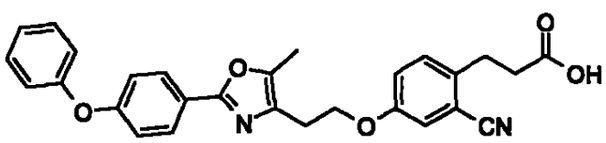
Ácido 2-{2-[(ciclobutanocarbonil-amino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico



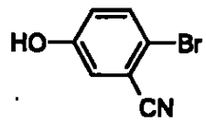
MS [ES] m/z 493 (M+1).

Ejemplo 571

Ácido 3-(2-ciano-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico

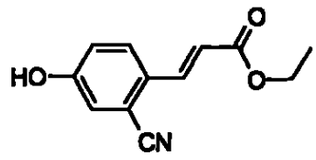


Etapa A: 2-Bromo-5-hidroxi-benzonitrilo



A una solución agitada de 3-cianofenol (2,00 g, 18,0 mmol) en acetonitrilo anhidro (20 ml) en una atmósfera de N_2 a -30°C se le añadió gota a gota $HBF_4.Et_2O$ al 54% (2,48 ml, 18,0 mmol). La temperatura se mantuvo por debajo de -20° C durante la adición. A esta solución agitada se le añadió en porciones NBS (3,27 g, 18,0 mmol) manteniendo la temperatura por debajo de -10°C. Después de completarse la adición, la solución se dejó calentar a 19°C. La mezcla de reacción se diluyó con 38% $NaHSO_3$ (10 ml) y se extrajo con MTBE (2 x 25 ml). La capa orgánica se lavó con H_2O (2 x 25 ml) y salmuera (25 ml), se secó ($MgSO_4$), se filtró, y se concentró para dar un sólido blanco (3,15 g). La purificación de una porción de este producto (1,0 g) por cromatografía radial (EtOAc al 30%/hexano) dio 0,51 g del compuesto del título en forma de un sólido blanco. p.f. 183-184°C. Anal. Calculado para C_7H_4BrNO: C, 42,46; H, 2,04; N, 7,07. Encontrado: C, 42,44; H, 1,93; N, 6,90,

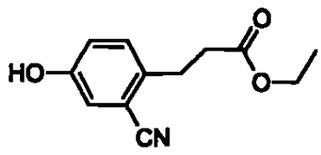
Etapa B: 2-(3-Etoxi-butan-1,3-dienil)-5-hidroxi-benzonitrilo



A una solución agitada de 2-bromo-5-hidroxi-benzonitrilo (1,4 g, 7,1 mmol), etil acrilato (2,12g, 21,2 mmol), acetato de paladio(II) (0,159 g, 7,0 mmol), diisopropiletilamina (0,82 g, 14,1 mmol), y tri-*orto*-tolilfosfina (0,430 g, 14,1 mmol) se le añadió propionitrilo (50 ml). La reacción se agitó durante una

noche a 80°C en una atmósfera de N_2. La mezcla se enfrió, se filtró, y se concentró. El material bruto (3,0 g) se purificó por cromatografía radial (EtOAc al 10-70%/hexanos) para dar el compuesto del título en forma de un sólido blanco (1,1 g). MS [EI] *m/z* 216 $(M+H)^+$.

Etapa C: 2-(3-Etoxi-but-3-enil)-5-hidroxi-benzonitrilo



A una solución de 2-(3-etoxi-butan-1,3-dienil)-5-hidroxi-benzonitrilo (600 mg) en EtOAc (50 ml) se le añadió Pd/C al 5% (0,3 g). La reacción se expuso a gas hidrógeno en un aparato Parr a 60 psi (413,68 kPa) durante una noche a temperatura ambiente. La mezcla de reacción se filtró y se concentró para dar el compuesto del título (410 mg). MS [EI] m/z 218 $(M+H)^+$.

Etapa D: Ácido 3-(2-ciano-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico

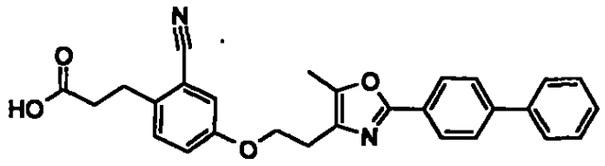
Una mezcla de 2-(3-etoxi-but-3-enil)-5-hidroxi-benzonitrilo (220 mg, 1,00 mmol), se agitó 2-[5-metil-2-(4-fenoxi-fenil)-oxazol-4-il]-etil éster del ácido tolueno-4-sulfónico (450 mg, 1,00 mmol; Preparación 6), y $CsCO_3$ (978 mg, 3,00 mmol) en DMF (10ml) durante una noche a 60°C en una atmósfera de N_2. La mezcla se enfrió, se diluyó con EtOAc (20 ml) y se lavó con salmuera (20 ml). La capa orgánica se secó (Na_2SO_4) y se concentró. La mezcla del producto se purificó por cromatografía radial (10-70% EtOAc/hexanos) para dar etil éster del ácido 3-(2-ciano-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico (201 mg). Una solución de este éster en EtOH (10 ml) y NaOH 5 N (10 ml) se calentó a 70°C durante una noche, se concentró, se acidificó con

HCl 1 N, y se extrajo con EtOAc. La capa orgánica se secó (Na_2SO_4) y se concentró para dar el compuesto del título (192 mg). MS [ES] m/z 469 (M+1).

Los siguientes Ejemplos 572 a 573 y 575 a 581 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 571.

Ejemplo 572

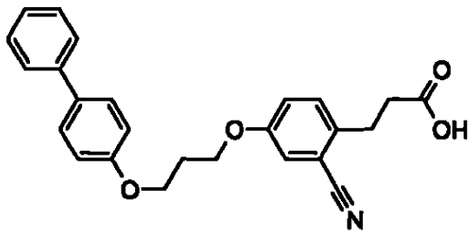
Ácido 3-{4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-cianofenil} propiónico:



MS [ES] m/z 453 (M+1).

Ejemplo 573

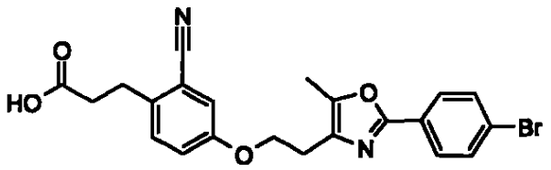
Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-cianofenil} propiónico



MS [ES] m/z 402 (M+1).

Ejemplo 575

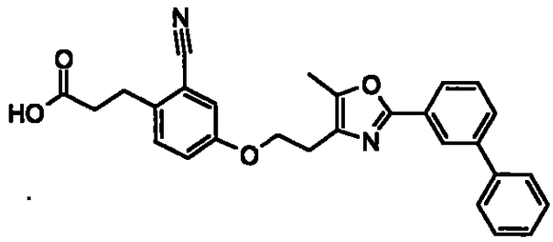
Ácido 3-(4-{2-[2-(4-bromo-fenil)-5-metiloxazol-4-il]etoxi}-2-cianofenil) propiónico



MS [ES] m/z 456 (M+1).

Ejemplo 576

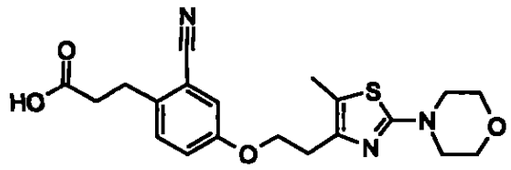
Ácido 3-{4-[2-(2-bifenil-3-il-5-metiloxazol-4-il)etoxi]-2-cianofenil} propiónico



MS [ES] m/z 453 (M+1).

Ejemplo 577

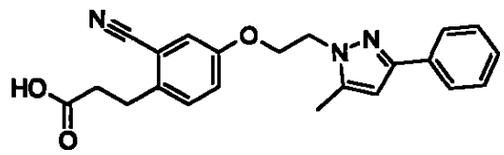
Ácido 3-{2-ciano-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil} propiónico



MS [ES] m/z 402 (M+1).

Ejemplo 578

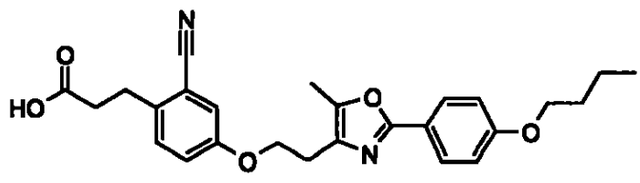
Ácido 3-{2-ciano-4-[2-(5-metil-3-fenilpirazol-1-il)etoxi]fenil} propiónico:



MS [ES] m/z 376 (M+1).

Ejemplo 579

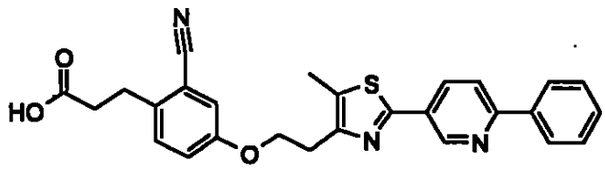
Ácido 3-(4-{2-[2-(4-butoxifenil)-5-metiloxazol-4-il]etoxi}-2-cianofenil) propiónico



MS [ES] m/z 449 (M+1).

Ejemplo 580

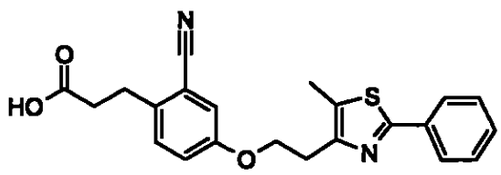
Ácido 3-(2-ciano-4-{2-[5-metil-2-(6-fenilpiridin-3-il)tiazol-4-il]etoxi}fenil) propiónico



MS [ES] m/z 470 (M+1).

Ejemplo 581

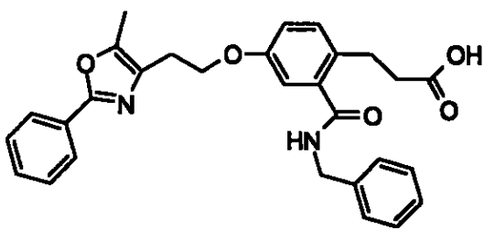
Ácido 3-{2-ciano-4-[2-(5-metil-2-feniltiazol-4-il)etoxi]fenil} propiónico



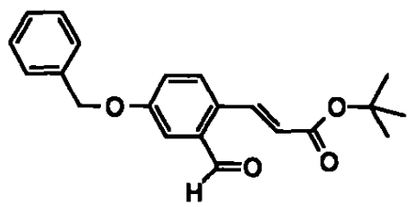
MS [ES] m/z 393 (M+1).

Ejemplo 582

Ácido 3-{2-bencilcarbamoil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

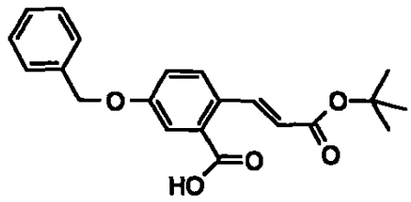


Etapa A: Éster terc-butílico del ácido 3-(4-benciloxi-2-formil-fenil)-acrílico



A una solución de éster terc-butílico del ácido 3-(2-formil-4-hidroxi-fenil)-acrílico (4,97 g, 20,0 mmol) en DMF (40 ml) se le añadió bromuro de bencilo (2,85 ml, 24,0 mmol) y Cs_2CO_3 (7,82 g, 24,0 mmol). La suspension se agitó a 80°C durante 30 min, y TLC indicó que la reacción se completó. La mezcla se inactivó con H_2O (500 ml) y se extrajo con EtOAc (2 x 100 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentró para dar un residuo, que se purificó por cromatografía en gel de sílice (hexanos/EtOAc 9/1) para producir el compuesto del título en forma de un sólido amarillo (6,70 g, 99%).

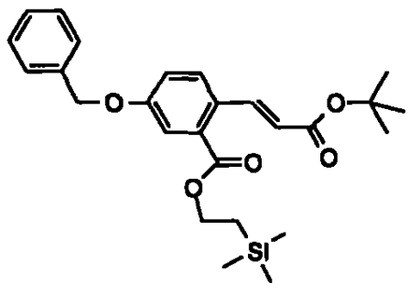
Etapa B: Ácido 5-benciloxi-2-(2-terc-butoxicarbonil-vinil)-benzoico



Una solución de éster terc-butílico del ácido 3-(4-benciloxi-2-formil-fenil)-acrílico (6,70 g, 19,8 mmol) en *terc*-butanol (150 ml) se trató con 2-metil-2-butano (50 ml) y se enfrió a 0°C. Se añadió una solución de $NaClO_2$ (17,0 g, 188 mmol) y NaH_2PO_4 (17,0 g, 142 mmol) en H_2O (200 ml), y la mezcla se agitó a 0°C durante 15 min. El baño de hielo se retiró, y la mezcla se agitó a temperatura ambiente durante 2 h. La capa orgánica se separó, y la capa acuosa se extrajo con EtOAc (2 x 100 ml). Las capas orgánicas combinadas

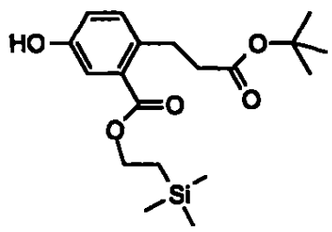
se secaron (Na_2SO_4) y se concentraron. El residuo se purificó usando cromatografía en gel de sílice (hexanos/EtOAc 9/1 a 0/10) para producir el compuesto del título en forma de un sólido blanco (6,78 g, 96%). ^1H RMN (400 MHz, $CDCl_3$): d1,52 (s, 9 H), 5,12 (s, 2 H), 6,20 (d, 1H, *J* = 16,2 Hz), 7,13 (dd, 1H, *J* = 3,6, 9,0 Hz), 7,34-7,45 (m, 5H), 7,58 (d, 1H, *J* = 8,8 Hz), 7,64 (d, 1H, *J* = 2,4 Hz), 8,41 (d, 1H, *J* = 16,2 Hz).

Etapa C: 2-Trimetilsilanil-etil éster del ácido 5-benciloxi-2-(2-terc-butoxicarbonil-vinil)-benzoico



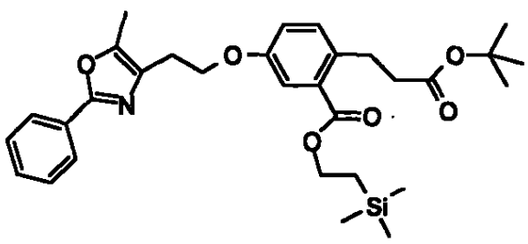
A una solución de ácido 5-benciloxi-2-(2-terc-butoxicarbonil-vinil)-benzoico (5,50 g, 15,5 mmol) en CH_2Cl_2 (100 ml) se le añadió 2-trimetilsilil-etanol (3,67 g, 31,0 mmol), EDC (5,36 g, 27,9 mmol), y DMAP (3,67 g, 31,0 mmol). La mezcla resultante se agitó a temperatura ambiente durante 12 h, se lavó con NH_4Cl acuoso (150 ml), y se extrajo con CH_2Cl_2 (100 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron. El residuo se purificó usando cromatografía en gel de sílice (hexanos/EtOAc 9/1) para producir el compuesto del título en forma de un aceite (5,90 g, 84%). ^1H RMN (400 MHz, $CDCl_3$): d0,07 (s, 9H), 1,14 (t, 2H, *J* = 8,8 Hz), 1,52 (s, 9 H), 4,41 (t, 2H, *J* = 8,8 Hz), 5,10 (s, 2 H), 6,20 (d, 1H, *J* = 15,6 Hz), 7,13 (dd, 1H, *J* = 3,0, 8,3 Hz), 7,34-7,44 (m, 5H), 7,50 (d, 1H, *J* = 3,0 Hz), 7,53 (d, 1H, *J* = 8,8 Hz), 8,41 (d, 1H, *J* = 16,1 Hz).

Etapa D: 2-Trimetilsilanil-etil éster del ácido 2-(2-terc-Butoxicarbonil-etil)-5-hidroxi-benzoico



Una solución de 2-trimetilsilanil-etil éster del ácido 5-benciloxi-2-(2-terc-butoxicarbonil-vinil)-benzoico (6,20 g, 13,6 mmol) en EtOH (95 ml) se trató con Pd/C (5%, 0,775 g). La suspensión resultante se trató con hidrógeno a 60 psi (413,685 kPa) durante 6 h a temperatura ambiente. El catalizador se filtró a través de una capa de celite, y el filtrado se concentró para dar un aceite (4,30 g, 86%). ^{1}H RMN (400 MHz, $CDCl_3$): d0,07 (s, 9H), 0,96 (t, 1H, *J* = 8,8 Hz), 1,12 (t, 1H, *J* = 8,8 Hz), 1,40 (s, 9 H), 2,52 (t, 1H, *J* = 7,8 Hz), 3,13 (t, 1H, *J* = 7,8 Hz), 3,73 (t, 1H, *J* = 8,5 Hz), 4,36 (t, 1H, *J* = 8,5 Hz), 5,00 (s a, 1 H), 6,88 (dd, 1H, *J* = 2,4, 8,3 Hz), 7,14 (d, 1H, *J* = 8,3 Hz), 7,35 (d, 1H, *J* = 2,4 Hz).

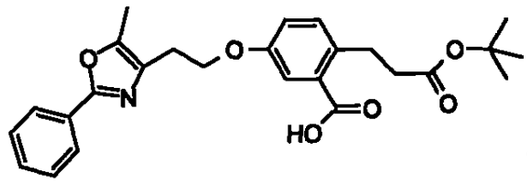
Etapa E: 2-trimetilsilanil-etil éster del ácido 2-(2-terc-butoxicarbonil-etil)-5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-benzoico



A una solución de 2-trimetilsilanil-etil éster del ácido 2-(2-terc-butoxicarbonil-etil)-5-hidroxi-benzoico (4,30 g, 11,7 mmol) y 2-(5-metil-2-fenil-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (4,61 g, 12,9 mmol) en DMF

(30 ml) se le añadió Cs_2CO_3 (4,59 g, 14,1 mmol). La suspension se agitó a 55°C durante 12 h. La mezcla de reacción se inactivó con H_2O (200 ml) y se extrajo con EtOAc (3 x 100 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentró para dar un residuo, que se purificó usando cromatografía en gel de sílice (hexanos/EtOAc 9/1 a 8/2) para producir el compuesto del título en forma de un aceite incoloro (5,04 g, 78%). ^{1}H RMN (400 MHz, $CDCl_3$): d0,06 (s, 9H), 1,11 (t, 2H, *J* = 8,8 Hz), 1,40 (s, 9 H), 2,36 (s, 3 H), 2,51 (t, 1H, *J* = 7,8 Hz), 2,97 (t, 2H, *J* = 6,8 Hz), 3,12 (t, 1H, *J* = 7,8 Hz), 4,24 (t, 2H, *J* = 6,8 Hz), 4,35 (t, 2H, *J* = 8,8 Hz), 6,88 (dd, 1H; *J* = 3,0, 8,3 Hz), 7,15 (d, 1H, *J* = 8,3 Hz), 7,37-7,44 (m, 4H), 7,97 (d, 2H, *J* = 7,8 Hz).

Etapa F: Ácido 2-(2-terc-butoxicarbonil-etil)-5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-benzoico



Una solución de 2-trimetilsilaniletil éster del ácido 2-(2-terc-butoxicarbonil-etil)-5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-benzoico (5,04 g, 9,13 mmol) en THF (100 ml) se trató con TBAF (20 ml, 1,0 M) a temperatura ambiente durante 1 h. La mezcla de reacción se concentró y se purificó usando cromatografía en gel de sílice (hexanos/EtOAc 1/1) para producir el compuesto del título en forma de un aceite incoloro (4,04 g, 98%). ^{1}H RMN (400 MHz, $CDCl_3$): d1,38 (s, 9 H), 2,37 (s, 3 H), 2,55 (t, 2H, *J* = 7,3 Hz), 2,98 (t, 2H, *J* = 6,5 Hz), 3,15 (t, 2H, *J* = 7,3 Hz), 4,26 (t, 2H, *J* = 6,5 Hz), 4,35 (t, 2H, *J* = 8,8 Hz),

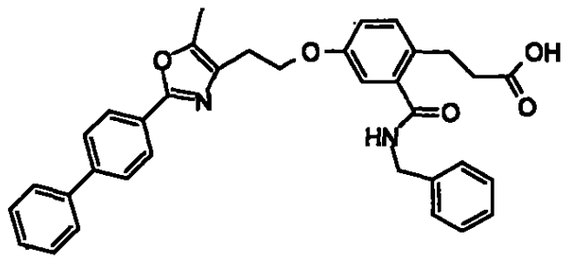
6,99 (dd, 1H, J = 2,9, 8,8 Hz), 7,18 (d, 1H, J = 8,3 Hz), 7,38-7,43 (m, 3H), 7,49 (d, 1H, J = 2,9 Hz), 7,97 (d, 2H, J = 7,8 Hz). MS (ES) m/z 522,3 $[M+H]^+$.

Etapa G: Ácido 3-[2-bencilcarbamoil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil]-propiónico

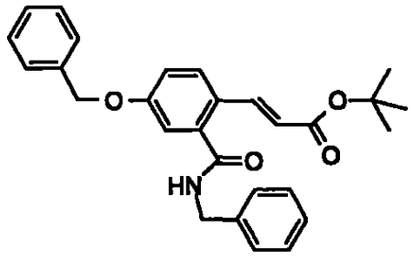
A una solución de ácido 2-(2-terc-butoxicarbonil-etil)-5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-benzoico (93 mg, 0,200 mmol) en CH_2Cl_2 (2 ml) se le añadió bencilamina (52 mg g, 0,49 mmol), EDC (54 mg, 0,28 mmol), trietilamina (0,057 ml, 0,40 mmol), y DMAP (catalizador). La mezcla resultante se agitó a temperatura ambiente durante 12 h y se lavó con NH_4Cl acuoso (2 ml). La capa orgánica se purificó usando una columna de gel de sílice (columna Sep-Pak, 10 g; hexanos/EtOAc 1/1) para producir el éster *terc*-butilo intermedio. El éster se trató con una mezcla de CH_2Cl_2 (1,0 ml), TFA (0,8 ml), y agua (0,1 ml) a temperatura ambiente durante 2 h. La mezcla de reacción se concentró y se secó al vacío para producir el producto del título en forma de un sólido blanco (35 mg, 36%). ^1H RMN (400 MHz, $CDCl_3$): d2,32 (s, 3 H), 2,59 (t, 2H, J = 7,3 Hz), 2,88-2,98 (m, 4H, J = 6,5 Hz), 4,16 (t, 2H, J = 6,5 Hz), 4,52 (s, 2H), 6,83 (dd, 1H, J = 2,6, 8,4 Hz), 6,87 (d, 1 H, J = 2,4 Hz), 7,10 (d, 1H, J = 8,3 Hz), 7,20-7,30 (m, 3H), 7,37-7,40 (m, 3 H), 7,88-7,91 (m, 2H). MS (ES) m/z 485,2 $[M+H]^+$, m/z 483,4 $[M-H]^-$.

Ejemplo 583

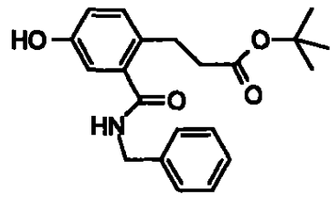
Ácido 3-(2-bencilcarbamoil-4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-fenil]-propiónico



Etapa A: Éster terc-butílico del ácido 3-(2-bencilaminocarbonil-4-benciloxi-fenil)-acrílico



A una solución de ácido 5-benciloxi-2-(2-terc-butoxicarbonil-vinil)-benzoico (1,45 g, 4,09 mmol) en CH_2Cl_2 (40 ml) se le añadió benclamina (0,613 g, 5,73 mmol), EDC (1,254 g, 6,54 mmol), y DMAP (1,00 g, 8,18 mmol). La mezcla resultante se agitó a temperatura ambiente durante 12 h, se lavó con NH_4Cl acuoso (50 ml), y se extrajo con CH_2Cl_2 (2X50 ml). Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron. El residuo después se purificó usando cromatografía en gel de sílice (hexanos/EtOAc 8/2) para producir el compuesto del título en forma de un aceite (720 mg, 40%). ^1H RMN (400 MHz, $CDCl_3$): d1,52 (s, 9 H), 4,63 (d, 2H, J = 5,5 Hz), 5,09 (s, 2 H), 5,97 (s a, 1 H), 6,22 (d, 1H, J = 15,6 Hz), 7,01 (dd, 1H, J = 2,7, 8,6 Hz), 7,10 (d, 1H, J = 2,8 Hz), 7,28-7,42 (m, 10H), 7,55 (d, 1H, J = 9,0 Hz), 7,88 (d, 1H, J = 16,0 Hz).



Una solución de éster terc-butílico del ácido 3-(2-bencilaminocarbonil-4-benciloxi-fenil)-acrílico (720 mg, 1,625 mmol) en EtOH (15 ml) y THF (5 ml) se trató con Pd/C (5%, 70 mg). La suspensión resultante se trató con hidrógeno usando un globo durante 4 h a temperatura ambiente. El catalizador se filtró a través de una capa de celite y el filtrado se concentró para dar un aceite (450 mg, 78%). ^{1}H RMN (400 MHz, $CDCl_3$): d1,34 (s, 9 H), 2,56 (t, 2H, *J* = 7,0 Hz), 2,90 (t, 2H, *J* = 7,0 Hz), 4,59 (d, 1H, *J* = 5,9 Hz), 6,74 (dd, 1H, *J* = 2,7, 8,2 Hz), 6,89 (d, 1H, *J* = 2,7 Hz), 7,01 (d, 1H, *J* = 8,2 Hz), 7,25-7,36 (m, 5H). MS (ES) m/z 356,2 $[M+H]^+$, m/z 354,0 $[M-H]^-$.

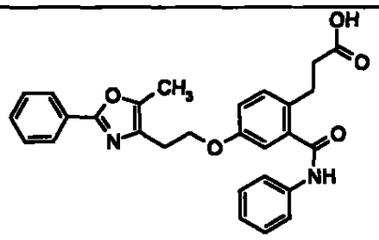
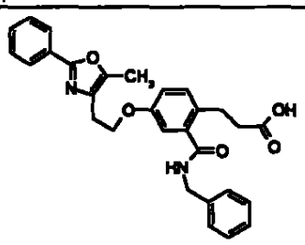
Etapa C: Ácido 3-[2-Bencilcarbamoil-4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-fenil]-propiónico

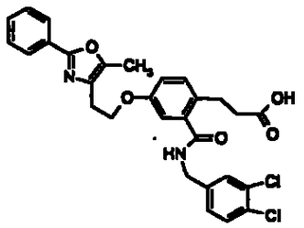
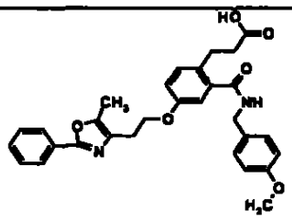
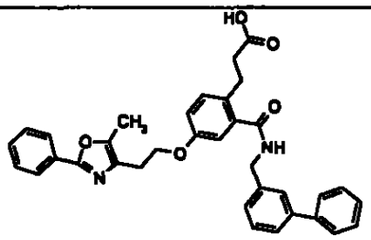
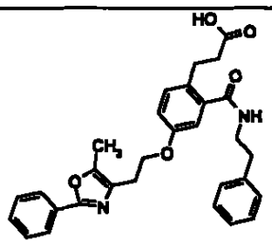
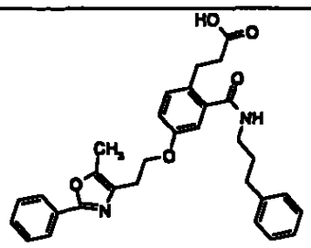
A una solución de éster terc-butílico del ácido 3-(2-bencilaminocarbonil-4-hidroxi-fenil)-propiónico (50 mg, 0,140 mmol) y 2-(5-metil-2-(4-fenilfenil)-oxazol-4-il)-etil éster del ácido tolueno-4-sulfónico (73 mg, 0,168 mmol) en DMF (1,0 ml) se le añadió K_2CO_3 (100 mg, 0,724 mmol). La suspension se agitó a 65°C durante 12 h. La mezcla de reacción se interrumpió con H_2O (10 ml) y se extrajo con EtOAc (3x10 ml). Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron para dar un residuo, que se purificó usando cromatografía en gel de sílice (hexanos/EtOAc 7/3) para producir el éster *terc*-butilo intermedio en forma de un aceite. El éster se trató con una mezcla de CH_2Cl_2 (1,0 ml), TFA (0,8 ml) y agua (0,1 ml) a temperatura

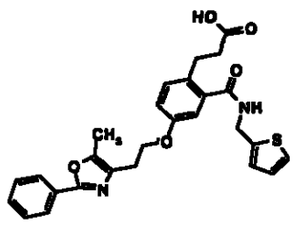
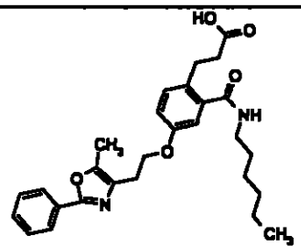
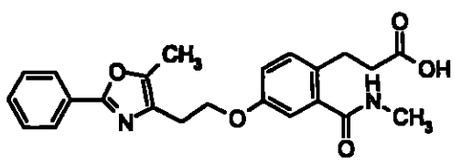
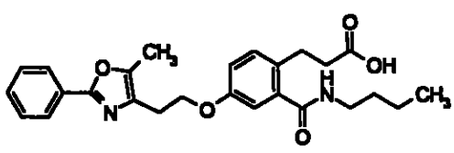
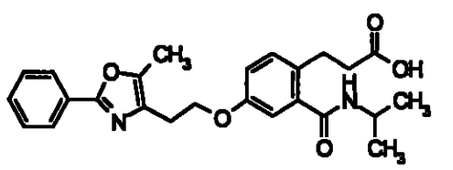
ambiente durante 2 h. La mezcla de reacción se concentró y se secó al vacío para producir el producto del título en forma de un sólido blanco (37 mg, 47%). ^{1}H RMN (400 MHz, $CDCl_3$): d2,36 (s, 3 H), 2,59 (t, 2H, *J* = 7,3 Hz), 2,94 (t, 4H, *J* = 7,2 Hz), 4,20 (t, 2H, *J* = 6,5 Hz), 4,55 (s, 2H), 6,85 (dd, 1H, *J* = 2,9, 8,2 Hz), 6,90 (d, 1 H, *J* = 2,4 Hz), 7,12 (d, 1H, *J* = 8,6 Hz), 7,20-7,36 (m, 6H), 7,42 (t, 2H, *J* = 7,4 Hz), 7,59 (d, 2H, *J* = 8,6 Hz), 7,64 (d, 2H, *J* = 8,2 Hz), 8,00 (d, 2H, *J* = 8,6 Hz). MS (ES) m/z 561,3 $[M+H]^+$, m/z 559,5 $[M-H]^-$.

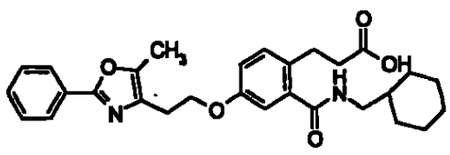
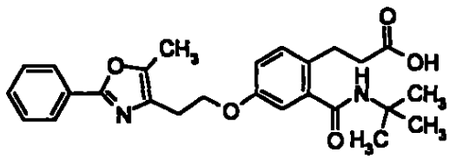
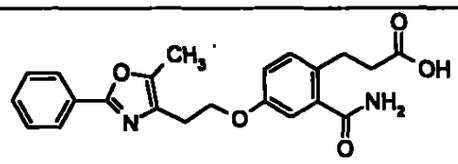
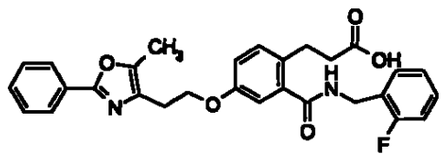
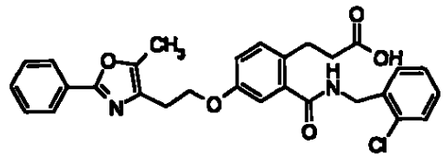
Ejemplos 584-643

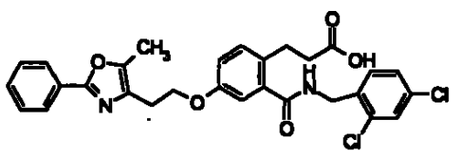
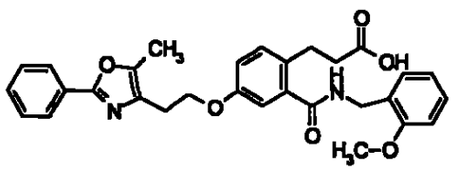
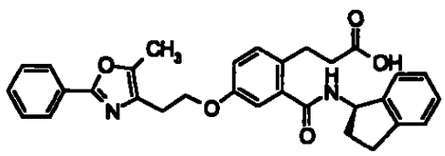
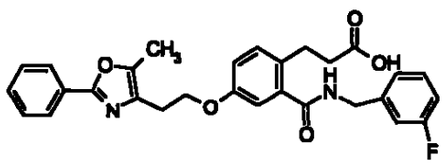
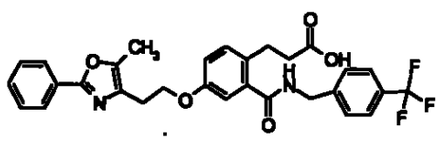
Ejemplos 584 a 643 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplos 582 y 583. Ejemplos 584 a 628 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 582. Ejemplos 629 a 643 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 583,

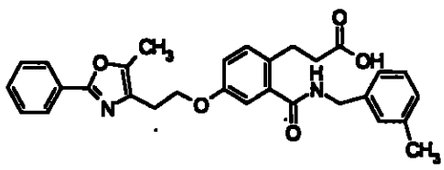
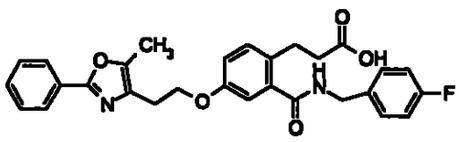
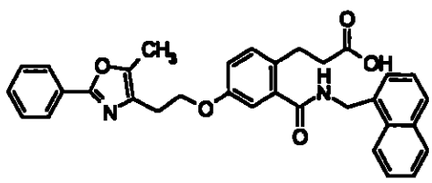
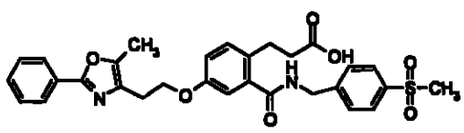
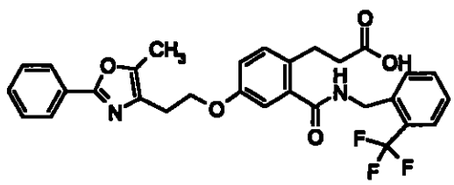
No.	Compuestos	Nombre	MS (ES+)
584		Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-fenil- carbamoil-fenil}-propiónico	471,2
585		Ácido 3-{2-bencilcarbamoil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	485,2

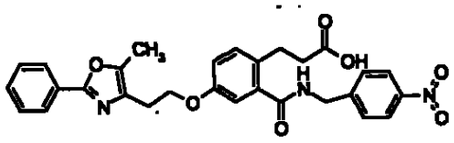
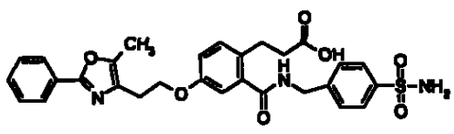
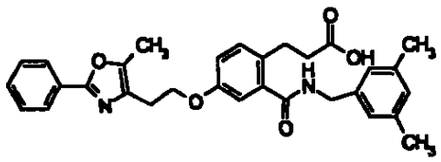
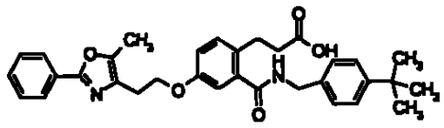
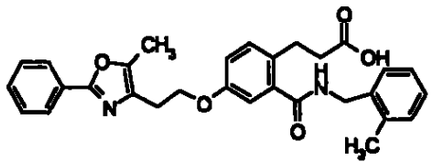
No.	Compuestos	Nombre	MS (ES+)
586		Ácido 3-{2-(3,4-dicloro-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	553
587		Ácido 3-{2-(4-metoxi-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	515,2
588		Ácido 3-{2-[(bifenil-3-il-metil)-carbamoil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	561,2
589		Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-fenetil-carbamoil-fenil}-propiónico	499,3
590		Ácido 3-[4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-(3-fenil-propilcarbamoil)-fenil]-propiónico	513,3

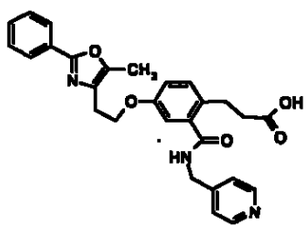
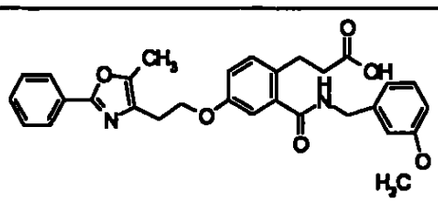
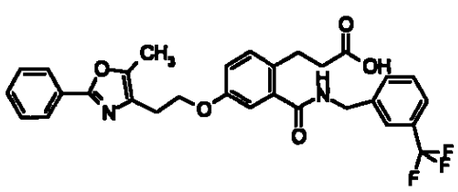
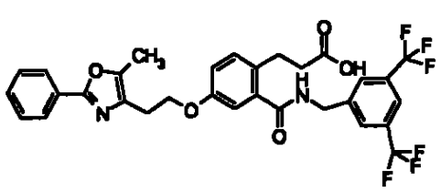
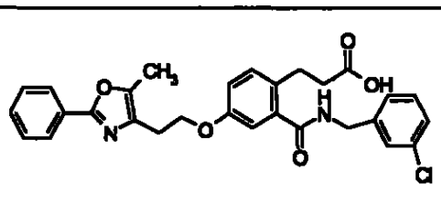
No.	Compuestos	Nombre	MS (ES+)
591		Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(tiofen-2-ilmetil)-carbamoil]-fenil}-propiónico	491,2
592		Ácido 3-{2-hexilcarbamoil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	479,3
593		Ácido 3-{2-metilcarbamoil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	409,1
594		Ácido 3-{2-butilcarbamoil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	451,1
595		Ácido 3-{2-isopropilcarbamoil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	437,2

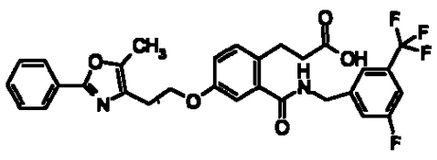
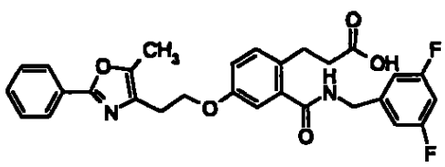
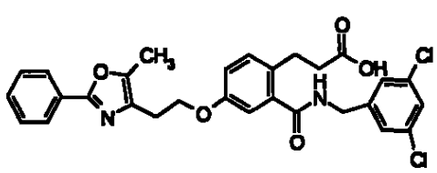
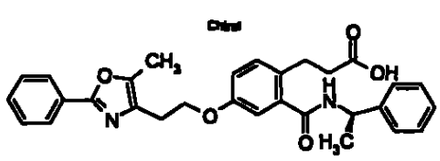
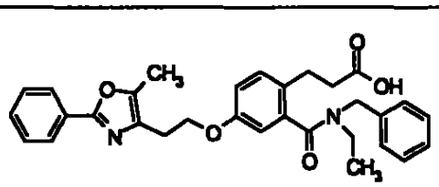
No.	Compuestos	Nombre	MS (ES+)
596		Ácido 3-[2-(ciclohexilmetil-carbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	491,2
597		Ácido 3-[2-terc-butilcarbamoil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	451,2
598		Ácido 3-[2-carbamoil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	395,1
599		Ácido 3-[2-(2-fluoro-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	503,1
600		Ácido 3-[2-(2-cloro-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	519,1

No.	Compuestos	Nombre	MS (ES+)
601		Ácido 3-{2-(2,4-dicloro-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	553
602		Ácido 3-{2-(2-metoxi-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	515,1
603		Ácido 3-{2-(indan-1-ilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	511,1
604		Ácido 3-{2-(3-fluoro-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	503,1
605		Ácido 3-[4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-(4-trifluoro metil-bencilcarbamoil)-fenil]-propiónico	553

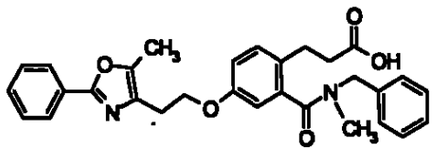
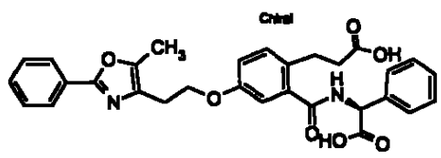
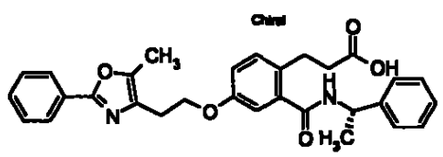
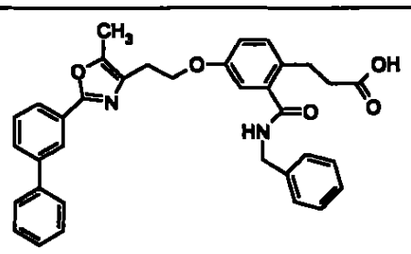
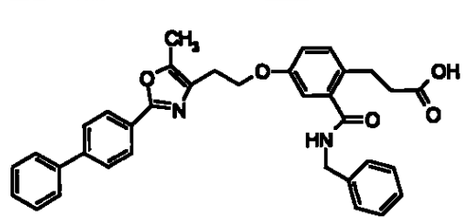
No.	Compuestos	Nombre	MS (ES+)
606		Ácido 3-{2-(3-metil-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	499,1
607		Ácido 3-{2-(4-fluoro-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	503,1
608		Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(naftalen-1-ilmetil)-carbamoil]-fenil}-propiónico	535,1
609		Ácido 3-{2-(4-metanosulfonil-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	563,1
610		Ácido 3-[4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-(2-trifluoro metil-bencilcarbamoil)-fenil]-propiónico	553,1

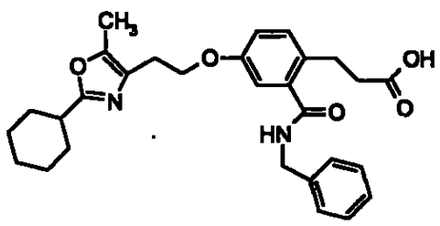
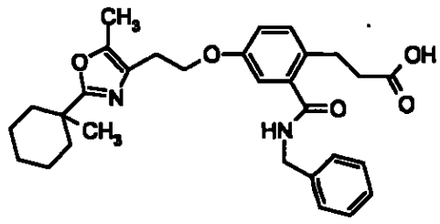
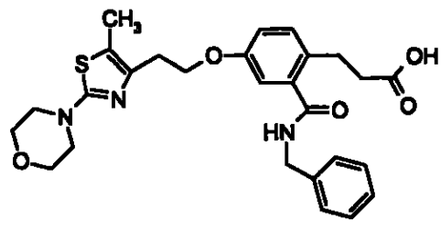
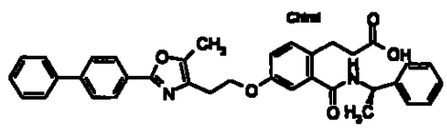
No.	Compuestos	Nombre	MS (ES+)
611		Ácido 3-{2-(4-nitro-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	530,1
612		Ácido 3-[4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-(4-sulfamoil-bencilcarbamoil)-fenil]-propiónico	564,1
613		Ácido 3-{2-(3,5-dimetil-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	513,2
614		Ácido 3-{2-(4-terc-butil-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	541,2
615		Ácido 3-{2-(2-metil-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	499,2

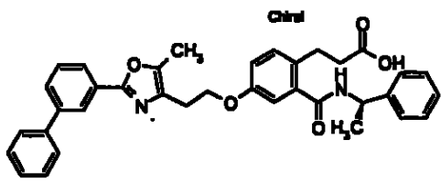
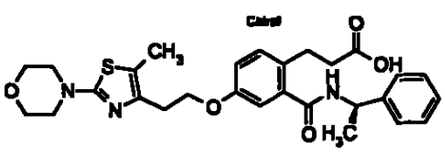
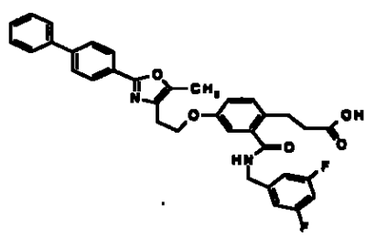
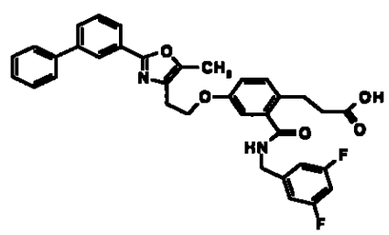
No.	Compuestos	Nombre	MS (ES+)
616		Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(piridin-4-ilmetil)-carbamoil]-fenil}-propiónico	486,2
617		Ácido 3-{2-(3-metoxi-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	515,2
618		Ácido 3-[4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-(3-trifluoro metil-bencilcarbamoil)-fenil]-propiónico	553,1
619		Ácido 3-{2-(3,5-bis-trifluoro metil-bencil-carbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	621,1
620		Ácido 3-{2-(3-cloro-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	519,1

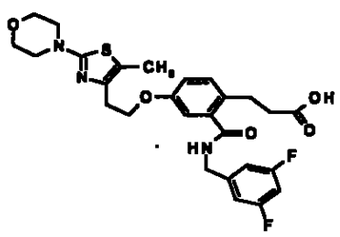
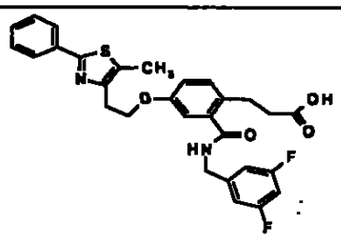
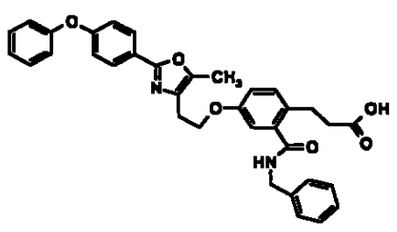
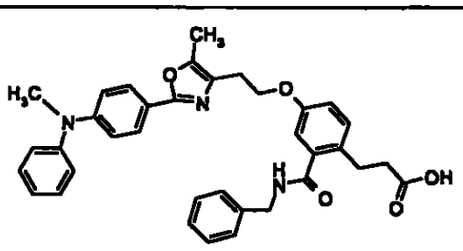
No.	Compuestos	Nombre	MS (ES+)
621		Ácido 3-{2-(3-fluoro-5-trifluoro metil-bencilo carbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	571,1
621		Ácido 3-{2-(3,5-difluoro-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	521,1
623		Ácido 3-{2-(3,5-dicloro-bencilcarbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	553
624		Ácido (R)-3-[4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-(1-fenil-etilcarbamoil)-fenil]-propiónico	499,2
625		Ácido 3-{2-(bencil-etil-carbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	513,2

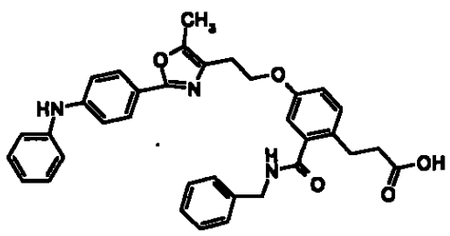
879

No.	Compuestos	Nombre	MS (ES+)
626		Ácido 3-{2-(bencil-metil-carbamoil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	499,2
627		Ácido (S)-3-{2-[(carboxi-fenilo -metil) carbamoil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico	529,1
628		Ácido (S)-3-[4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-(1-fenil-etilcarbamoil)-fenil]-propiónico	499,2
629		Ácido 3-{2-bencilcarbamoil-4-[2-(2-bifenil-3-il-5-metil-oxazol-4-il)-etoxi]-fenil}-propiónico	561,3
630		Ácido 3-{2-bencilcarbamoil-4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-fenil}-propiónico	561,3

No.	Compuestos	Nombre	MS (ES+)
631		Ácido 3-{2-bencilcarbamoil-4-[2-(2-ciclohexil-5-metil-oxazol-4-il)-etoxi]-fenil}-propiónico	491,3
632		Ácido 3-{2-bencilcarbamoil-4-{2-[5-metil-2-(1-metil-ciclohexil)-oxazol-4-il]-etoxi}-fenil)-propiónico	505,4
633		Ácido 3-{2-bencilcarbamoil-4-[2-(5-metil-2-morfolin-4-il-tiazol-4-il)-etoxi]-fenil}-propiónico	510,3
634		Ácido (R)-3-[4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-(1-fenil-etilcarbamoil)- fenil]-propiónico	575,3

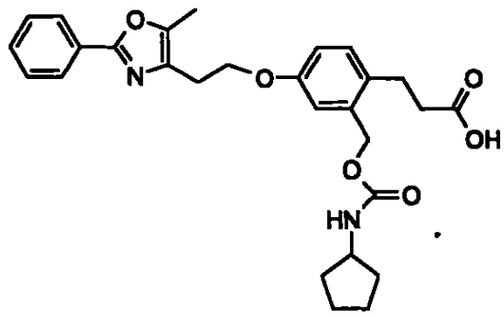
No.	Compuestos	Nombre	MS (ES+)
635		Ácido (R)-3-[4-[2-(2-bifenil-3-il-5-metil-oxazol-4-il)-etoxi]-2-(1-fenil-etilcarbamoil)-fenil]-propiónico	575,3
636		Ácido (R)-3-[4-[2-(5-metil-2-morfolin-4-il-tiazol-4-il)-etoxi]-2-(1-fenilo etilcarbamoil)-fenil]-propiónico	524,2
637		Ácido 3-[4-[2-(2-bifenil-4-il-5-metil-oxazol-4-il)-etoxi]-2-(3,5-difluoro-bencilcarbamoil)-fenil]-propiónico	597,3
638		Ácido 3-[4-[2-(2-bifenil-3-il-5-metil-oxazol-4-il)-etoxi]-2-(3,5-difluoro-bencilcarbamoil)-fenil]-propiónico	597,3

No.	Compuestos	Nombre	MS (ES+)
639		Ácido 3-{2-(3,5-difluoro-bencilcarbamoil)-4-[2-(5-metil-2-morfolin-4-il-tiazol-4-il)-etoxi]-fenil}-propiónico	546,1
640		Ácido 3-{2-(3,5-difluoro-bencilcarbamoil)-4-[2-(5-metil-2-fenil-tiazol-4-il)-etoxi]-fenil}-propiónico	537,1
641		Ácido 3-(2-bencilcarbamoil-4-{2-[5-metil-2-(4-fenoxi-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico	577,3
642		Ácido 3-[2-bencilcarbamoil-4-(2-{5-metil-2-[4-(metil-fenil-amino)-fenil]-oxazol-4-il}-etoxi)-fenil]-propiónico	590,2

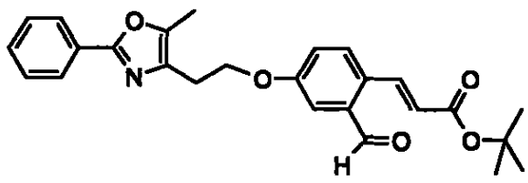
No.	Compuestos	Nombre	MS (ES+)
643		Ácido 3-(2-bencilcarbamoil-4-{2-[5-metil-2-(4-fenilamino-fenil)-oxazol-4-il]-etoxi}-fenil)-propiónico	576,2

Ejemplo 644

Ácido 3-{2-ciclopentilcarbamoiloximetil-4-[2-(2-feniloxazol-4-il)etoxi]fenil}-propiónico



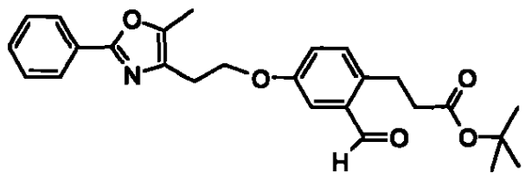
Etapa A: Éster *terc*-butílico del ácido 3-{2-formil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}acrílico



Un matraz de fondo redondo de 100 ml secado a la llama se cargó con 2-(5-metil-2-feniloxazol-4-il) etil éster del ácido tolueno-4-sulfónico (3,74 g, 10,5 mmol), éster terc-butílico del ácido 3-(2-formil-4-hidroxifenil)acrílico (2,0 g, 8,05

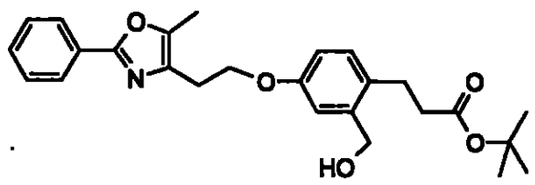
mmol), y DMF anhidro (40 ml). Se añadió carbonato de cesio (3,94 g, 12,1 mmol), y la reacción se calentó a 55° C en una atmósfera de nitrógeno durante 18 h. Los compuestos volátiles se retiraron *al vacío*, y el residuo bruto se disolvió en EtOAc (250 ml). La capa orgánica se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró para dar un aceite amarillo (1,70 g, 49%). ^1H RMN (400 MHz, $CDCl_3$) d 1,54 (s, 9H), 2,38 (s, 3H), 3,01 (t, J = 6,6 Hz, 2H), 4,34 (t, J = 6,6 Hz, 2H), 6,24 (d, J = 15,6 Hz, 1H), 7,12 (dd, J = 8,8, 2,9 Hz, 1H), 7,38 (d, J = 2,9 Hz, 1H), 7,40-7,45 (m, 3H), 7,58 (d, J = 8,8 Hz, 1H), 7,98 (dd, J = 6,4, 2,0 Hz, 2H), 8,33 (d, J = 15,6 Hz, 1H), 10,3 (s, 1H). MS (ES) *m/e* 434 (M+1).

Etapa B: Éster *terc*-butílico del ácido 3-{2-formil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}acrílico



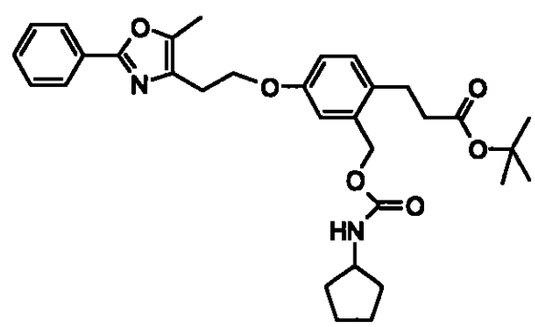
Un matraz de fondo redondo de 100 ml se cargó con éster *terc*-butilo del ácido 3-{2-formil-4-[2-(5-metil-2-feniloxazol-4-il)-etoxi]fenil}acrílico (1,69 g, 3,90 mmol), THF (40 ml), y después catalizador Pd/C al 10% (0,17 g). La reacción se agitó vigorosamente en una atmósfera de hidrógeno durante 18 h. La mezcla se filtró a través de Celite y se concentró para dar un sólido amarillo (1,70 g, cuantitativo). ^1H RMN (400 MHz, $CDCl_3$) d 1,39 (d, J = 4,9 Hz, 9H), 2,37 (d, J = 2,9 Hz, 3H), 2,51 (t, J = 7,6 Hz, 2H), 2,99 (t, J = 6,6 Hz, 2H), 3,23 (t, J = 7,1 Hz, 2H), 4,29 (t, J = 6,6 Hz, 2H), 7,04-7,10 (m, 1H), 7,21 (d, J = 8,3 Hz, 1H), 7,34 (d, J = 2,4 Hz, 1H), 7,38-7,45 (m, 3H), 7,97 (dd, J = 7,3, 2,0 Hz, 2H), 10,2 (s, 1H). MS (ES) *m/e* 436 (M+1).

Etapa C: Éster *terc*-butílico del ácido 3-{2-Hidroximetil-4-[2-(2-fenil-oxazol-4-il)etoxi]fenil}propiónico



Un matraz de fondo redondo de 100 ml se cargó con éster terc-butílico del ácido 3-{2-formil-4-[2-(2-feniloxazol-4-il)etoxi]fenil}propiónico (1,82 g, 4,18 mmol) y etanol absoluto (20 ml). La solución agitada se enfrió en un baño de hielo/etanol y se trató con borohidruro de sodio (0,31 g, 8,36 mmol). El baño frío se retiró, y la mezcla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 2 h. La mezcla de reacción se vertió en EtOAc (100 ml) y agua fría (100 ml). La capa orgánica se lavó con salmuera, se secó (Na_2SO_4), y se concentró para dar un aceite amarillo (1,62 g, 88%). ^{1}H RMN (400 MHz, $CDCl_3$) d 1,38 (s, 9H), 2,37 (s, 3H), 2,54 (t, J = 7,6 Hz, 2H), 2,88 (t, J = 7,6 Hz, 2H), 2,97 (t, J = 6,6 Hz, 2H), 4,23 (t, J = 6,6 Hz, 2H), 4,66 (s, 2H), 6,78 (dd, J = 8,3, 2,9 Hz, 1H), 6,94 (d, J = 2,4 Hz, 1H), 7,09 (d, J = 8,3 Hz, 1H), 7,38-7,45 (m, 3H), 7,97 (dd, J = 8,1, 1,7 Hz, 2H). MS (ES) *m/e* 438 (M+1).

Etapa D: Éster *terc*-butílico del ácido 3-{2-ciclopentilcarbamoiloximetil-4-[2-(2-feniloxazol-4-il)etoxi]fenil}-propiónico



Un matraz de fondo redondo de 15 ml se cargó con éster *terc*-butílico del ácido 3-{2-hidroximetil-4-[2-(2-feniloxazol-4-il)etoxi]fenil}propiónico (0,10 g, 0,23 mmol), con isocianato de ciclopentilo (0,15 ml, 1,38 mmol), y CH_2Cl_2 anhidro (0,75 ml). Se añadió una solución de HCl 1,0 M en éter (0,115 ml, 0,115 mmol), y la mezcla de reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 24 h. La mezcla de reacción se diluyó con CH_2Cl_2, (30 ml), se lavó con salmuera, se secó (Na_2SO_4), y se concentró para dar un aceite. El producto bruto se purificó usando cromatografía radial (EtOAc:hexanos 10:90 a 35:65) para dar un aceite incoloro (0,105 g, 83%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,42 (s, 9H), 1,56-1,65 (m, 4H), 1,94-2,04 (m, 2H), 2,37 (s, 3H), 2,46 (t, J = 7,6 Hz, 2H), 2,87 (t, J = 8,1 Hz, 2H), 2,96 (t, J = 6,6 Hz, 2H), 3,97 (s a, 1H), 4,22 (t, J = 6,6 Hz, 2H), 4,76 (s a, 1H), 5,07 (s, 2H), 6,90 (dd, J = 8,3, 2,4 Hz, 1H), 6,89 (s, 1H), 7,10 (d, J = 8,8 Hz, 1H), 7,40-7,45 (m, 3H), 7,96-7,98 (m, 2H). MS (ES) *m/e* 549 (M+1).

Etapa E: Ácido 3-{2-ciclopentilcarbamoiloximetil-4-[2-(2-feniloxazol-4-il)etoxi]fenil}-propiónico

Un matraz de fondo redondo de 15 ml se cargó con éster *terc*-butílico del ácido 3-{2-ciclopentilcarbamoiloximetil-4-[2-(2-feniloxazol-4-il)etoxi]fenil}propiónico (0,097 g, 0,18 mmol), CH_2Cl_2 (1,2 ml), y después ácido trifluoroacético (1,2 ml). La solución se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 4 h y se concentró. El residuo se purificó usando cromatografía radial (MeOH:CH_2Cl_2 2:98 a 10:90) para dar un sólido blanco (0,085 g, 93%) . ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,37 (s a, 2H), 1,63 (s a, 4H), 1,93-2,05 (m, 2H), 2,39 (s, 3H), 2,64 (s a, 2H), 2,91-3,18 (m, 4H), 3,99 (s

a, 1H), 4,21 (s, 2H), 4,87 (s a, 1H), 5,10 (s a, 2H), 6,80 (s, 1H), 6,89 (s, 1H), 7,00-7,25 (s a, 1H), 7,36-7,52 (m, 3H), 7,95 (s, 2H). MS (ES) *m/e* 493 (M+1).

Los siguientes Ejemplos 645 a 651 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 644.

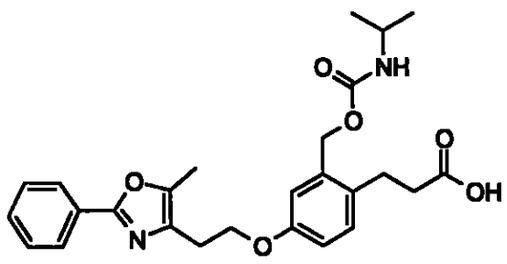
Ejemplo 645

Éster *terc*-butílico del ácido 3-{2-isopropilcarbamoiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico

MS (ES) *m/e* 523 (M+1).

Ejemplo 646

Ácido 3-{2-isopropilcarbamoiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



^{1}H RMN (400 MHz, $CDCl_3$) d 1,13 (d, J = 5,4 Hz, 6H), 2,37 (s, 3H), 2,61 (t, J = 7,8 Hz, 2H), 2,92-2,98 (m, 4H), 3,80 (s a, 1H), 4,21 (t, J = 6,6 Hz, 2H), 4,66 (s a, 1H), 5,08 (s, 2H), 6,81 (dd, J = 8,6, 2,7 Hz, 1H), 6,90 (s, 1H), 7,11 (d, J = 8,3 Hz, 1H), 7,41-7,44 (m, 3H), 7,97 (dd, J = 4,4, 2,9 Hz, 2H). MS (ES) *m/e* 467 (M+1).

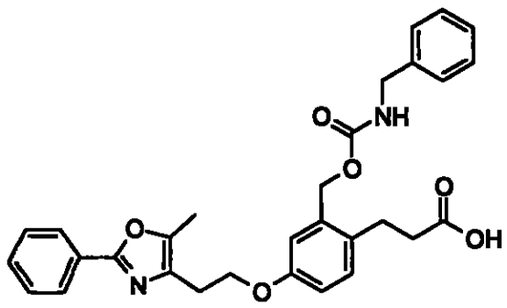
Ejemplo 647

Éster *terc*-butílico del ácido 3-{2-bencilcarbamoiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico

MS (ES) *m/e* 571 (M+1).

Ejemplo 648

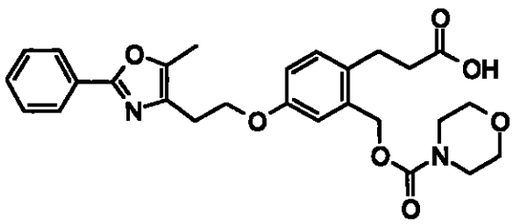
Ácido 3-{2-bencilcarbamoiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



^{1}H RMN (400 MHz, $CDCl_3$) δ 2,37 (s, 3H), 2,60 (t, J = 7 Hz, 2H), 2,92-2,97 (m, 4H), 4,20 (t, J = 7 Hz, 2H), 4,36 (d, J = 5,9 Hz, 2H), 5,13 (s, 2H), 5,18 (s a, 1H), 6,80 (d, J = 8,3 Hz, 1H), 6,91 (s, 1H), 7,10 (d, J = 8,3 Hz, 1H), 7,24-7,30 (m, 5H), 7,42 (s, 3H), 7,97 (s, 2H). MS (ES) *m/e* 515 (M+1).

Ejemplo 649

2-(2-Carboxietil)-5-[2-(5-metil-2-feniloxazol-4-il)etoxi]bencilo éster del ácido morfolina-4-carboxílico



MS (ES) *m/e* 495 (M+1).

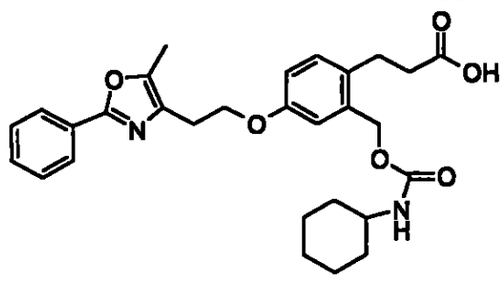
Ejemplo 650

Éster *terc*-butílico del ácido 3-{2-ciclohexilcarbamoiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico

MS (ES) *m/e* 563 (M+1)

Ejemplo 651

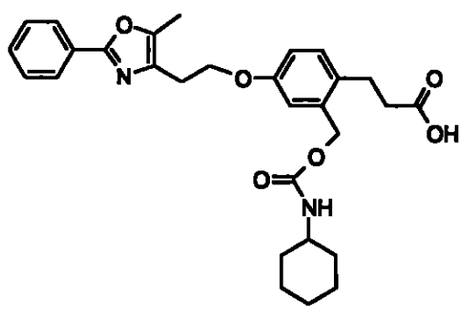
Ácido 3-{2-ciclohexilcarbamoiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



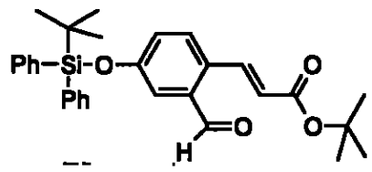
^{1}H RMN (400 MHz, $CDCl_3$) δ 1,08-1,18 (m 3H), 1,21-1,42 (m, 2H), 1,57 (s a, 1H), 1,66-1,70 (m, 2H), 1,90 (s a, 2H), 2,40 (s, 3H), 2,61 (t, J = 7,7 Hz, 2H), 2,94 (t, J = 7,8 Hz, 2H), 3,01 (t, J = 6,4 Hz, 2H), 3,48 (s a, 1H), 4,22 (t, J = 6,4 Hz, 2H), 4,74 (s a, 1H), 5,07 (s, 2H), 6,79-6,89 (m, 1H), 6,90 (s, 1H), 7,11 (d, J = 8,3 Hz, 1H), 7,44-7,46 (m, 3H), 7,98 (dd, J = 6,7, 2,8 Hz, 2H). MS (ES) *m/e* 507 (M+1).

Ejemplo 652

Ácido 3-{2-ciclohexilcarbamoiloximetil-4-[2-(2-feniloxazol-4-il)etoxi]fenil}-propiónico

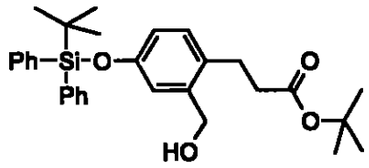


Etapa A: Éster *terc*-butílico del ácido 3-[4-(terc-butildifenilsilaniloxi)-2-formilfenil]acrílico



Un matraz de fondo redondo de 200 ml secado a la llama se cargó con éster *terc*-butílico del ácido 3-(2-formil-4-hidroxifenil)acrílico (10,0 g, 40,3 mmol), *terc*-butilclorodifenilsilano (12,6 ml, 48,3 mmol), y CH_2Cl_2 seco (150 ml). Se añadió trietilamina (11,2 ml, 80 mmol) y *N,N*-dimetilaminopiridina (1,0 g, 1,0 mmol), y la mezcla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 16 h. La mezcla de reacción se diluyó con CH_2Cl_2 adicional, se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró para dar un aceite. El producto bruto se purificó usando el sistema de cromatografía de media presión Biotage (EtOAc:hexanos 5:95) para dar a aceite amarillo pálido (18,3 g, 93%). ^{1}H RMN (400 MHz, $CDCl_3$) d 1,12 (s, 9H), 1,51 (d, J = 15,1 Hz, 9H), 6,15 (d, J = 5,1 Hz, 1H), 6,87 (dd, J = 8,6, 2,7 Hz, 1H), 7,34-7,47 (m, 7H), 7,68-7,73 (m, 5H), 8,28 (d, J = 15,6 Hz, 1H), 10,1 (s, 1H). MS (ES) *m/e* 487 (M+1).

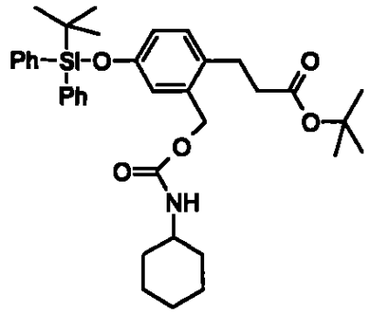
Etapa B: Éster *terc*-butílico del ácido 3-[4-(*terc*-butildifenilsilaniloxi)-2-hidroximetilfenil]propiónico



Un frasco de hidrogenación Parr de 500 ml se cargó con éster *terc*-butílico del ácido 3-[4-(terc-butildifenilsilaniloxi)-2-formilfenil]acrílico (18,3 g, 37,6 mmol), THF (60 ml), y metanol (120 ml). Se añadió trietilamina (2 ml) y

después Pd/C al 5% (5,9 g). La mezcla se agitó con hidrógeno a una presión de 60 psi (413,685 kPa) durante 48 h. La mezcla se filtró a través de Celite y se concentró para dar un aceite. Este aceite se purificó usando el sistema de cromatografía de media presión Biotage (EtOAc:hexanos 15:85) para dar un aceite amarillo pálido (12,8 g, 69%). ^{1}H RMN (400 MHz, $CDCl_3$) d 1,09 (s, 9H), 1,35 (s, 9H), 2,49 (t, J = 7,6 Hz, 2H), 2,83 (t, J = 7,6 Hz, 2H), 4,55 (s, 2H), 6,56 (dd, J = 8,3, 2,4 Hz, 1H), 6,83 (d, J = 2,9 Hz, 1H), 6,87 (d, J = 8,3 Hz, 1H), 7,33-7,44 (*m*, 6H), 7,70 (dd, J = 7,8, 1,5 Hz, 4H). MS (ES) *m/e* 508 ($M+NH_4$).

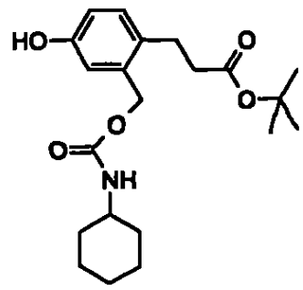
Etapa C: Éster *terc*-butílico del ácido 3-[4-(*terc*-butildifenilsilaniloxi)-2-ciclohexilcarbamoil-oximetilfenil]propiónico



Un matraz de fondo redondo de 100 ml en una atmósfera de N_2 se cargó con éster *terc*-butílico del ácido 3-[4-(*terc*-butildifenilsilaniloxi)-2-hidroximetilfenil]propiónico (3,0 g, 6,11 mmol), isocianato de ciclohexilo (4,7 ml, 36,7 mmol), y CH_2Cl_2 anhidro (25 ml). Se añadió una solución de HCl 1,0 M en éter (3,06 ml, 3,06 mmol), y la mezcla de reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 16 h. La mezcla se diluyó con CH_2Cl_2 (100 ml), se lavó con salmuera, se secó (Na_2SO_4), y se concentró hasta un aceite pardo. El aceite bruto se purificó usando el sistema de cromatografía de media presión Biotage (EtOAc:hexanos 5:95) para dar un aceite incoloro

(3,1 g, 82%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,08-1,24 (m, 1H), 1,26-1,40 (m, 11H), 1,56-1,62 (m, 2H), 1,68-1,72 (m, 2H), 2,41 (t, J = 8,3 Hz, 2H), 2,80 (t, J = 7,8 Hz, 2H), 3,47 (s a, 1H), 4,56 (s a, 1H), 4,95 (s, 2H), 6,57 (dd, J = 8,3, 2,7 Hz, 1H), 6,80 (s, 1H), 6,87 (d, J = 8,6 Hz, 1H), 7,33-7,44 (m, 6H), 7,69-7,72 (m, 4H). MS (ES) *m/e* 616 (M+1).

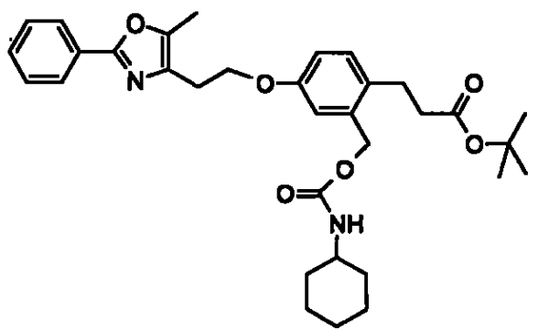
Etapa D: Éster *terc*-butílico del ácido 3-(2-ciclohexilcarbamoiloximetil-4-hidroxifenil)propiónico



Un matraz de fondo redondo de 500 ml se cargó con éster *terc*-butílico del ácido 3-[4-(*terc*-butil-difenilsilaniloxi)-2-ciclohexilcarbamoiloximetilfenil]propiónico (3,1 g, 5,03 mmol) y THF anhidro (180 ml). Se añadió fluoruro de tetrabutilamonio (15,1 ml, 15,1 mmol, 1,0M en THF), y la mezcla de reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 4 h. La mezcla se concentró, y el residuo se diluyó con EtOAc (100 ml), se lavó con salmuera, se secó sobre (Na_2SO_4), y se concentró para dar un aceite. Esta aceite bruto se purificó usando el sistema de cromatografía de media presión Biotage (EtOAc:hexanos 10:90 a 50:50) para dar un aceite incoloro (1,67 g, 88%). ^{1}H RMN (400 MHz, $CDCl_3$) d 1,04-1,19 (m, 3H), 1,24-1,38 (m, 2H), 1,42 (s, 9H), 1,57-1,62 (m, 1H), 1,66-1,71 (m, 2H), 1,91-2,05 (m, 2H), 2,47 (t, J = 7,8 Hz, 2H), 2,88 (t, J = 7,8 Hz, 2H), 3,48-3,50 (m, 1H), 4,77-4,78 (m, 1H), 5,07 (s, 2H), 5,40 (s, 1H), 6,73 (dd, J = 8,3,

2,9 Hz, 1H), 6,84 (d, J = 2,4 Hz, 1H), 7,07 (d, J = 8,3 Hz, 1H). MS (ES) *m/e* 378 (M+1).

Etapa E: Éster *terc*-butílico del ácido 3-{2-ciclohexilcarbamoiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



Un tubo Carousel de 40 ml se cargó con éster *terc*-butílico del ácido 3-(2-ciclohexil-carbamoiloximetil-4-hidroxifenil)propiónico (0,10 g, 0,26 mmol) en DMF anhidra (1,0 ml). Se añadió 2-(5-metil-2-feniloxazol-4-il)etil éster del ácido tolueno-4-sulfónico (0,104g, 0,292 mmol) y carbonato de cesio (0,13 g, 0,40 mmol). La mezcla se agitó y se calentó a 55° C en una atmósfera de nitrógeno durante 30 h y se concentró. El residuo se diluyó con EtOAc (50 ml) y se lavó dos veces con salmuera (2x), se secó (Na_2SO_4), y se concentró. El residuo bruto se purificó usando cromatografía radial (EtOAc: CH_2Cl_2 2:98 a 5:95) para dar un sólido blanco (0,085 g, 57%). ^1H RMN (400 MHz, $CDCl_3$) δ 1,07-1,19 (m, 3H), 1,24-1,38 (m, 2H), 1,42 (s, 9H), 1,56-1,60 (m, 1H), 1,67-1,70 (m, 2H), 1,91-1,93 (m, 2H), 2,37 (s, 3H), 2,46 (t, J = 7,8 Hz, 2H), 2,88 (t, J = 7,8 Hz, 2H), 2,96 (t, J = 7,8 Hz, 2H), 3,48-3,50 (m, 1H), 4,22 (t, J = 6,8 Hz, 2H), 4,69-4,71 (m, 1H), 5,07 (s, 2H), 6,80 (dd, J = 8,3, 2,4 Hz, 1H), 6,90 (d, J = 2,4 Hz, 1H), 7,10 (d, J = 8,3 Hz, 1H), 7,39-7,45 (m, 3H), 7,98 (dd, J = 4,2, 2,2 Hz, 2H). MS (ES) *m/e* 563 (M+1).

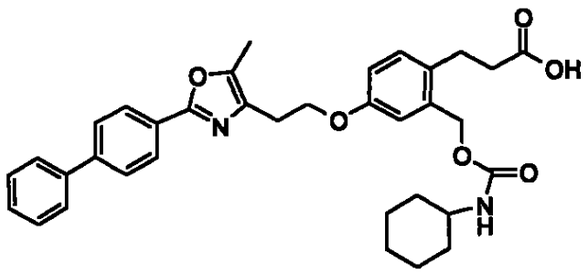
Etapa F: Ácido 3-{2-ciclohexilcarbamoiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico

Un matraz de fondo redondo de 25 ml se cargó con éster *terc*-butílico del ácido 3-{2-ciclohexilcarbamoiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}-propiónico (0,080 g, 0,14 mmol) y CH_2Cl_2 (2 ml). Se añadió ácido trifluoroacético (2ml), y la solución se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 1,5 h. La solución se concentró para dar un sólido blanco (0,068 g, 94%) . ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,08-1,18 (m 3H), 1,21-1,42 (m, 2H), 1,57 (s a, 1H), 1,66-1,70 (m, 2H), 1,90 (s a, 2H), 2,40 (s, 3H), 2,61 (t, J = 7,7 Hz, 2H), 2,94 (t, J = 7,8 Hz, 2H), 3,01 (t, J = 6,4 Hz, 2H), 3,48 (s a, 1H), 4,22 (t, J = 6,4 Hz, 2H), 4,74 (s a, 1H), 5,07 (s, 2H), 6,79-6,89 (m, 1H), 6,90 (s, 1H), 7,11 (d, J = 8,3 Hz, 1H), 7,44-7,46 (m, 3H), 7,98 (dd, J = 6,7, 2,8 Hz, 2H). MS (ES) *m/e* 507 (M+1).

Los siguientes Ejemplos 653 a 661 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 652.

Ejemplo 653

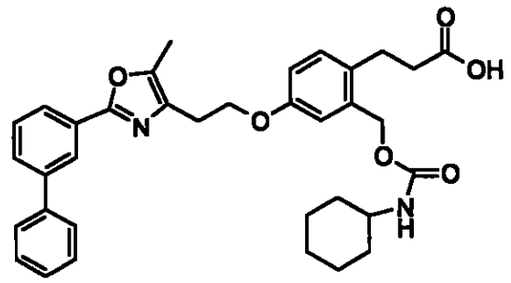
Éster *terc*-butílico del ácido 3-{4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-ciclohexilcarbamoiloximetilfenil}propiónico



MS (ES) *m/e* 639 (M+1).

Ejemplo 654

Ácido 3-{4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-ciclohexilcarbamoiloximetilfenil}propiónico



^{1}H RMN (400 MHz, $CDCl_3$) δ 1,14-1,25 (m, 3H), 1,31-1,34 (m, 2H), 1,56-1,66 (m, 1H), 1,69-1,70 (m, 2H), 1,89 (s a, 2H), 2,46 (s, 3H), 2,62 (t, J = 7,6 Hz, 2H), 2,93 (t, J = 7,8 Hz, 2H), 3,11 (t, J = 5,9 Hz, 2H), 3,47 (s a, 1H), 4,24 (t, J = 5,9 Hz, 2H), 4,83 (s a, 1H), 5,08 (s, 2H), 6,80 (d, J = 6,8 Hz, 1H), 6,90 (d, J = 2,9 Hz, 1H), 7,11 (d, J = 8,3 Hz, 1H), 7,41 (d, J = 7,3 Hz, 1H), 7,48 (t, J = 7,6 Hz, 2H), 7,64 (d, J = 7,3 Hz, 2H), 7,74 (d, J = 8,3 Hz, 2H), 8,09 (d, J = 8,3 Hz, 2H). MS (ES) *m/e* 583 (M+1).

Ejemplo 655

Éster terc-butílico del ácido 3-{4-[2-(2-bifenil-3-il-5-metiloxazol-4-il)etoxi]-2-ciclohexilcarbamoiloximetilfenil}propiónico

MS (ES) *m/e* 639 (M+1)

Ejemplo 656

Ácido 3-{4-[2-(2-bifenil-3-il-5-metiloxazol-4-il)etoxi]-2-ciclohexilcarbamoiloximetilfenil}propiónico

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,26-1,41 (m, 3H), 1,44-1,56 (m, 2H), 1,75 (s a, 1H), 1,84-1,88 (m, 2H), 2,08-2,10 (m, 2H), 2,63 (s, 3H), 2,80 (t, J = 7,8 Hz, 2H), 3,12 (t, J = 7,9 Hz, 2H), 3,27 (t, J = 6,1 Hz, 2H), 3,66 (s a, 4,42 (t, J = 6,1 Hz,

2H), 4,97 (s a, 1H), 5,27 (s, 2H), 7,04 (d, J = 6,4 Hz, 1H), 7,08 (d, J = 2,4 Hz, 1H), 7,30 (d, J = 8,3 Hz, 1H), 7,55-7,76 (m, 4H), 7,85-7,86 (m, 2H), 7,92 (d, J = 7,8 Hz, 1H), 8,15 (d, J = 7,8 Hz, 1H), 8,44 (d, J = 1,5 Hz, 1H). MS (ES) *m/e* 583 (M+1).

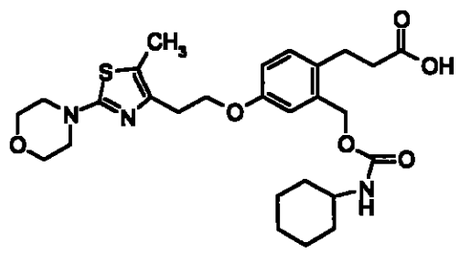
Ejemplo 657

Éster *terc*-butílico del ácido 3-{2-ciclohexilcarbamoiloximetil-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil}propiónico

MS (ES) *m/e* 588 (M+1)

Ejemplo 658

Ácido 3-{2-ciclohexilcarbamoiloximetil-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil}propiónico



^{1}H RMN (400 MHz, $CDCl_3$) δ 1,11-1,37 (m, 5H), 1,57-1,61 (m, 1H), 1,68-1,72 (m, 2H), 1,90-1,93 (m, 2H), 2,29 (s, 3H), 2,58 (t, J = 7,8 Hz, 2H), 2,90 (t, J = 7,6 Hz, 2H), 3,06 (t, J = 5,1 Hz, 2H), 3,47-3,50 (m, 1H), 3,66 (t, J = 4,6 Hz, 4H), 3,85 (t, J = 4,9 Hz, 4H), 4,20 (t, J = 5,4 Hz, 2H), 5,06 (s,.2H), 6,74 (d, J = 8,3 Hz, 1H), 6,86 (s, 1H), 7,08 (d, J = 8,3 Hz, 1H). MS (ES) *m/e* 532 (M+1).

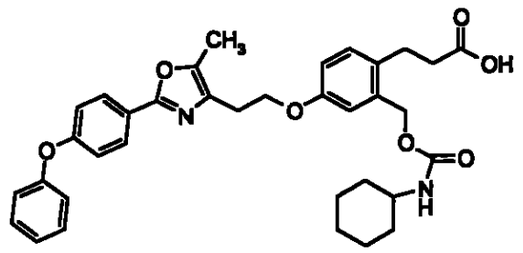
Ejemplo 659

Éster *terc*-butílico del ácido 3-(2-ciclohexilcarbamoiloximetil-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil)propiónico

MS (ES) *m/e* 655 (M+1)

Ejemplo 660

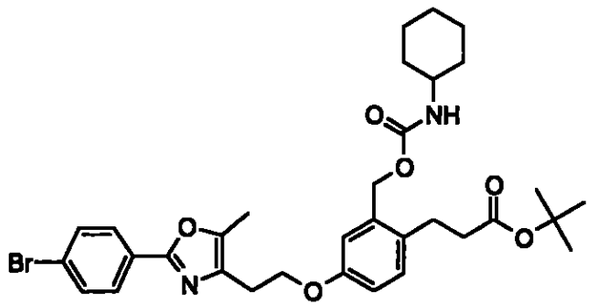
Ácido 3-(2-ciclohexilcarbamoiloximetil-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil)propiónico



^{1}H RMN (400 MHz, $CDCl_3$) δ 1,15-1,24 (m, 3H), 1,26-1,34 (m, 2H), 1,57 (s a, 1H), 1,67-1,70 (m, 2H), 1,90 (s a, 2H), 2,43 (s, 3H), 2,61 (t, 7,6 Hz, 2H), 2,93 (t, J = 7,3 Hz, 2H), 3,08 (t, J = 5,6 Hz, 2H), 3,47-3,52 (m, 1H), 4,22 (t, J = 5,6 Hz, 1H), 4,84 (s a, 1H, 1H), 6,79 (d, 2,4 Hz, 1H), 6,88 (d, J = 2,4 Hz, 1H), 7,00-7,12 (m, 5H), 7,21 (t, J = 7,6 Hz, 1H), 7,41 (t, J = 7,8 Hz, 2H), 7,99 (d, 8,8 Hz, 2H). MS (ES) *m/e* 599 (M+1).

Ejemplo 661

Éster *terc*-butílico del ácido 3-(4-{2-[2-(4-bromofenil)-5-metiloxazol-4-il]etoxi}-2-ciclohexilcarbamoiloximetilfenil)propiónico

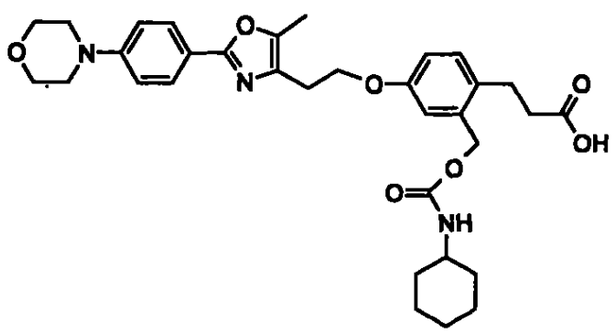


MS (ES) *m/e* 641 (M+1).

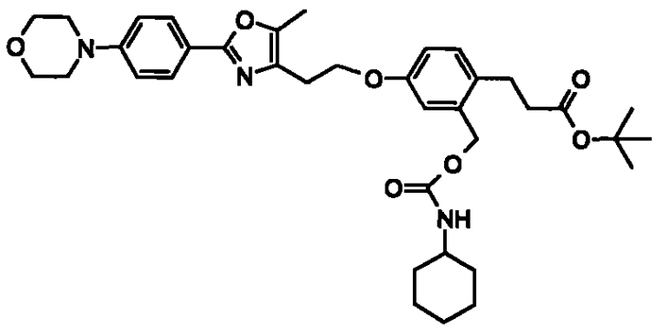
897
898

Ejemplo 662

Ácido 3-(2-ciclohexilcarbamoiloximetil-4-{2-[5-metil-2-(4-morfolin-4-ilfenil)oxazol-4-il]etoxi}fenil)propiónico



Etapa A: Éster *terc*-butílico del ácido 3-(2-ciclohexilcarbamoiloximetil-4-{2-[5-metil-2-(4-morfolin-4-ilfenil)oxazol-4-il]etoxi}fenil)propiónico



Un microvial de 1 ml en una atmósfera de nitrógeno se cargó con éster *terc*-butílico del ácido 3-(4-{2-[2-(4-bromofenil)-5-metiloxazol-4-il]etoxi}-2-ciclohexilcarbamoiloximetilfenil)-propiónico (0,30 g, 0,468 mmol; Ejemplo 39), tolueno anhidro (0,5 ml), y después morfolina (0,053 ml, 0,61 mmol). Se añadieron secuencialmente tris(dibencilidenoacetona)-dipaladio(0) (0,004 g, 0,0044 mmol), 2-(di-*terc*-butilfosfina)bifenilo (0,006 g, 0,020 mmol), y *terc*-butóxido de sodio (0,063g, 0,655 mmol). La mezcla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 5 h y se vertió en EtOAc (50

ml). La capa orgánica se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró para dar un aceite amarillo oscuro. Este producto bruto se purificó usando cromatografía radial (EtOAc:hexanos 15:85 a 50:50) para dar un aceite amarillo (0,058 g, 19%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,07-1,18 (m, 3H), 1,29-1,40 (m, 1H), 1,42 (s, 9H), 1,52-1,70 (m, 4H), 1,91-1,93 (m, 2H), 2,34 (s, 3H), 2,46 (t, J = 8,1 Hz, 2H), 2,87 (t, J = 7,8 Hz, 2H), 2,94 (t, J = 6,8 Hz, 2H), 3,24 (t, J = 4,9 Hz, 4H), 3,48-3,50 (m, 1H), 3,86 (t, J = 4,9 Hz, 4H), 4,20 (t, J = 6,6 Hz, 2H), 5,07 (s, 2H), 6,79 (dd, J = 8,6, 2,7 Hz, 1H), 6,85-6,93 (m, 3H), 7,09 (d, J = 8,3 Hz, 1H), 7,87 (dd, J = 11,5, 2,7 Hz, 2H). MS (ES) *m/e* 648 (M+1).

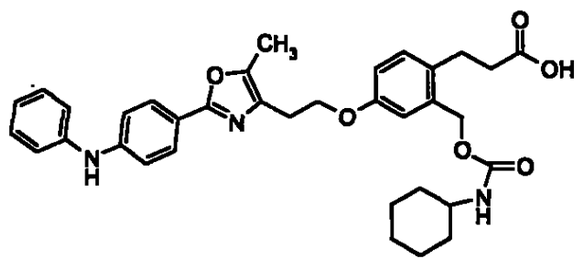
Etapa B: Ácido 3-(2-ciclohexilcarbamoiloximetil-4-{2-[5-metil-2-(4-morfolin-4-ilfenil)oxazol-4-il]etoxi}fenil)propiónico

Un matraz de fondo redondo de 15 ml se cargó con ácido 3-(2-ciclohexilcarbamoiloximetil-4-{2-[5-metil-2-(4-morfolin-4-ilfenil)oxazol-4-il]etoxi}fenil)propiónico (0,058 g, 0,09 mmol) y CH_2Cl_2 (1 ml). Se añadió ácido trifluoroacético (0,5 ml), y la solución se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 1,5 h. La mezcla se concentró para dar un sólido amarillo (0,052 g, 98%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,03-1,11 (m, 3H), 1,18-1,30 (m, 2H), 1,45-1,50 (m, 1H), 1,60-1,63 (m, 2H), 1,82-1,85 (m, 2H), 2,38 (s, 3H), 2,52 (t, J = 7,6 Hz, 2H), 2,84 (t, J = 7,6 Hz, 2H), 3,04 (t, J = 5,6 Hz, 2H), 3,30 (t, J = 4,9 Hz, 4H), 3,39 (s a, 1H), 3,80 (t, J = 4,9 Hz, 4H), 4,17 (t, J = 5,9 Hz, 2H), 4,86 (s a, 1H), 4,99 (s, 2H), 6,70 (d, J = 8,3 Hz, 1H), 6,81 (d, J = 2,4 Hz, 1H), 7,03 (d, J = 8,3 Hz, 1H), 7,90 (d, J = 9,3 Hz, 2H). MS (ES) *m/e* 592 (M+1).

Los siguientes Ejemplos 663 a 664 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 662.

Ejemplo 663

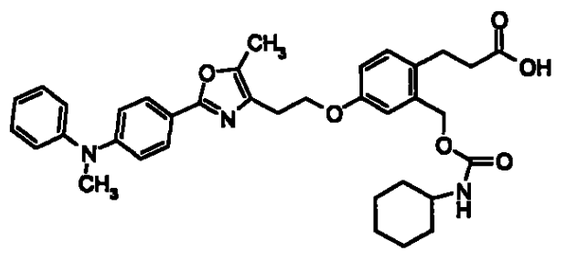
Ácido 3-(2-ciclohexilcarbamoiloximetil-4-{2-[5-metil-2-(4-fenilaminofenil)oxazol-4-il]etoxi}fenil)propiónico



^{1}H RMN (400 MHz, $CDCl_3$) δ 1,11-1,42 (m, 5H), 1,56 (s a, 1H), 1,66-1,69 (m, 2H), 1,89-1,92 (m, 2H), 2,38 (s, 3H), 2,60 (t, J = 7 Hz, 2H), 2,91 (t, J = 7 Hz, 2H), 3,03 (t, J = 5,6 Hz, 2H), 4,22 (t, J = 6,1 Hz, 2H), 4,86 (s a, 1H), 5,06 (s, 2H), 6,78 (d, J = 7,8 Hz, 1H), 6,89 (s, 1H), 7,04-7,10 (m, 4H), 7,16 (d, J = 7,8 Hz, 2H), 7,34 (t, J = 7,8 Hz, 2H), 7,88 (d, J = 8,3 Hz, 2H). MS (ES) *m/e* 598 (M+1).

Ejemplo 664

Ácido 3-[2-ciclohexilcarbamoiloximetil-4-(2-{5-metil-2-[4-(metilfenilamino)fenil]oxazol-4-il}etoxi)fenil]propiónico

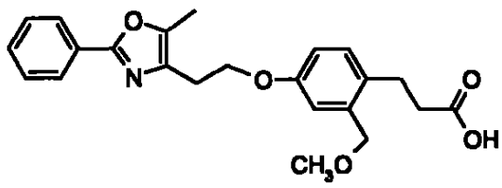


^{1}H RMN (400 MHz, $CDCl_3$) δ 1,02-1,35 (m, 5H), 1,56 (s a, 1H), 1,67-1,70 (m, 2H), 1,89 (s a, 2H), 2,41 (s, 3H), 2,60 (t, J = 7 Hz, 2H), 2,91 (t, J = 7 Hz, 2H), 3,09 (t, J = 7 Hz, 2H), 3,39 (s, 3H), 3,47 (s a, 1H), 4,24 (t, J = 7 Hz, 2H), 4,95

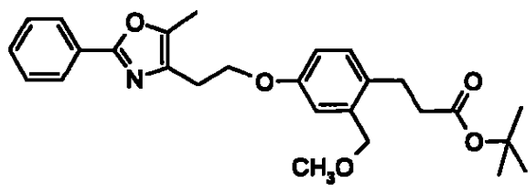
(s a, 1H), 5,06 (s, 2H), 6,81 (d, J = 8,3 Hz, 2H), 6,89 (s, 1H), 7,09 (d, J = 7,8 Hz, 1H), 7,23 (t, J = 7,6 Hz, 3H), 7,43 (t, J = 7,8 Hz, 3H), 7,87 (d, J = 8,8 Hz, 2H). MS (ES) *m/e* 612 (M+1).

Ejemplo 665

Ácido 3-{2-metoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



Etapa A: Éster *terc*-butílico del ácido 3-{2-metoximetil-4-[2-(5-metil-2-feniloxazol-4-il) etoxi] fenil} propiónico



Un matraz de fondo redondo de 15 ml se cargó con éster *terc*-butílico del ácido 3-{2-hidroximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico (0,10 g, 0,23 mmol) y yoduro de metilo (0,21 ml, 2,3 mmol) en DMF anhidra (1 ml) en una atmósfera de nitrógeno. La mezcla se enfrió en un baño de hielo y se trató en una porción con NaH (0,018 g, 0,25 mmol, dispersión en aceite al 60%). La mezcla de reacción se agitó durante 2 h, se concentró, y se diluyó con EtOAc (40 ml). La capa orgánica se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró. El producto bruto se purificó usando cromatografía radial (EtOAc:hexanos 10:90 a 25:75) para dar un aceite amarillo (0,060 g, 58%). MS (ES) *m/e* 648 (M+1).

Etapa B: Ácido 3-{2-metoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}

propiónico

Un matraz de fondo redondo de 15 ml se cargó con éster *terc*-butílico del ácido 3-{2-metoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico (0,060 g, 0,13 mmol), CH_2Cl_2 (1,2 ml), y después ácido trifluoroacético (0,6 ml). La solución se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 16 h y se concentró. El residuo se diluyó con CH_2Cl_2 (30 ml) y se lavó con salmuera. La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró para dar un sólido blanco (0,046 g, 89%) . MS (ES) *m/e* 648 (M+1).

Los siguientes Ejemplos 666 a 673 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 665.

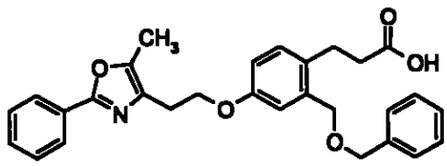
Ejemplo 666

Éster *terc*-butílico del ácido 3-{2-benciloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico

MS (ES) *m/e* 528 (M+1)

Ejemplo 667

Ácido 3-{2-benciloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 472 (M+1).

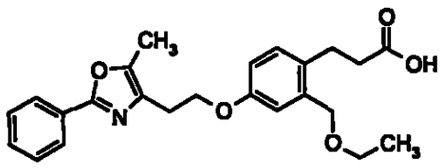
Ejemplo 668

Éster *terc*-butílico del ácido 3-{2-etoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico

MS (ES) *m/e* 466 (M+1)

Ejemplo 669

Ácido 3-{2-etoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 410 (M+1).

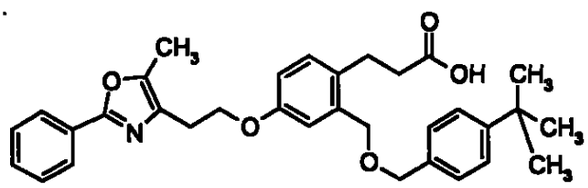
Ejemplo 670

Éster *terc*-butílico del ácido 3-{2-(4-*terc*-butil-benciloximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico

MS (ES) *m/e* 584 (M+1)

Ejemplo 671

Ácido 3-{2-(4-*terc*-butil-benciloximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 410 (M+1).

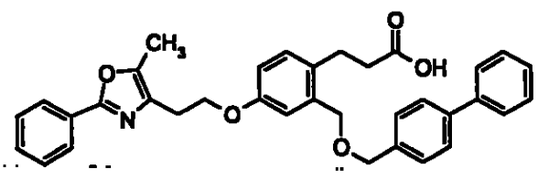
Ejemplo 672

Éster *terc*-butílico del ácido 3-{2-(bifenil-4-ilmetoximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico

MS (ES) *m/e* 604 (M+1)

Ejemplo 673

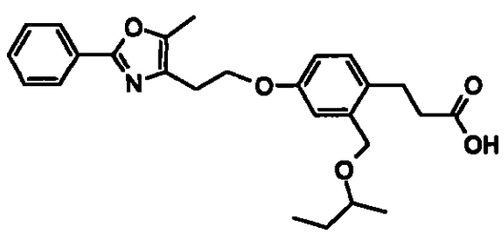
Ácido 3-{2-(bifenil-4-ilmetoximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 410 (M+1).

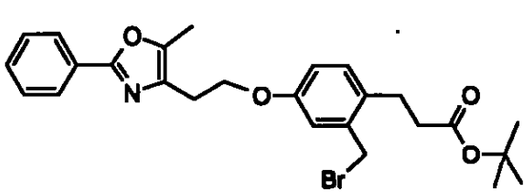
Ejemplo 674

Ácido 3-{2-*sec*-butoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



Etapa A: Éster *terc*-butílico del ácido 3-{2-bromometil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}

propiónico



Un matraz de fondo redondo de 100 ml se cargó con éster terc-butílico del ácido 3-{2-hidroximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico (1,0 g, 2,29 mmol), THF anhidro (25 ml), y después trifenilfosfina (1,20 g, 4,57 mmol) y CBr_4 (1,52 g, 4,57 mmol). La mezcla amarilla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 1 h y se vertió en EtOAc (100 ml). La capa orgánica se lavó con salmuera, se secó (Na_2SO_4), y se concentró. El producto bruto se purificó usando cromatografía radial (EtOAc:hexanos

15:85 a 25:75) para dar un aceite incoloro (0,95 g, 83%). MS (ES) *m/e* 501 (M+1).

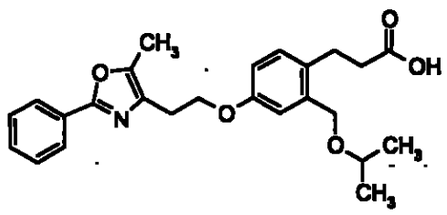
Etapa B: Ácido 3-{2-*sec*-butoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico

Un matraz de fondo redondo de 15 ml secado a la llama se cargó con 2-butanol (0,92 ml, 1,0 mmol), DMF anhidra (1 ml), y después NaH (0,013 g, 0,2 mmol, dispersión en aceite al 60%). La mezcla de reacción se enfrió en un baño de hielo durante 15 min, y se añadió éster *terc*-butílico del ácido 3-{2-bromometil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico ((0,050 g,0,10 mmol) en DMF anhidra (0,5 ml). La mezcla de reacción se agitó en una atmósfera de nitrógeno durante 2 h. Se formó una mezcla del producto del ácido libre y *terc*-butil éster. La reacción se vertió en EtOAc (40 ml), se lavó con salmuera (3x), se secó (Na_2SO_4), y se concentró. El aceite bruto se disolvió después directamente en CH_2Cl_2 (1 ml) y se trató con TFA (1,5 ml). La solución se agitó a temperatura ambiente durante 16 h y se concentró. El residuo del producto bruto se purificó usando cromatografía radial (EtOAc:hexanos 15:85 a 1:1) para dar un aceite amarillo (0,012 g, 27%). MS (ES) *m/e* 438 (M+1).

Los siguientes Ejemplos 675 a 680 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 674.

Ejemplo 675

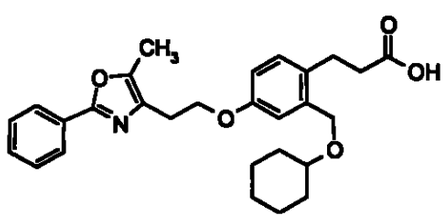
Ácido 3-{2-isopropoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-fenil}propiónico



MS (ES) *m/e* 424 (M+1).

Ejemplo 676

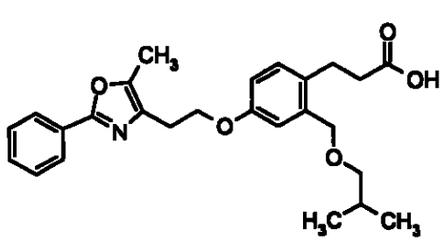
Ácido 3-{2-ciclohexiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 464 (M+1).

Ejemplo 677

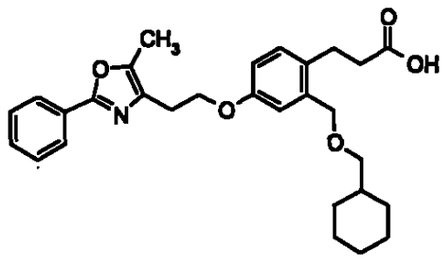
Ácido 3-{2-isobutoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 438 (M+1).

Ejemplo 678

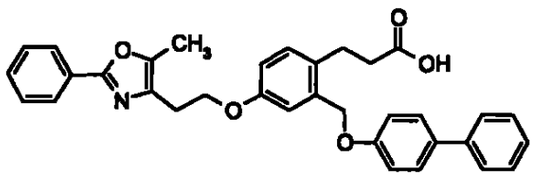
Ácido 3-{2-ciclohexilmetoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 478 (M+1).

Ejemplo 679

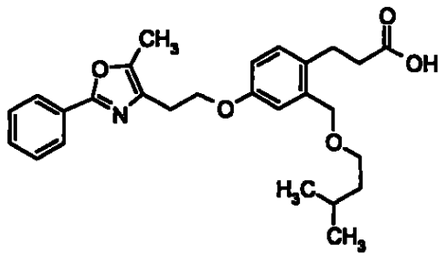
Ácido 3-{2-(bifenil-4-iloximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 534 (M+1).

Ejemplo 680

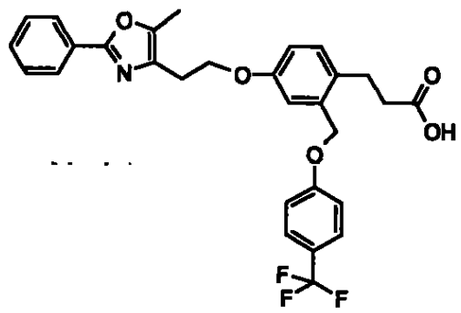
Ácido 3-{2-(3-metilbutoximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 452 (M+1).

Ejemplo 681

Ácido 3-[4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-(4-trifluorometilfenoximetil)-fenil]propiónico

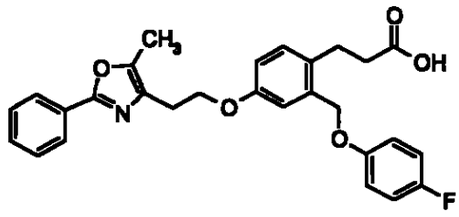


Procedimiento general para síntesis paralela usando el aparato DynaVac Carousel. Un tubo de vidrio de 50 ml con tapa a rosca y entrada de nitrógeno se cargó con éster *terc*-butílico del ácido 3-{2-bromometil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico (0,040 g, 0,080 mmol), 4-trifluorometilfenol (0,019 g 0,12 mmol), DMF anhidra (0,5 ml), y después carbonato de cesio (0,039 g, 0,12 mmol). La mezcla se agitó a temperatura ambiente durante 16 h. El análisis de MS de la reacción indicó la formación del producto del éster intermedio [MS (ES) *m/e* 582 (M+1)]. La mezcla de reacción se vertió en éter (30 ml). La capa orgánica se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró. El residuo se diluyó con CH_2Cl_2 (1 ml) y ácido trifluoroacético (5 ml) se le añadió. La mezcla se agitó a temperatura ambiente durante 1,5 h y se concentró. La mezcla del producto bruto se purificó por HPLC de fase inversa y de masa dirigida para proporcionar el compuesto del título (0,045 g, 64%). MS (ES) *m/e* 526 (M+1).

Los siguientes Ejemplos 682 a 691 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 681.

Ejemplo 682

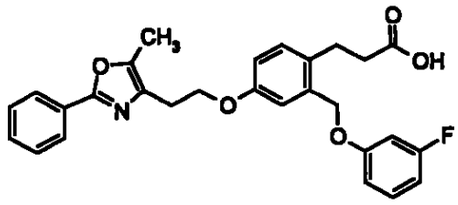
Ácido 3-{2-(4-fluorofenoximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 476 (M+1).

Ejemplo 683

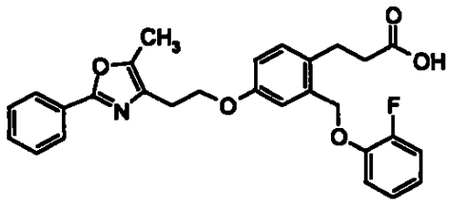
Ácido 3-{2-(3-fluorofenoximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 476 (M+1).

Ejemplo 684

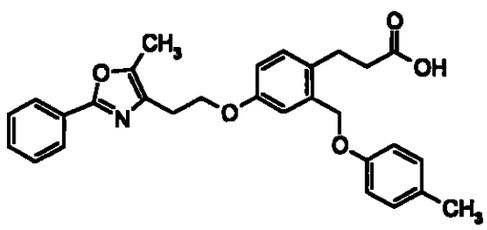
Ácido 3-{2-(2-fluorofenoximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 476 (M+1).

Ejemplo 685

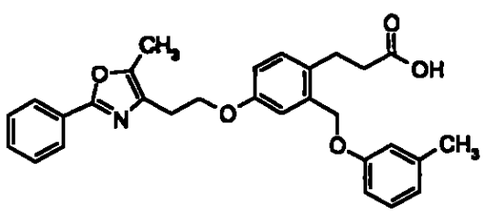
Ácido 3-{4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-*p*-toliloximetilfenil}propiónico



MS (ES) *m/e* 472 (M+1).

Ejemplo 686

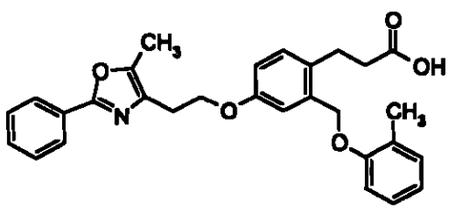
Ácido 3-{4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-*m*-toliloximetilfenil}propiónico



MS (ES) *m/e* 472 (M+1).

Ejemplo 687

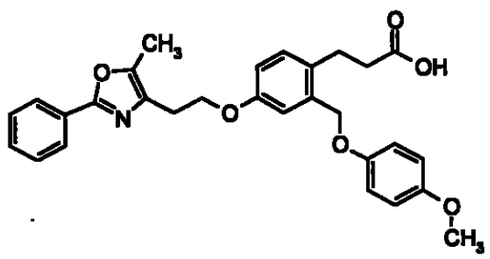
Ácido 3-{4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-*o*-toliloximetilfenil}propiónico



MS (ES) *m/e* 472 (M+1).

Ejemplo 688

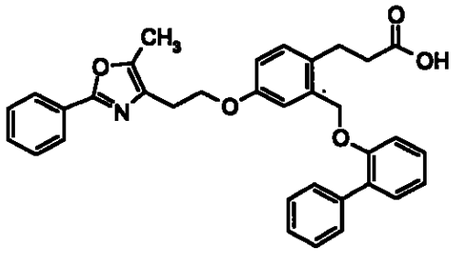
Ácido 3-{2-(4-metoxifenoximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 488 (M+1).

Ejemplo 689

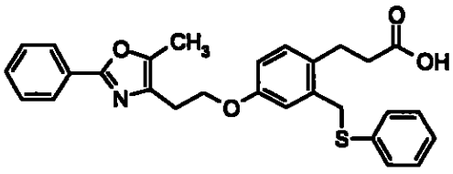
Ácido 3-{2-(bifenil-2-iloximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 534 (M+1).

Ejemplo 690

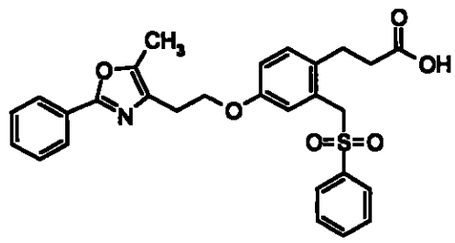
Ácido 3-{4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-fenilsulfanilmetilfenil}propiónico



MS (ES) *m/e* 474 (M+1).

Ejemplo 691

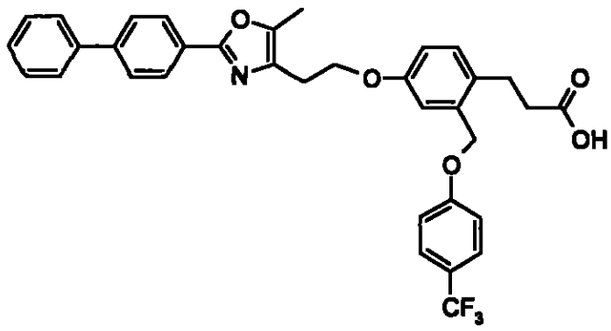
Ácido 3-{2-bencenosulfonilmetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil}propiónico



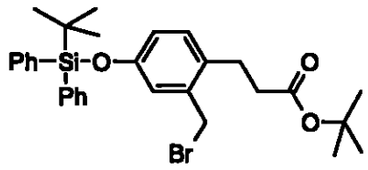
MS (ES) *m/e* 506 (M+1).

Ejemplo 692

Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(4-trifluorometilfenoxi-metil)-fenil]-propiónico



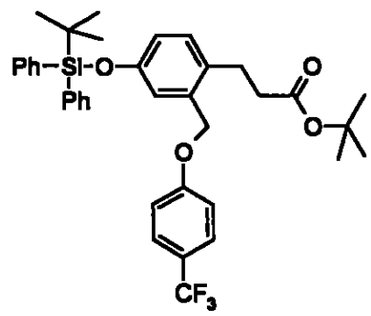
Etapa A: Éster *terc*-butílico del ácido 3-[2-bromometil-4-(terc-butildifenilsilaniloxi)fenil]propiónico



Un matraz de fondo redondo de 200 ml se cargó con éster *terc*-butílico del ácido 3-[4-(*terc*-butil-difenilsilaniloxi)-2-hidroximetilfenil]propiónico (3,03 g, 6,18 mmol), THF anhidro (75 ml), y después trifenilfosfina (3,24 g, 12,4 mmol) y CBr_4 (4,10 g, 12,4 mmol). La mezcla amarilla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 1 h y se concentró. El residuo se diluyó

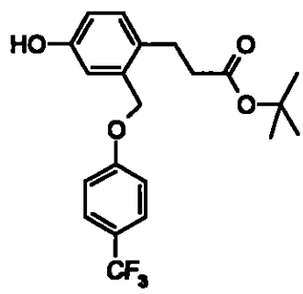
con EtOAc (500 ml). La capa orgánica se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró para dar un sólido. El producto bruto se purificó usando el sistema de cromatografía de media presión Biotage (EtOAc:hexanos 10:90) para dar un aceite amarillo (2,95 g, 86%), MS (ES) *m/e* 572 ($M+NH_4$).

Etapa B: Éster *terc*-butílico del ácido 3-[4-(*terc*-butildifenilsilaniloxi)-2-(4-trifluorometilfenoximetil) fenil]-propiónico



Un matraz de fondo redondo de 50 ml se cargó con éster *terc*-butílico del ácido 3-[2-bromometil-4-(*terc*-butildifenilsilaniloxi)fenil]propiónico (1,0 g, 1,81 mmol), DMF anhidra (10 ml), y después 4-trifluorometilfenol (0,44 g, 2,7 mmol) y carbonato de cesio (0,88 g, 2,7 mmol). La mezcla de reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 18 h y se concentró. El residuo se diluyó con EtOAc (100 ml). La capa orgánica se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró para dar un aceite amarillo. El residuo bruto se purificó usando radial (EtOAc:hexanos 15:85 a 50:50) para dar un aceite amarillo (0,66 g, 58%). MS (ES) *m/e* 635 (M+1).

Etapa C: Éster *terc*-butílico del ácido 3-[4-hidroxi-2-(4-trifluorometilfenoximetil)fenil]propiónico



Un matraz de fondo redondo de 100 ml se cargó con éster *terc*-butílico del ácido 3-[4-(terc-butildifenilsilaniloxi)-2-(4-trifluorometilfenoximetil)fenil]propiónico (0,65 g, 1,02 mmol), THF anhidro (40 ml), y después fluoruro de tetrabutilamonio (3,1 ml, 3,1 mmol, 1,0 M en THF). La reacción se agitó en una atmósfera de nitrógeno durante 1,5 h y se concentró. El residuo se diluyó con EtOAc (100 ml). La capa orgánica se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró hasta un aceite naranja. El aceite bruto se purificó usando cromatografía radial (EtOAc:hexanos 15:85) para dar un sólido blanco (0,31 g, 77%). MS (ES) *m/e* 395 (M-1).

Etapa D: Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(4-trifluorometilfenoxi-metil)-fenil]-propiónico

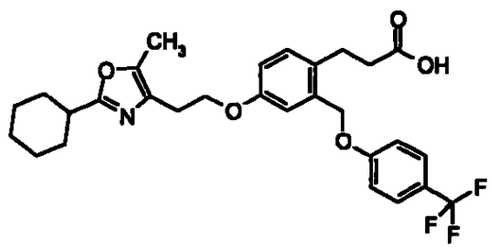
Procedimiento General para síntesis paralela usando el aparato DynaVac Carousel: Un tubo de vidrio de 50 ml con tapa a rosca y entrada de nitrógeno se cargó con éster *terc*-butílico del ácido 3-[4-hidroxi-2-(4-trifluorometilfenoximetil)fenil]propiónico (0,050 g, 0,146 mmol), 2-(2-bifenil-4-il-5-metiloxazol-4-il)etil éster del ácido tolueno-4-sulfónico (0,078 g, 0,18 mmol), DMF anhidra (0,5 ml), y después carbonato de cesio (0,072 g, 0,22 mmol). La mezcla se agitó a temperatura ambiente durante 16 h. El análisis MS de la reacción indicó la formación del éster intermedio MS (ES) *m/e* 658 (M+1). La mezcla de reacción se vertió en éter (30 ml). La capa orgánica se lavó con

salmuera (2x), se secó (Na_2SO_4), y se concentró. El residuo bruto se diluyó con CH_2Cl_2 (2 ml) y después ácido trifluoroacético (1 ml). La mezcla se agitó a temperatura ambiente durante 2 h y se concentró en una atmósfera de N_2. El producto bruto se purificó por HPLC de fase inversa y de masa dirigida para proporcionar el compuesto del título (0,053 g, 71%) . ^{1}H RMN (250 MHz, $CDCl_3$) δ 2,41 (s, 3H), 2,70 (t, J = 7,7 Hz, 2H), 2,95-3,05 (m, 4H), 4,28 (t, J = 6,6 Hz, 2H), 5,09 (s, 2H), 6,90 (dd, J = 8,5, 2,8 Hz, 1H), 7,01 (d, J = 2,6 Hz, 1H), 7,06 (d, J = 8,6 Hz, 2H), 7,21 (d, J = 8,5 Hz, 1H), 7,41-7,72 (m, 9H), 8,07 (d, J = 8,4 Hz, 2H). MS (ES) *m/e* 602 (M+1).

Los siguientes Ejemplos 693 a 697 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 692.

Ejemplo 693

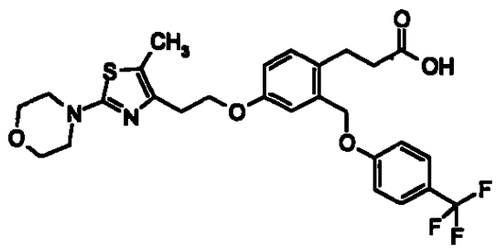
Ácido 3-[4-[2-(2-ciclohexil-5-metiloxazol-4-il)etoxi]-2-(4-trifluorometilfenoximetil)fenil]propiónico



MS (ES) *m/e* 532 (M+1).

Ejemplo 694

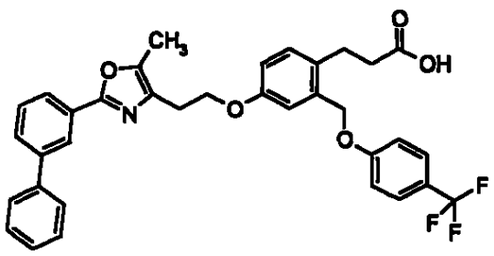
Ácido 3-[4-[2-(5-metil-2-morfolin-4-il-tiazol-4-il)etoxi]-2-(4-trifluorometilfenoximetil)fenil]propiónico



MS (ES) *m/e* 551 (M+1).

Ejemplo 695

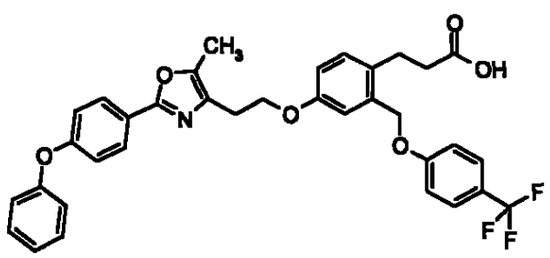
Ácido 3-[4-[2-(2-bifenil-3-il-5-metiloxazol-4-il)etoxi]-2-(4-trifluorometil-fenoximetil)fenil]propiónico



MS (ES) *m/e* 602 (M+1).

Ejemplo 696

Ácido 3-[4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}-2-(4-trifluorometilfenoximetil)fenil]propiónico



MS (ES) *m/e* 618 (M+1).

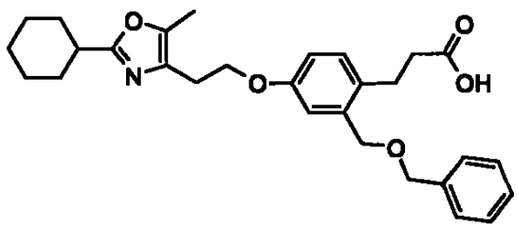
Ejemplo 697

Ácido 3-[4-[4-metil-2-(4-trifluorometilfenil)tiazol-5-ilmetoxi]-2-(4-trifluorometilfenoximetil)fenil]propiónico

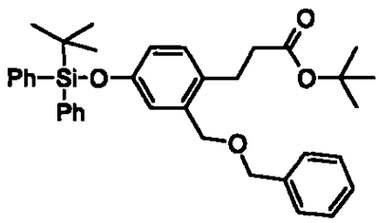
MS (ES) *m/e* 596 (M+1)

Ejemplo 698

Ácido 3-{2-benciloximetil-4-[2-(2-ciclohexil-5-metil-oxazol-4-il)-etoxi]-fenil}-propiónico



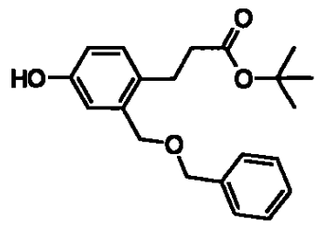
Etapa A: Éster *terc*-butílico del ácido 3-[2-benciloximetil-4-(terc-butil-difenil-silaniloxi)-fenil]-propiónico



Un matraz de fondo redondo de 100 ml se cargó con éster *terc*-butílico del ácido 3-[4-(terc-butil-difenilsilaniloxi)-2-hidroximetilfenil]propiónico (1,52 g, 3,10 mmol), DMF anhidra (15 ml), y después bromuro de bencilo (1,84 ml, 15,5 mmol) en una atmósfera de nitrógeno. La solución se enfrió a -10°C, y se añadió NaH (0,124 g, 3,10 mmol, dispersión en aceite al 60%). La mezcla se agitó durante 5 h, y se vertió en EtOAc (150 ml). La capa orgánica se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró hasta un aceite pardo. El

aceite bruto se purificó usando cromatografía radial (EtOAc:hexanos 2:98 a 5:95) para dar aceite amarillo pálido (1,04 g, 58%). MS (ES) *m/e* 598 ($M+NH_4$).

Etapa B: Éster terc-butílico del ácido 3-(2-benciloximetil-4-hidroxi-fenil)-propiónico



Un matraz de fondo redondo de 250 ml se cargó con éster terc-butílico del ácido 3-[2-benciloximetil-4-(terc-butil-difenil-silaniloxi)-fenil]-propiónico (1,03 g, 1,77 mmol), THF anhidro (60 ml), y después con fluoruro de tetrabutilamonio (5,3 ml, 5,3 mmol, 1,0 M en THF). La mezcla de reacción se agitó en una atmósfera de nitrógeno durante 1 h, se concentró, y se diluyó con EtOAc (100 ml). La capa orgánica se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró para dar un aceite. El aceite bruto se purificó usando cromatografía radial (EtOAc:hexanos 10:90 a 50:50) para dar un sólido blanco (0,52 g, 86%). MS (ES) *m/e* 343 (M-1).

Etapa C: Ácido 3-{2-benciloximetil-4-[2-(2-ciclohexil-5-metil-oxazol-4-il)-etoxi]-fenil}-propiónico

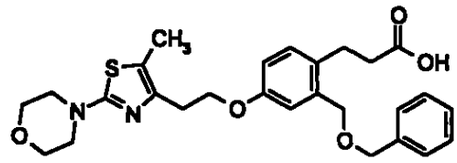
Procedimiento General para la síntesis paralela de análogos usando el aparato DynaVac Carousel: Un tubo de vidrio de 50 ml con tapa a rosca y entrada se nitrógeno se cargó con éster terc-butílico del ácido 3-(2-benciloximetil-4-hidroxi-fenil)-propiónico (0,050 g, 0,146 mmol), 2-(2-bifenil-4-il-5-metiloxazol-4-il)etil éster del ácido tolueno-4-sulfónico (0,078 g, 0,18 mmol), DMF anhidra (0,5 ml), y después con carbonato de cesio (0,072 g, 0,22 mmol). La mezcla se agitó a temperatura ambiente durante 16 h. El análisis MS de la reacción indicó que se había formado el éster intermedio, MS (ES) *m/e* 534

(M+1). La reacción bruta se vertió en éter (30 ml), y se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró al vacío. El residuo bruto se disolvió en CH_2Cl_2 (2 ml) y se añadió ácido trifluoroacético (1,0 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y se concentró en una atmósfera de N_2. El producto bruto se purificó HPLC de fase inversa dirigida de masas para proporcionar 0,053 g (71%) del ácido 3-{4-[2-(2-Ciclohexil-5-metiloxazol-4-il)etoxi]-2-fenoximetilfenil}propiónico . MS (ES) *m/e* 478 (M+1).

Los siguientes Ejemplos 699 a 704 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 698.

Ejemplo 699

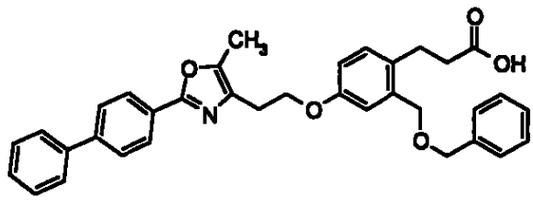
Ácido 3-{2-benciloximetil-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 497 (M+1).

Ejemplo 670

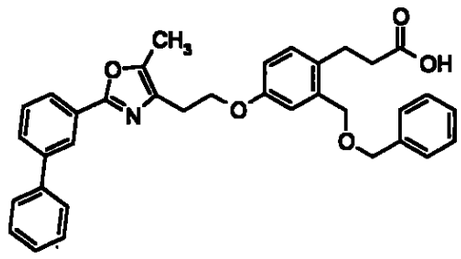
Ácido 3-{2-benciloximetil-4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]fenil}propiónico



MS (ES) *m/e* 548 (M+1).

Ejemplo 671

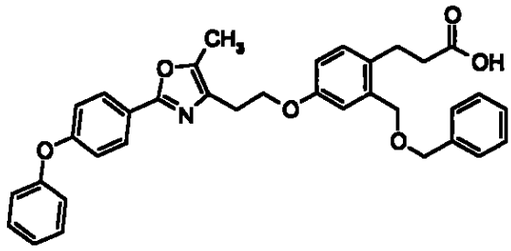
Ácido 3-{2-benciloximetil-4-[2-(2-bifenil-3-il-5-metiloxazol-4-il)etoxi]-fenil}propiónico



MS (ES) *m/e* 548 (M+1).

Ejemplo 672

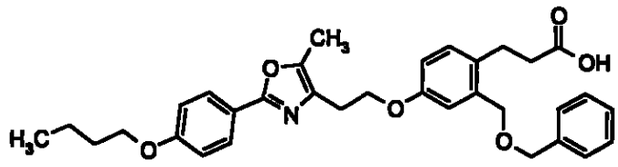
Ácido 3-(2-benciloximetil-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil)propiónico



MS (ES) *m/e* 564 (M+1).

Ejemplo 673

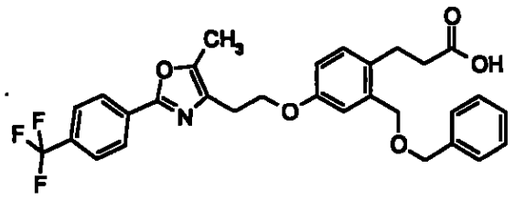
Ácido 3-(2-benciloximetil-4-{2-[2-(4-butoxifenil)-5-metiloxazol-4-il]etoxi}fenil)propiónico



MS (ES) *m/e* 544 (M+1).

Ejemplo 674

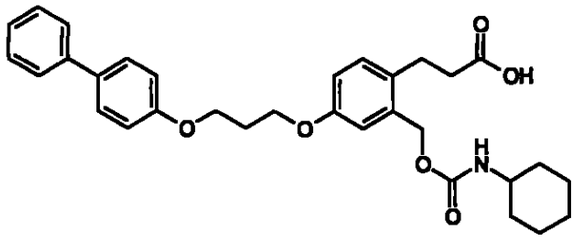
Ácido 3-(2-benciloximetil-4-{2-[5-metil-2-(4-trifluorometilfenil)oxazol-4-il]etoxi}fenil)propiónico



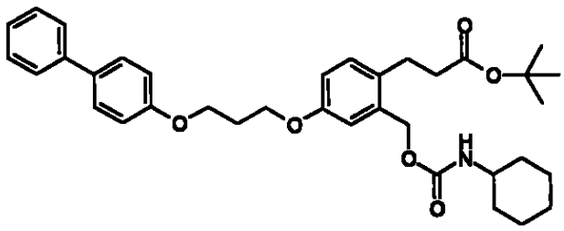
MS (ES) *m/e* 540 (M+1).

Ejemplo 705

Ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-ciclohexilcarbamoiloximetil-fenil}-propiónico



Etapa A: Éster terc-butílico del ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-ciclohexilcarbamoiloximetil-fenil}-propiónico



Una mezcla de éster terc-butílico del ácido 3-(2-ciclohexilcarbamoiloximetil-4-hidroxi-fenil)-propiónico (50 mg, 0,13 mmol; Ejemplo 652 Etapa D), 4-(3-bromo-propoxi)-bifenilo (58 mg, 0,2 mmol;

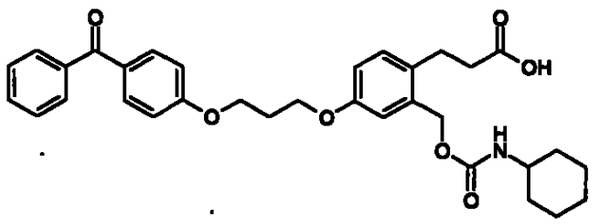
Tetrahedron 1994, *50*, 3427), y carbonato potásico (53 mg, 0,39 mmol) en acetonitrilo (6 ml) se calentó a 80°C durante una noche. Se añadieron acetato de etilo (20 ml) y H_2O (20 ml). La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo (3x). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, y se concentraron. La mezcla bruta se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo 4/1) para dar el compuesto del título (50 mg, 65%). ^{1}H-RMN (300 MHz, $CDCl_3$): d 7,54 (m, 4H), 7,42 (t, 2H, *J* = 7,6), 7,32 (d, 1H, *J* = 8,4), 7,12 (d, 1H, *J* = 8,3), 6,99 (d, 2H, *J* = 8,7), 6,93 (d, 1H, *J* = 2,2), 6,82 (dd, 1H, *J* = 8,4, 2,7), 5,09 (s, 2H), 4,74 (d, 1H, *J* = 7,5), 4,18 (m, 4H), 3,56-3,42 (m, 1H), 2,90 (t, 2H, *J* = 7,8), 2,48 (t, 2H, *J* = 7,8), 2,28 (qn, 2H, *J* = 6,0), 1,95-1,88 (m, 2H), 1,75-1,08 (m, 8H), 1,44 (s, 9H).

Etapa B: Ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-ciclohexilcarbamoiloximetil-fenil}-propiónico

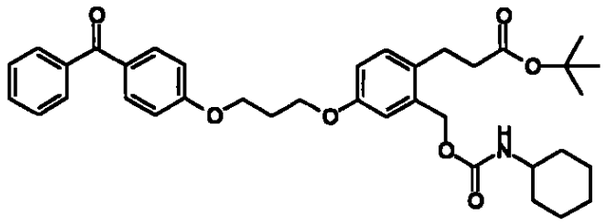
Se añadió ácido trifluoroacético (0,032 ml, 0,42 mmol) a una solución de éster terc-butílico del ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-ciclohexilcarbamoiloximetil-fenil}-propiónico (50 mg, 0,085 mmol) en CH_2Cl_2 (5 ml) a temperatura ambiente. La mezcla de reacción se agitó durante una noche y se concentró al vacío para dar el compuesto del título (41 mg, 90%). ^{1}H-RMN (200 MHz, $CDCl_3$): d 9,4 (s a, 1H), 7,58-7,49 (m, 4H), 7,42 (m, 2H), 7,32 (m, 1H), 7,13 (d, 1H, *J* = 8,3), 7,00-6,93 (m, 3H), 6,84 (dd, 1H, *J* = 7,8, 2,7), 5,11 (s, 2H), 4,76 (s a, 1H), 4,17 (m, 4H), 3,57-3,35 (m, 1H), 2,95 (t, 2H, *J* = 7,8), 2,63 (t, 2H, *J* = 7,8), 2,27 (qn, 2H, *J* = 6,0), 1,99-1,05 (m, 10H).

Ejemplo 706

Ácido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-2-ciclohexilcarbamoiloximetil-fenil}-propiónico



Etapa A: Éster terc-butílico del ácido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-2-ciclohexilcarbamoiloximetil-fenil}-propiónico



Una mezcla de éster terc-butílico del ácido 3-(2-ciclohexilcarbamoiloximetil-4-hidroxi-fenil)-propiónico (50 mg, 0,13 mmol; Ejemplo 652 Etapa D), [4-(3-bromo-propoxi)-fenil]-fenil-metanona (64 mg, 0,2 mmol, *Bull. Chem. Soc. Jpn.* 1990, *63*, 1342) y carbonato potásico (53 mg, 0,39 mmol) en acetonitrilo (6 ml) se calentó a 80°C durante una noche. Se añadieron acetato de etilo (20 ml) y H_2O (20 ml). La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo (3x). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, y se concentraron. La mezcla bruta se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo 4/1) para dar el compuesto del título (50 mg, 62%). ^{1}H-RMN (300 MHz, $CDCl_3$): d 7,74 (d, 2H, *J* = 8,5), 7,68 (d, 2H, *J* = 7,7), 7,48 (d, 1H, *J* = 8,4), 7,40 (m, 2H), 7,05 (d, 1H, *J* = 8,5), 6,90 (d, 2H, *J* = 8,6), 6,85 (s, 1H), 6,74 (dd, 1H, *J* = 8,5, 2,2), 5,04 (s, 2H), 4,68 (d, 1H, *J* = 7,3), 4,17 (t, 2H, *J* = 5,9), 4,09 (t,

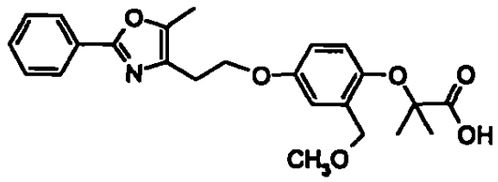
2H, *J* = 5,9), 3,43 (m, 1H), 2,82 (t, 2H, *J* = 7,8), 2,40 (t, 2H, *J* = 7,8), 2,21 (qn, 2H, *J* = 5,9), 1,85 (m, 2H), 1,67-1,02 (m, 8H), 1,36 (s, 9H).

Etapa B: Ácido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-2-ciclohexilcarbamoiloximetil-fenil}-propiónico

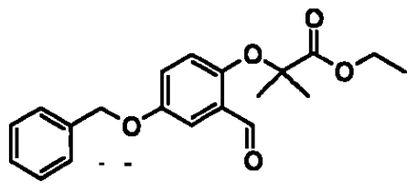
Se añadió ácido trifluoroacético (0,031 ml, 0,4 mmol) a una solución de éster terc-butílico del ácido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-2-ciclohexilcarbamoiloximetil-fenil}-propiónico (50 mg, 0,08 mmol) en CH_2Cl_2 (5 ml) a temperatura ambiente. La mezcla de reacción se agitó durante una noche y se concentró al vacío para dar el compuesto del título. (39 mg, 88%). ^{1}H-RMN (200 MHz, $CDCl_3$): d 7,83-7,72 (m, 4H), 7,57-7,43 (m, 3H), 7,12 (d, 1H, *J* = 8,6), 6,98-82 (m, 4H), 5,10 (s, 2H), 4,82 (s a, 1H), 4,23 (t, 2H, *J* = 5,9), 4,15 (t, 2H, *J* = 5,9), 3,57-3,36 (m, 1H), 2,94 (m, 2H), 2,62 (m, 2H), 2,28 (qn, 2H, *J* = 5,9), 1,98-1,02 (m, 10H).

Ejemplo 708

Ácido 2-{2-metoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico

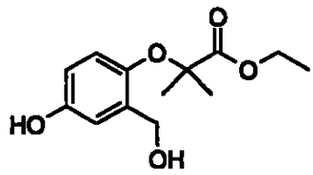


Etapa A: Éster etílico del ácido 2-(4-benciloxi-2-formil-fenoxi)-2-metil-propiónico



Se calentaron 5-benciloxi-2-hidroxi-benzaldehído (Kappe, T.; Witoszynskyj, T. *Arch. Pharm.*, 1975, *308* (5), 339-346) (169 g, 741 mmol), bromoisobutirato de etilo (164 ml, 1,11 mol), y carbonato de cesio (240 g, 741 mmol) en DMF seca (600 ml a 80 °C durante 15 h. Se añadieron más carbonato de cesio (5 g) y bromoisobutirato de etilo (20 ml) y la mezcla de reacción se calentó durante 6 h. La mezcla de reacción se enfrió, se diluyó con EtOAc (4 l), y se lavó con agua (3 x 2 l). La capa orgánica se secó (Na_2SO_4) y se concentró hasta un aceite pardo. El producto bruto se recristalizó en EtOAc (150 ml) con hexanos hasta la turbidez para dar el compuesto del título en forma de un sólido amarillo pálido (210 g, 83%): p.f. 65 °C; ^{1}H RMN (400 MHz, $CDCl_3$) d 1,24 (t, 3H, *J* = 7,1 Hz), 1,62 (s, 6H), 4,23 (q, 2H, *J* = 7,1 Hz), 6,81 (d, 1H, *J* = 8,8 Hz), 7,10 (dd, 1H, *J* = 4,6, 9,0 Hz), 7,30-7,43 (m, 6H); MS (ES) *m/e* 343,1 [M+1].

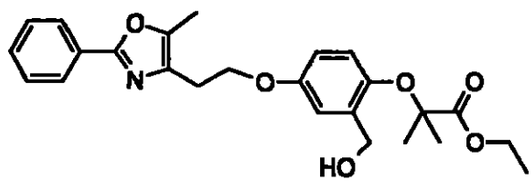
Etapa B: Éster etílico del ácido 2-(4-hidroxi-2-hidroximetil-fenoxi)-2-metil-propiónico



Se trató éster etílico del ácido 2-(4-benciloxi-2-formil-fenoxi)-2-metil-propiónico (185 g, 540 mmol) en etanol (700 ml) con Pd al 10%/C (205 g) e hidrógeno (60 psi (413,68 kPa)) a 50 °C durante 2 d. La mezcla se filtró a

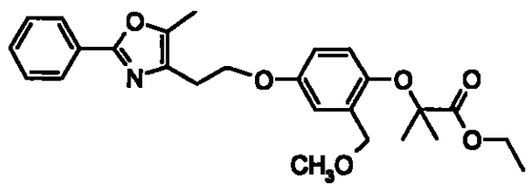
través de Celite, se lavó con etanol (1,5 l), y se concentró. El residuo se recristalizó en EtOAc/hexanos para dar el compuesto del título (116 g). ^{1}H RMN (400 MHz, $CDCl_3$) d 1,26 (t, 3H, *J* = 7,3 Hz), 1,52 (s, 6H), 2,14 (s, 3H), 4,23 (q, 2H, *J* = 7,3 Hz), 4,59 (s a, 2H), 6,61-6,68 (m, 2H), 6,77 (d, 1H, *J* = 2,8 Hz).

Etapa C: Éster etílico del ácido 2-{2-hidroximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico



Un matraz de fondo redondo de 25 ml en una atmósfera de nitrógeno se cargó con 2-(5-metil-2-feniloxazol-4-il)etil éster del ácido tolueno-4-sulfónico (0,77 g, 2,17 mmol), éster etílico del ácido 2-(4-hidroxi-2-hidroximetilfenoxi)-2-metilpropiónico (0,5 g, 1,97 mmol), y etanol absoluto (10 ml). Se añadió carbonato potásico (0,54 g, 3,94 mmol, malla 325) y la reacción se calentó a 80° C durante 12 h. La mezcla se concentró y el residuo bruto se diluyó con EtOAc (75 ml). La capa orgánica se lavó con salmuera (2x), se secó (Na_2SO_4), y se concentró para dar un aceite. El producto bruto se purificó usando cromatografía radial (EtOAc:Hex 5:95 a 35:65) para dar un aceite incoloro (0,17 g, 20%). MS (ES) *m/e* 452 (M+1).

Etapa D: Éster etílico del ácido 2-{2-metoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico



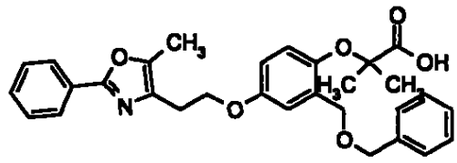
Un matraz de fondo redondo de 15 ml en una atmósfera de nitrógeno se cargó con éster etílico del ácido 2-{2-hidroximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico (0,075 g, 0,17 mmol), DMF anhidra (1 ml), y después con yoduro de metilo (0,16 ml, 1,7 mmol). La solución se enfrió en un baño de hielo y se trató con NaH (0,014 g, 0,34 mmol, dispersión en aceite al 60%). La mezcla se agitó durante 2 h, se vertió en EtOAc (6 ml) y salmuera (10 ml), y se acidificó usando ácido sulfúrico diluido. La capa orgánica se separó, se secó (Na_2SO_4), y se concentró para dar un aceite. El producto bruto se purificó usando cromatografía radial (EtOAc:Hex 15:85) para dar un aceite incoloro (0,039 g, 51%). MS (ES) *m/e* 454 (M+1).

Etapa E: Ácido 2-{2-metoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico

Un matraz de fondo redondo de 25 ml se cargó con éster etílico del ácido 2-{2-metoximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico (0,039 g, 0,087 mmol), etanol (2 ml), y después con NaOH acuoso 2 N (0,22 ml, 0,44 mmol). La solución se calentó a 55° C durante 1 h. La mezcla se concentró, se acidificó usando H_2SO_4 al 5% (1,5 ml), y se repartió entre CH_2Cl_2 (15 ml) y salmuera (15 ml). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró y para dar un sólido blanco (0,024 g, 66%). MS (ES) *m/e* 426 (M+1).

Ejemplo 709

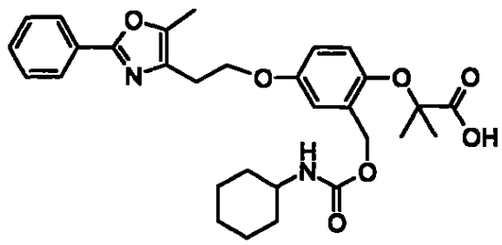
Ácido 2-{2-benciloximetil-4-[2-(5-metil-2-feniloxazol-4-il)-etoxi]fenoxi}-2-metilpropiónico



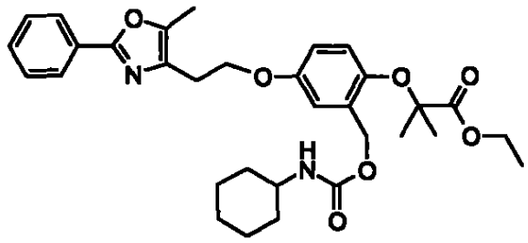
El compuesto anterior se prepara siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 708, MS (ES) *m/e* 502 (M+1).

Ejemplo 710

Ácido 2-{2-ciclohexilcarbamoiloximetil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico



Etapa A: Éster etílico del ácido 3-{2-ciclohexilcarbamoiloximetil-4-[2-(2-feniloxazol-4-il)etoxi]fenil}-propiónico



Un matraz de fondo redondo de 15 ml en una atmósfera de N_2 se cargó con éster etílico del ácido 2-{2-hidroximetil-4-[2-(5-metil-2-feniloxazol-4-

il)etoxi]fenoxi}-2-metilpropiónico (0,075 g, 0,17 mmol), isocianato de ciclohexilo (0,13 ml, 1,0 mmol), CH_2Cl_2 anhidro (0,5 ml), y después con HCl 1,0 N en éter (0,086 ml, 0,086 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 h y se diluyó con CH_2Cl_2 (10 ml). La capa orgánica se lavó con salmuera, se secó (Na_2SO) y se concentró para dar 0,10 g de un aceite bruto, que se usó directamente en la siguiente etapa. MS (ES) *m/e* 564 (M+1).

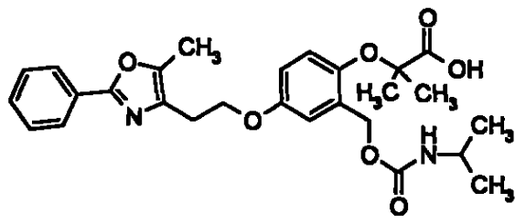
Etapa B: Ácido 3-{2-ciclohexilcarbamoiloximetil-4-[2-(2-feniloxazol-4-il)etoxi]fenil}-propiónico

A un matraz de fondo redondo de 15 ml se le añadieron éster etílico del ácido 3-{2-ciclohexilcarbamoiloximetil-4-[2-(2-feniloxazol-4-il)etoxi]fenil}propiónico (0,10 g, 0,17 mmol), etanol (2 ml), y después NaOH 2 N (0,48 ml, 0,96 mmol). La solución se calentó a 55°C durante 2 h. La mezcla se concentró, se acidificó usando H_2SO_4 al 5%(1,5 ml), y se repartió entre CH_2Cl_2 (15 ml) y salmuera (15 ml). La capa orgánica se secó (Na_2SO_4), se filtró y se concentró. El residuo bruto se sometió a purificación por HPLC dirigida de masas para dar un sólido blanco (0,058 g, 63%). MS (ES) *m/e* 537 (M+1).

Los siguientes Ejemplos 711 a 713 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 710.

Ejemplo 711

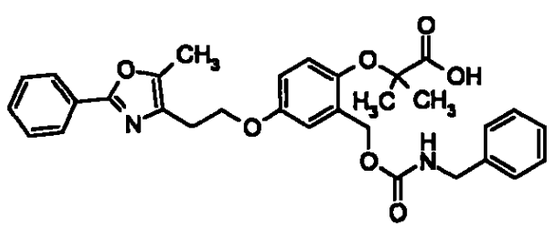
Ácido 2-{2-Isopropilcarbamoiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico



MS (ES) *m/e* 497 (M+1).

Ejemplo 712

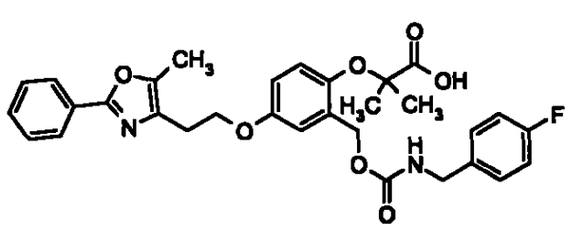
Ácido 2-{2-bencilcarbamoiloximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico



MS (ES) *m/e* 545 (M+1).

Ejemplo 713

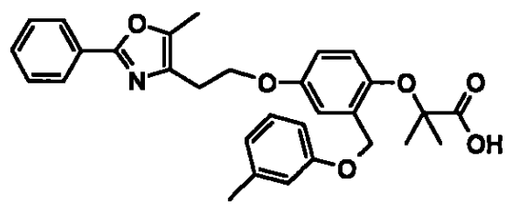
Ácido 2-{2-(4-fluorobencilcarbamoiloximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico



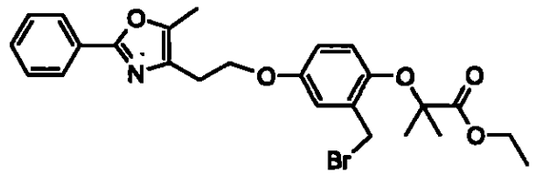
MS (ES) *m/e* 563 (M+1).

Ejemplo 714

Ácido 2-metil-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-m-toliloximetil-fenoxi}-propiónico



Etapa A: Éster etílico del ácido 2-{2-bromometil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico



Un matraz de fondo redondo de 100 ml se cargó con éster etílico del ácido 2-{2-hidroximetil-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenoxi}-2-metil-propiónico (1,0 g, 2,25 mmol), disuelto en THF anhidro (75 ml), y después con trifenilfosfina (1,18 g, 4,50 mmol) y CBr_4 (1,49 g, 4,50 mmol). La mezcla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 1 h y se vertió en EtOAc (135 ml). La capa orgánica se lavó con salmuera (50 ml), se secó (Na_2SO_4), y se concentró. El producto bruto se purificó usando cromatografía radial (EtOAc:hexanos 15:85) para dar a el compuesto del título en forma de un aceite incoloro (0,95 g, 76%).

Etapa B: Ácido 2-metil-2-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-m-toliloximetil-fenoxi}-propiónico

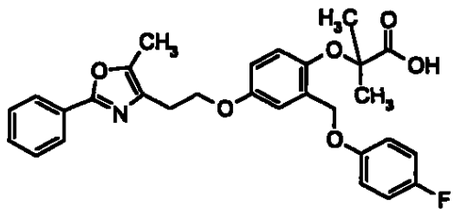
Procedimiento General para la síntesis paralela de análogos usando el aparato DynaVac Corousel: Un tubo de vidrio de 50 ml con tapa a rosca y entrada de nitrógeno se cargó con éster etílico del ácido 2-{2-bromometil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metil-propiónico (0,040 g, 0,080 mmol), *m*-cresol (0,012 ml, 0,12 mmol), etanol absoluto (1 ml), y

después con carbonato potásico (0,022 g, 0,16 mmol; malla 325). La mezcla se calentó a 80° C durante 4 h. El análisis MS de la reacción indicó que se había formado éster etílico del ácido 2-metil-2-{4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-*m*-toliloximetilfenoxi}-propiónico: MS (ES) *m/e* 530 (M+1). La mezcla de reacción se trató con NaOH 2 N (0,4 ml), se calentó a 55°C durante 3 h, se enfrió, y se concentró. El residuo se trató con HCl 5 N (0,75 ml) y CH_2Cl_2 (1 ml) y se vertió en un cartucho ChemElute de 3 ml para retirar la capa acuosa. El cartucho se lavó con CH_2Cl_2, y el disolvente se retiró al vacío. El residuo bruto se purificó por HPLC de fase inversa dirigida de masas para proporcionar el compuesto del título (0,032 g, 38%). MS (ES) *m/e* 502 (M+1).

Los siguientes Ejemplos 715 a 723 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 714.

Ejemplo 715

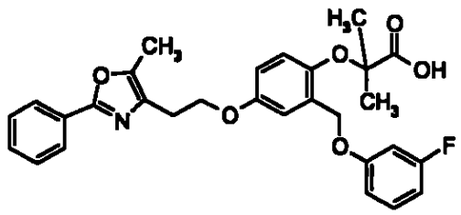
Ácido 2-{2-(4-fluorofenoximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico



MS (ES) *m/e* 506 (M+1).

Ejemplo 716

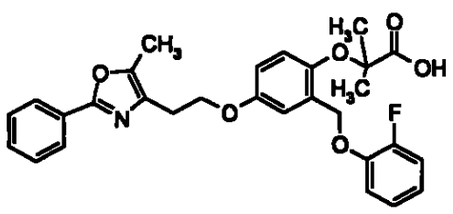
Ácido 2-{2-(3-fluorofenoximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico



MS (ES) *m/e* 506 (M+1).

Ejemplo 717

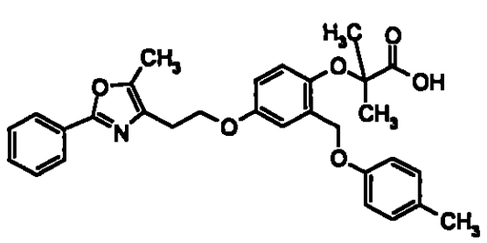
Ácido 2-{2-(2-fluorofenoximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico



MS (ES) *m/e* 506 (M+1).

Ejemplo 718

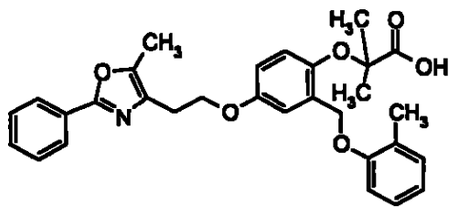
Ácido 2-metil-2-{4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-*p*-toliloximetilfenoxi}propiónico



MS (ES) *m/e* 502 (M+1).

Ejemplo 719

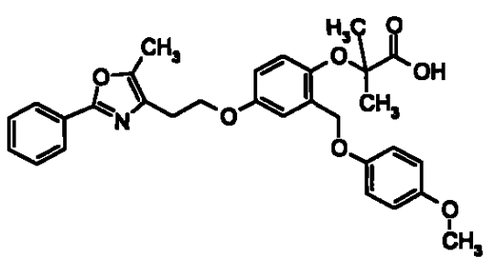
Ácido 2-metil-2-{4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-*o*-toliloximetilfenoxi}propiónico



MS (ES) *m/e* 502 (M+1).

Ejemplo 720

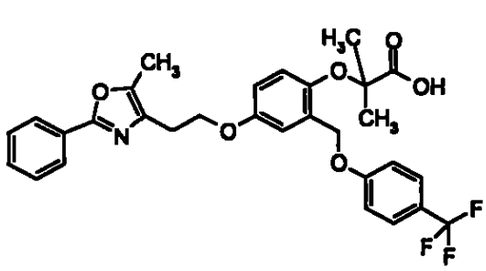
Ácido 2-{2-(4-metoxifenoximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico



MS (ES) *m/e* 518 (M+1).

Ejemplo 721

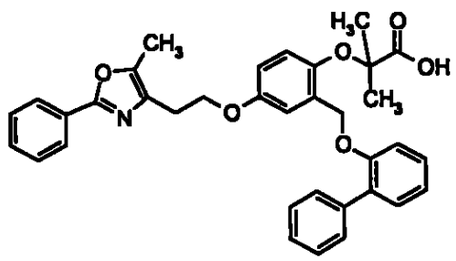
Ácido 2-metil-2-[4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-(4-trifluorometilfenoximetil)fenoxi]propiónico



MS (ES) *m/e* 556 (M+1).

Ejemplo 722

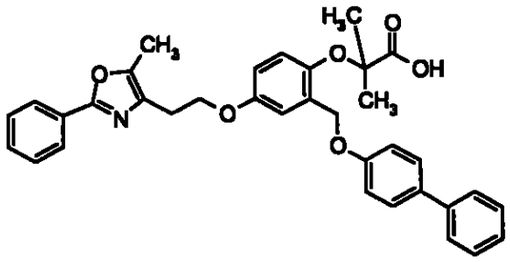
Ácido 2-{2-(bifenil-2-iloximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico



MS (ES) *m/e* 564 (M+1).

Ejemplo 723

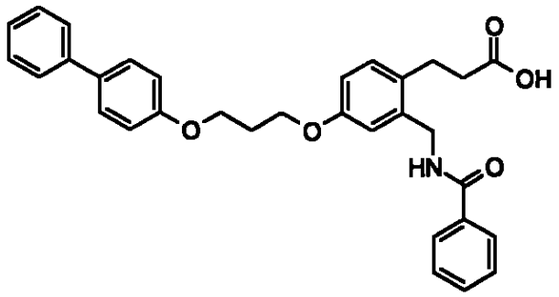
Ácido 2-{2-(bifenil-4-iloximetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenoxi}-2-metilpropiónico



MS (ES) *m/e* 564 (M+1).

Ejemplo 724

Ácido 3-{2-(benzoilaminometil)-4-[3-(bifenil-4-iloxi)propoxi]fenil} propiónico



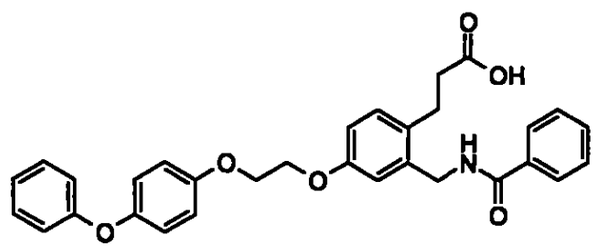
Una solución de 4-(3-bromo-propoxi)-bifenilo (291 mg, 1,00 mmol; Preparación 12) y éster terc-butílico del ácido 3-[2-(benzoilamino-metil)-4-

hidroxi-fenil]-propiónico (320 mg, 0,90 mmol; Preparación 21) en DMF (5 ml) se trató con K_2CO_3 (100 mg) y se calentó a 60°C durante 48 h. La mezcla de reacción se diluyó con agua (50 ml) y se extrajo con EtOAc (3 x 20 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4), se concentraron, y se purificaron usando cromatografía en gel de sílice (EtOAc al 10-30%/hexanos) para dar éster terc-butílico del ácido 3-{2-(benzoilaminometil)-4-[3-(bifenil-4-iloxi)propoxi]fenil} propiónico (450 mg). Este material se trató con una mezcla de CH_2Cl_2 (1,0 ml)/TFA (0,8 ml)/agua (0,1 ml) a temperatura ambiente durante 2 h. La mezcla de reacción se concentró y se secó al vacío para producir el producto del título en forma de un sólido blanco (380 mg, 75%). MS (ES) *m/e* 510,1 (M+1).

Los siguientes Ejemplos 725 a 757 se prepararon siguiendo un procedimiento sustancialmente similar al descrito en el Ejemplo 724,

Ejemplo 725

Ácido 3-{2-(Benzoilaminometil)-4-[2-(4-fenoxi-fenoxi)etoxi]fenil} propiónico

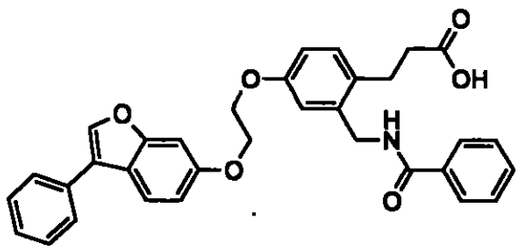


MS [ES] m/z 512 (M+1).

Ejemplo 726

Ácido 3-{2-(benzoilaminometil)-4-[2-(3-fenilbenzofurano-6-iloxi)etoxi]-fenil}-

propiónico

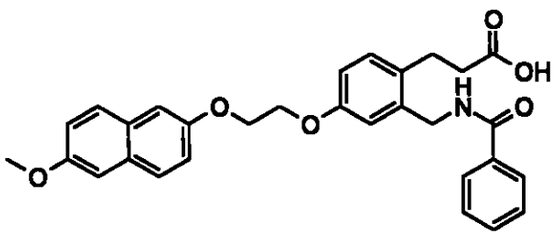


MS [ES] m/z 536 (M+1).

Ejemplo 727

Ácido 3-{2-(benzoilaminometil)-4-[2-(6-metoxinaftalen-2-iloxi)etoxi]-fenil}

propiónico

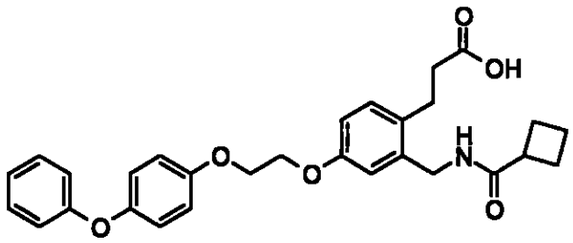


MS [ES] m/z 500 (M+1).

Ejemplo 728

Ácido 3-{2-[(ciclobutanocarbonilamino)metil]-4-[2-(4-fenoxifenoxi)-etoxi]fenil}

propiónico

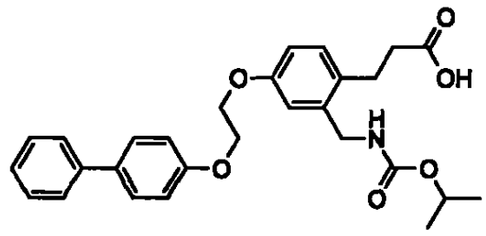


MS [ES] m/z 490 (M+1).

935
939

Ejemplo 729

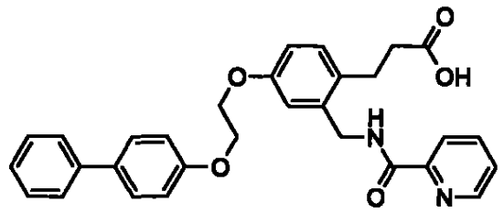
Ácido 3-[4-[2-(bifenil-4-iloxi)etoxi]-2-(isopropoxicarbonilaminometil)-fenil] propiónico



MS [ES] m/z 473 (M+1).

Ejemplo 730

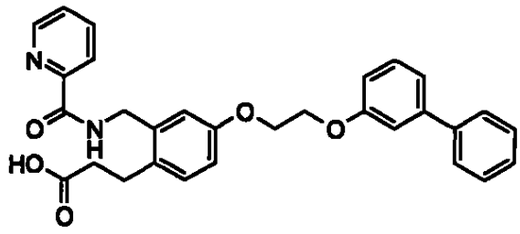
Ácido 3-(4-[2-(bifenil-4-iloxi)etoxi]-2-{[(piridina-2-carbonil)amino]metil}-fenil) propiónico



MS [ES] m/z 497 (M+1).

Ejemplo 731

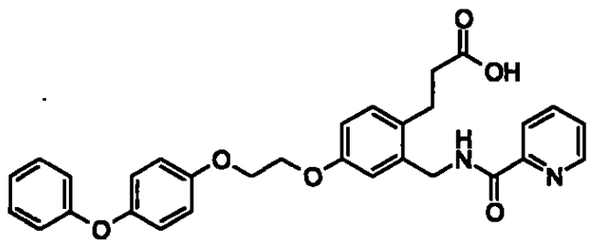
Ácido 3-(4-[2-(bifenil-3-iloxi)etoxi]-2-{[(piridina-2-carbonil)amino]metil} fenil)propiónico



MS [ES] m/z 497 (M+1).

Ejemplo 732

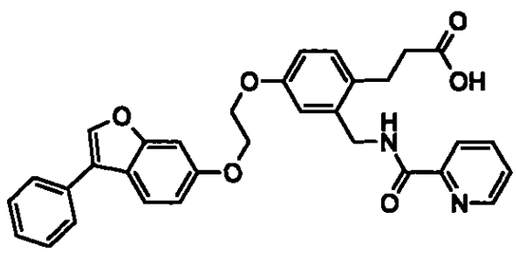
Ácido 3-(4-[2-(4-fenoxi-fenoxi)etoxi]-2-{[(piridina-2-carbonil)amino]-metil}fenil) propiónico



MS [ES] m/z 501 (M+1).

Ejemplo 733

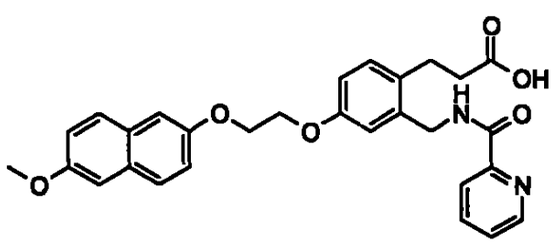
Ácido 3-(4-[2-(3-fenilbenzofurano-6-iloxi)etoxi]-2-{[(piridina-2-carbonil)-amino]metil}fenil) propiónico



MS [ES] m/z 537 (M+1).

Ejemplo 734

Ácido 3-(4-[2-(6-Metoxinaftalen-2-iloxi)etoxi]-2-{[(piridina-2-carbonil)-amino]metil}fenil) propiónico

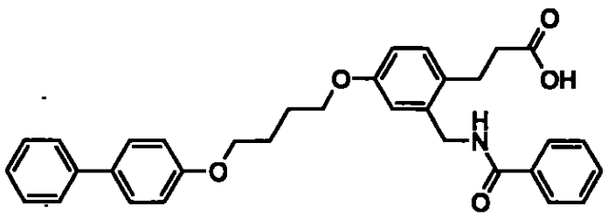


437
941

MS [ES] m/z 501 (M+1).

Ejemplo 735

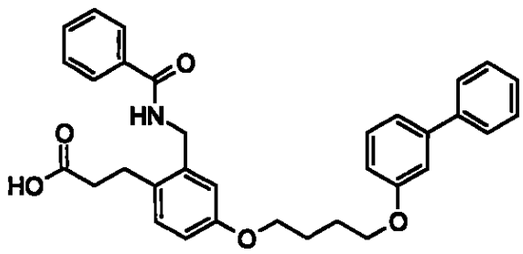
Ácido 3-{2-(benzoilaminometil)-4-[4-(bifenil-4-iloxi)butoxi]fenil} propiónico:



MS [ES] m/z 524 (M+1).

Ejemplo 736

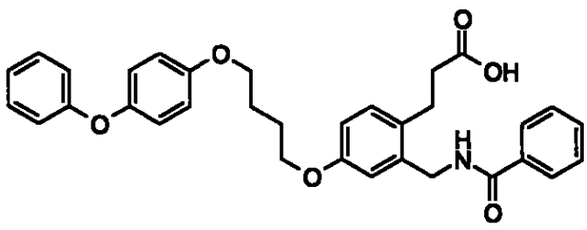
Ácido 3-{2-(benzoilaminometil)-4-[4-(bifenil-3-iloxi)butoxi]fenil} propiónico:



MS [ES] m/z 524 (M+1).

Ejemplo 737

Ácido 3-{2-(benzoilaminometil)-4-[4-(4-fenoxifenoxi)butoxi]fenil} propiónico:

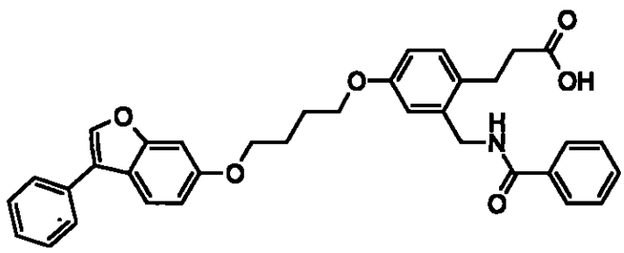


MS [ES] m/z 540 (M+1).

Ejemplo 738

Ácido 3-{2-(benzoilaminometil)-4-[4-(3-fenilbenzofurano-6-iloxi)butoxi] fenil}-

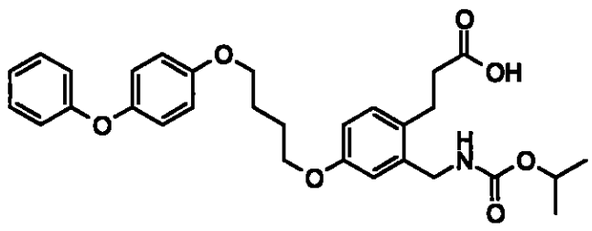
propiónico



MS [ES] m/z 564 (M+1).

Ejemplo 739

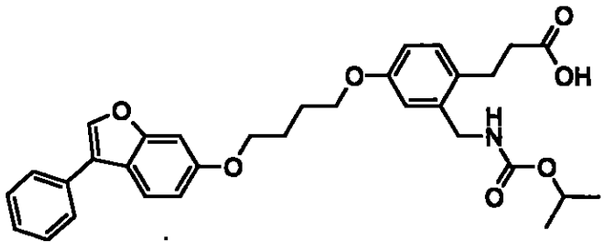
Ácido 3-{2-(isopropoxicarbonilaminometil)-4-[4-(4-fenoxifenoxi)butoxi]fenil} propiónico



MS [ES] m/z 522 (M+1).

Ejemplo 740

Ácido 3-{2-(isopropoxicarbonilaminometil)-4-[4-(3-fenilbenzofurano-6-iloxi)butoxi]fenil} propiónico

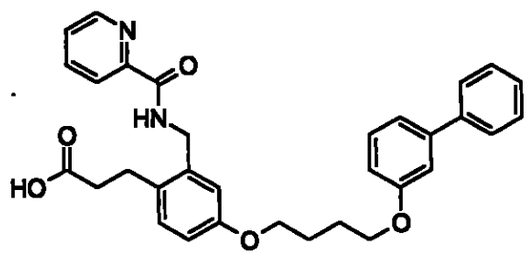


MS [ES] m/z 546 (M+1).

939
943

Ejemplo 741

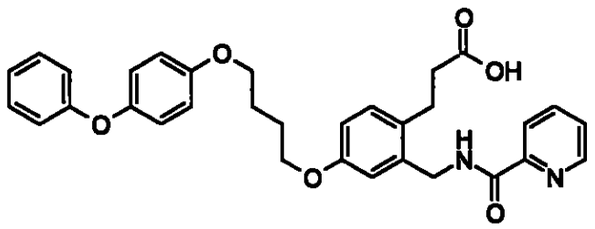
Ácido 3-(4-[4-(bifenil-3-iloxi)butoxi]-2-{[(piridina-2-carbonil)amino]metil}-fenil) propiónico



MS [ES] m/z 525 (M+1).

Ejemplo 742

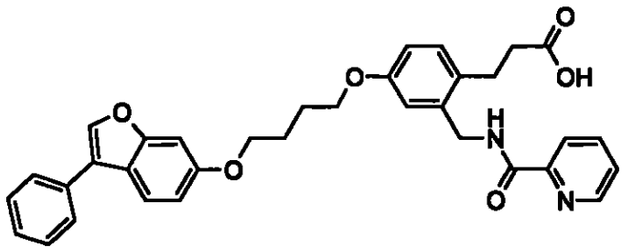
Ácido 3-(4-[4-(4-fenoxifenoxi)butoxi]-2-{[(piridina-2-carbonil)amino]-metil}fenil) propiónico



MS [ES] m/z 541 (M+1).

Ejemplo 743

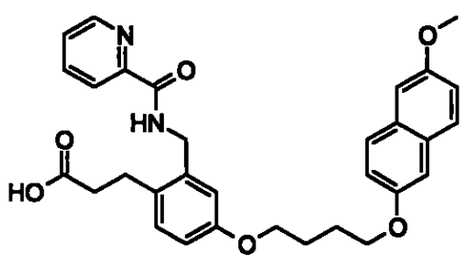
Ácido 3-(4-[4-(3-fenilbenzofurano-6-iloxi)butoxi]-2-{[(piridina-2-carbonil)-amino]metil} fenil) propiónico



MS [ES] m/z 565 (M+1).

Ejemplo 744

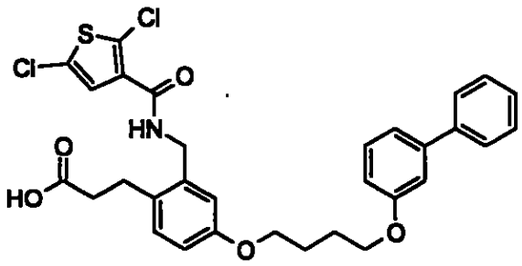
Ácido 3-(4-[4-(6-metoxinaftalen-2-iloxi)butoxi]-2-{[(piridina-2-carbonil)-amino]metil}fenil) propiónico



MS [ES] m/z 529 (M+1).

Ejemplo 745

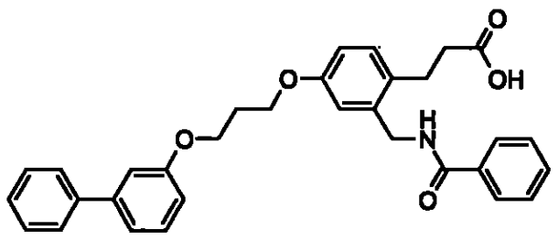
Ácido 3-(4-[4-(bifenil-3-iloxi)butoxi]-2-{[(2,5-diclorotiofeno-3-carbonil)-amino]metil}fenil) propiónico



MS [ES] m/z 599 (M+1).

Ejemplo 746

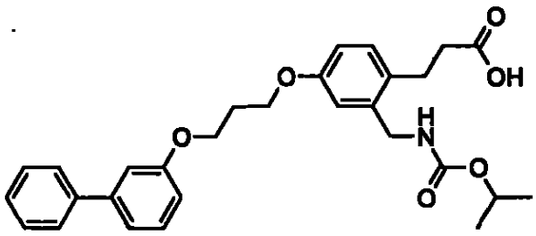
Ácido 3-{2-(benzoilaminometil)-4-[3-(bifenil-3-iloxi)propoxi]fenil} propiónico:



MS [ES] m/z 510 (M+1).

Ejemplo 747

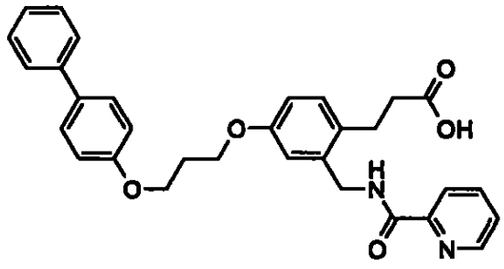
Ácido 3-[4-[3-(bifenil-3-iloxi)propoxi]-2-(isopropoxicarbonilaminometil)-fenil] propiónico



MS [ES] m/z 492 (M+1).

Ejemplo 748

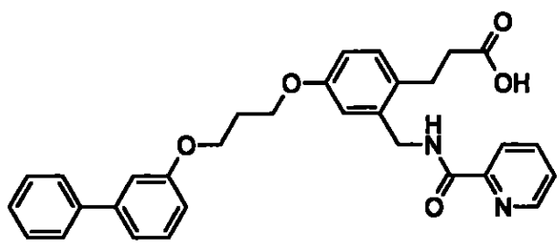
Ácido 3-(4-[3-(bifenil-4-iloxi)propoxi]-2-{[(piridina-2-carbonil)amino]metil}-fenil) propiónico



MS [ES] m/z 511 (M+1).

Ejemplo 749

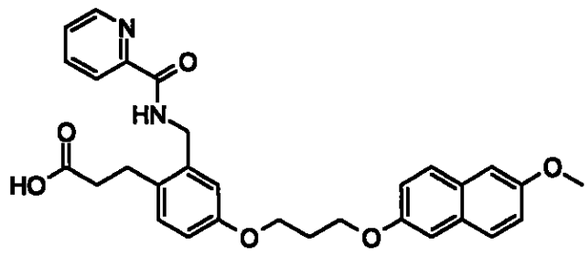
Ácido 3-(4-[3-(bifenil-3-iloxi)propoxi]-2-{[(piridina-2-carbonil)amino]metil} fenil) propiónico



MS [ES] m/z 511 (M+1).

Ejemplo 750

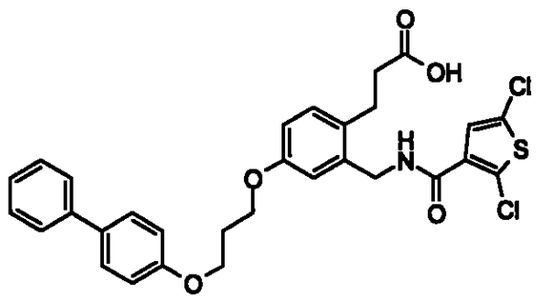
Ácido 3-(4-[3-(6-metoxinaftalen-2-iloxi)propoxi]-2-{[(piridina-2-carbonil)-amino]metil}fenil) propiónico



MS [ES] m/z 515 (M+1).

Ejemplo 751

Ácido 3-(4-[3-(bifenil-4-iloxi)propoxi]-2-{[(2,5-diclorotiofeno-3-carbonil)-amino]metil}fenil) propiónico

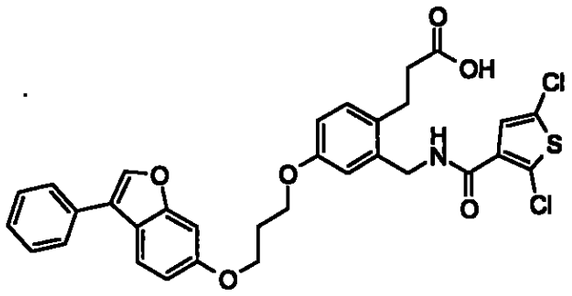


MS [ES] m/z 585 (M+1).

945
947

Ejemplo 752

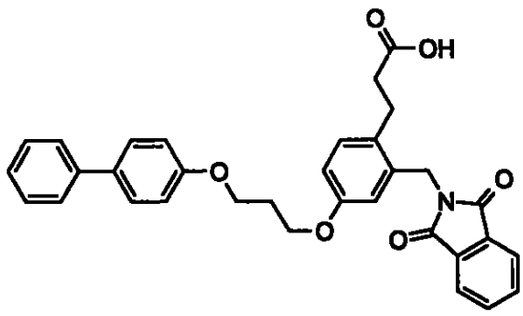
Ácido 3-{2-[[(2,5-diclorotiofeno-3-carbonil)amino]metil}-4-[3-(3-fenil-benzofurano-6-iloxi)propoxi]fenil} propiónico



MS [ES] m/z 625 (M+1).

Ejemplo 753

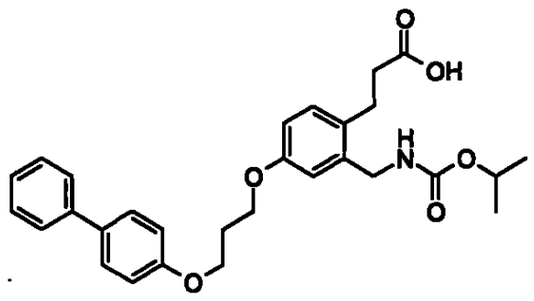
Ácido 3-[4-[3-(bifenil-4-iloxi)propoxi]-2-(1,3-dioxo-1,3-dihidroisoindol-2-ilmetil)fenil] propiónico



MS [ES] m/z 536 (M+1).

Ejemplo 754

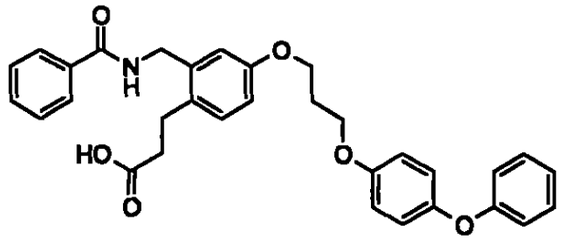
Ácido 3-[4-[3-(Bifenil-4-iloxi)propoxi]-2-(isopropoxicarbonilaminometil)-fenil] propiónico



MS [ES] m/z 492 (M+1).

Ejemplo 755

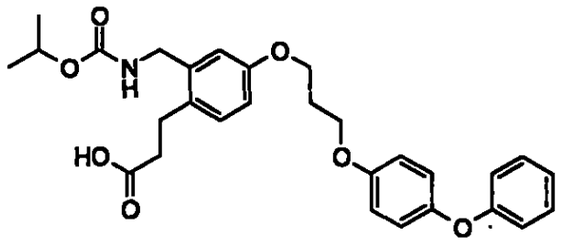
Ácido 3-{2-(benzoilaminometil)-4-[3-(4-fenoxifenoxi)propoxi]fenil} propiónico



MS [ES] m/z 526 (M+1).

Ejemplo 756

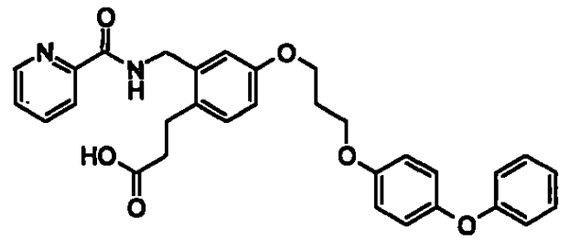
Ácido 3-{2-(isopropoxicarbonilaminometil)-4-[3-(4-fenoxifenoxi)propoxi]-fenil} propiónico



MS [ES] m/z 508 (M+1).

Ejemplo 757

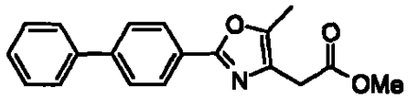
Ácido 3-(4-[3-(4-fenoxifenoxi)propoxi]-2-{[(piridina-2-carbonil)amino]-metil}fenil) propiónico



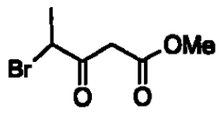
MS [ES] m/z 527 (M+1).

Ejemplo 758

Éster metílico del ácido (2-bifenil-4-il-5-metil-oxazol-4-il)-acético

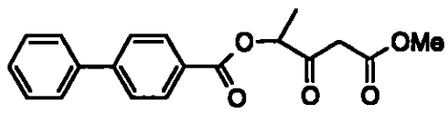


Etapa 1: Éster metílico del ácido 4-bromo-3-oxo-pentanoico



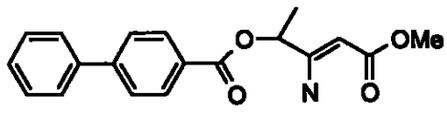
Se añadió gota a gota durante 2 h una solución de bromo (28,3 g, 0,177 mol) en cloroformo (30 ml) a una solución de propionilacetato de metilo (23,5 g, 0,177 mol) en cloroformo (155 ml) a 0-5°C. La mezcla se agitó durante 30 min, y se retiró el baño de refrigeración. La mezcla se agitó durante 18 h, y se añadió agua enfriada con hielo (200 ml). La capa orgánica se recogió y se lavó con agua fría (2 x 200 ml), tiosulfato sódico acuoso al 10% (2 x 200 ml) y salmuera (200 ml). La solución filtrada se secó (Na_2SO_4) y se concentró para dar 36,5 g del compuesto del título en forma de un líquido transparente.

Etapa 2: 3-Metoxicarbonil-1-metil-2-oxo-propil éster del ácido bifenil-4-carboxílico



Una mezcla de ácido bifenil-4-carboxílico (800 g, 4,03 mol) en acetona (4,6 l) se trató gota a gota durante 13 min con trietilamina (0,6 L, 4,3 mol, 1,07 eq) mientras se mantenía la temperatura a 15-30°C. Se añadió gota a gota durante 21 min éster metílico del ácido 4-bromo-3-oxo-pentanoico (880 g, 4,21 mol, 1,04 eq) a 15-30°C. La mezcla se agitó durante una noche a temperatura ambiente. Se añadió gota a gota durante 85 minutos agua (9,6 l) a 15-30°C. La mezcla se agitó durante 2 h. El producto precipitado se recogió por filtración y se lavó dos veces con agua (1 l). El producto se secó al vacío a 50°C para producir 1291 g (rendimiento del 98%, pureza del 96% por HPLC) del compuesto del título.

Etapa 3: 2-Amino-3-metoxicarbonil-1-metil-alil éster del ácido bifenil-4-carboxílico



Una mezcla de 3-metoxicarbonil-1-metil-2-oxo-propil éster del ácido bifenil-4-carboxílico (1275 g, 3,9 mol, 1 eq) y acetato amónico (640 g, 8,3 mol) en etanol (10 l) se calentó con agitación a 70-75°C hasta que se consumió completamente el compuesto ceto éster (1-2 h). La mezcla después se mantuvo a 0-5°C durante 1,5 h. El sólido precipitado se recogió por filtración y se lavó con hexanos (2,5 l). El producto se secó durante una noche al vacío a

50°C para obtener 1244 g (rendimiento del 90%, pureza del 98% por HPLC) del compuesto del título.

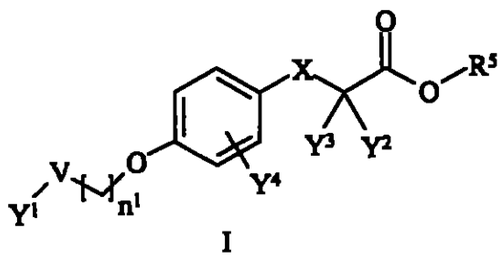
Etapa 4: Éster metílico del ácido (2-bifenil-4-il-5-metil-oxazol-4-il)-acético

Una mezcla de 2-amino-3-metoxicarbonil-1-metil-alil éster del ácido bifenil-4-carboxílico (566 g, 1,74 mol, 1 eq) y acetato amónico (283 g, 3,67 mol) en ácido acético glacial (11,3 l) se calentó a reflujo durante 2 h, se enfrió, y se concentró. El residuo se coevaporó con tolueno (2 x 2,5 l) y EtOAc (2,5 l). La mezcla se diluyó con EtOAc (6,6 l) y se transfirió con EtOAc (2,2 l) matraz de separación con salida en el fondo. La mezcla se lavó dos veces con agua (2,2 l), $NaHCO_3$ acuoso saturado (1,1 l), y salmuera (2 x 2,2 l). La capa orgánica se secó (Na_2SO_4, 550 g), se filtró con la ayuda de EtOAc (1,1 l), y se concentró. El residuo se disolvió en isopropanol (2 l) a 50°C y se dejó enfriar durante una noche a temperatura ambiente. La mezcla se mantuvo a 0°C-5°C durante 1 h. El sólido precipitado se rompió y se recogió por filtración. El sólido se lavó con isopropanol frío (4 x 0,55 l) y se secó durante una noche en una estufa de vacío a 50°C para producir 428 g del compuesto del título (72% en la Etapa 2).

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes:

REIVINDICACIONES

1. Un compuesto de fórmula I,



I

y sales, solvatos, hidratos o estereoisómeros farmacéuticamente aceptables de los mismos, donde:

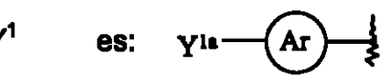
n^1 es 2, 3, 4 ó 5;

V es un enlace o O;

X es CH_2 o O;

p es 0 ó 1;

m es 1-4;

Y^1 es:  donde,

 es: arilo o heteroarilo,

donde arilo y heteroarilo están opcionalmente sustituidos con uno o más grupos seleccionados independientemente entre el grupo compuesto por:

hidrógeno, alquilo C_1-C_6, alcoxi C_1-C_6, halo, haloalquilo y haloalquiloxi;

Y^{1a} es: hidrógeno,

alquilo (C_0-C_3)-arilo,

C(O)-arilo,

heteroarilo,

cicloalquilo,

heterocicloalquilo,

ariloxi,

$NR^5(CH_2)_mOR^5$,

aril-Z-arilo,

aril-Z-heteroarilo,

aril-Z-cicloalquilo,

aril-Z-heterocicloalquilo,

heteroaril-Z-arilo,

heteroaril-Z-heterocicloalquilo o

heterocicloalquil-Z-arilo,

donde arilo, cicloalquilo, ariloxi, heteroarilo, y heterocicloalquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre el grupo compuesto por:

halo,

hidroxilo,

nitro,

ciano,

alquilo C_1-C_6,

alcoxi C_1-C_6 opcionalmente sustituido con $N(R^5)_2$,

haloalquilo,

$N(R^5)_2$,

$N[C(O)R^5]_2$,

$N[S(O)_2R^5]_2$,

$NR^5S(O)_2R^5$,

$NR^5C(O)R^5$,

$NR^5C(O)OR^5$,

$C(O)N(R^5)_2$,

$C(O)OR^5$ y

$C(O)R^5$;

Z es: un enlace,

-oxígeno-

$-C(O)NR^5-$

$-NR^5C(O)-$,

$-NR^5C(O)O-$,

-C(O)-,

$-NR^5-$,

$-[O]_p(CH_2)_m-$,

$-(CH_2)_m[O]_p-$,

$-NR^5(CH_2)_m-$ o

$-(CH_2)_m NR^5-$;

cada uno de Y^2 e Y^3 es independientemente:

hidrógeno,

alquilo C_1-C_6 o

alcoxi C_1-C_6;

Y^4 es: alquil (C_1-C_3)-$NR^5C(O)$-alquil (C_0-C_{10})-Y^7,
alquil (C_1-C_3)-$NR^5C(O)$-alquenil (C_2-C_{10})-Y^7,
alquil (C_1-C_3)-$NR^5C(O)$-alquinil (C_2-C_{10})-Y^7;
alquil (C_1-C_3)-$NR^5C(O)O$-alquil (C_0-C_{10})-Y^7,
alquil (C_1-C_3)-$NR^5C(O)NR^5$-alquil (C_0-C_{10})-Y^7,
alquil (C_1-C_3)-$NR^5C(S)NR^5$-alquil (C_0-C_{10})-Y^7,
alquil (C_0-C_3)-$C(O)NR^5$-alquil (C_0-C_{10})-Y^7,
alquil (C_1-C_3)-$OC(O)NY^{10}Y^{11}$,
alquil (C_1-C_3)-$NY^{10}Y^{11}$,
alquil (C_1-C_3)-O-alquil (C_0-C_{10})-Y^7,
alquil (C_1-C_3)-S-alquil (C_0-C_{10})-Y^7 o
CN;

Y^7 es: hidrógeno,
arilo,
heteroarilo,
alquilo C_1-C_{12},
alcoxi C_1-C_6,
cicloalquilo,
heterocicloalquilo,
ariloxi,
C(O)-heteroarilo o
SR^6,
donde alquilo, arilo, ariloxi, alcoxi, heteroarilo, cicloalquilo, y heterocicloalquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre R^7:

cada uno de Y^{10} e Y^{11} es independientemente:

hidrógeno,

arilo,

heteroarilo,

alquilo C_1-C_{10},

cicloalquilo,

$SO_2(R^6)$; o

Y^{10} e Y^{11} conjuntamente son un anillo heterocicloalquilo de 5 a 10 miembros o un anillo heterocicloalquilo condensado con arilo, y el anillo heterocicloalquilo contiene opcionalmente uno o más heteroátomos seleccionados entre N, O o S; y donde,

arilo, heteroarilo, heterocicloalquilo y alquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre R^7;

R^5 es: hidrógeno o alquilo C_1-C_6;

R^6 es: hidrógeno,

alquilo C_1-C_{10},

cicloalquilo,

arilo, o

heteroarilo,

donde alquilo, cicloalquilo, arilo y heteroarilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre R^7;

R^7 es: halo,

nitro,

oxo,

ciano,

hidroxilo,

bencilo,

fenilo,

fenoxi,

heteroarilo,

$C(O)R^6$,

alquilo C_1-C_{10},

alcoxi C_1-C_6,

haloalquilo C_1-C_6,

haloalquiloxi C_1-C_6,

$O(CH_2)_m$-fenilo,

$(CH_2)_mOC(O)$-arilo,

$C(O)OR^5$,

$S(O)_2R^5$,

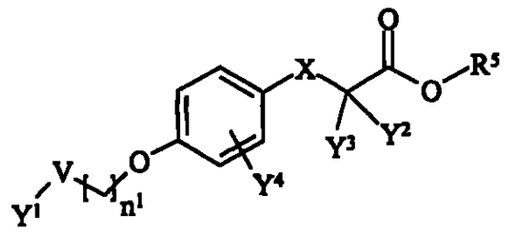
$S(O)_2N(R^5)_2$,

SR^5 o

$N(R^5)_2$,

donde fenilo y fenoxi están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre halo o trifluorometilo.

2. Un compuesto representado por la siguiente fórmula estructural Ia:



Ia

o una sal, hidrato o solvato farmacéuticamente aceptable del mismo, donde:

Y^1 es un grupo sin sustituir o sustituido seleccionado entre el grupo compuesto por:

arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aril-alquilo C1-C4, heteroaril-alquilo C1-C4, cicloalquil-alquilo C1-C4, y t-butilo;

Y^2 se selecciona entre el grupo compuesto por:

H, alquilo C1-C10, cicloalquilo, (alquilo C1-C10)-Y^5 , O-Y^6;

Y^5 se selecciona entre el grupo compuesto por:

un grupo arilo, arilo sustituido, -COR^4, -$COOR^4$, -$CONR^6R^7$,-CSR^4 , y -$C(S)NR^6R^7$;

Y^6 se selecciona entre el grupo compuesto por:

un grupo alifático, un grupo alifático sustituido, un grupo arilo, arilo sustituido, -COR^4, -$COOR^4$, -$CONR^6R^7$, -CSR^4, y -$C(S)NR^6R^7$;

cada uno de R^4, R^6 y R^7 se seleccionan independientemente entre el grupo compuesto por:

H, un grupo alifático, un grupo alifático sustituido, un grupo arilo y un grupo arilo sustituido;

Y^3 se selecciona entre el grupo compuesto por:

H, un grupo alifático, un grupo alifático sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, y (alquilo C1-C10)-R^8; R^8 se selecciona entre el grupo compuesto por arilo, arilo sustituido, heteroarilo, y heteroarilo sustituido; y

R^5 se selecciona entre el grupo compuesto por:

H, un grupo alifático, un grupo alifático sustituido, heteroarilo, heteroarilo sustituido, un arilo, un arilo sustituido, y (alquilo C1-C10)-R^9;

R^9 se selecciona entre el grupo compuesto por:

arilo, arilo sustituido, heteroarilo, y heteroarilo sustituido, aminoalquilo, y cicloalquilo;

V es un enlace o O;

X es CH_2 o O;

Y^4 se selecciona entre el grupo compuesto por:

-alquil (C1-C3)-O-W-Y^7, -C(O)NY^8Y^9, -alquil (C1-C3)-$NY^{10}Y^{11}$, y -alquil (C1-C3)-$N(Y^{13})$W-alquil (C0-C5)-Y^{14} ;

W se selecciona entre el grupo compuesto por:

un enlace, -$CONY^{12}$, -C(O)-, -OCH_2-, alquilo C1-C6, -CO_2-, -$CHOY^{15}$-, -$CSNY^{16}$ y

-SO_2-;

Y^7 se selecciona entre el grupo compuesto por:

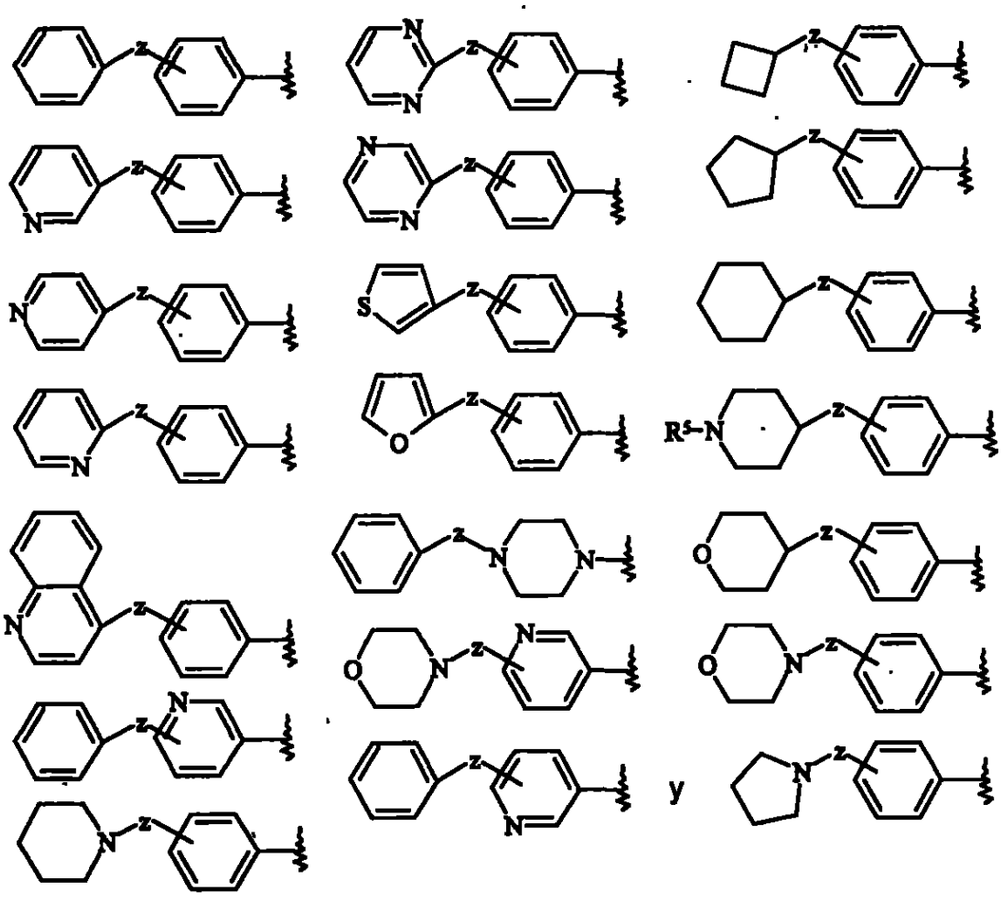
arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, un grupo alifático, un grupo alifático ramificado y alquilo (C1-C10) sustituido;

cada uno de Y^8, Y^9, Y^{10}, Y^{11}, Y^{12}, Y^{13}, Y^{14}, Y^{15}, e Y^{16} se selecciona independientemente entre el grupo compuesto por:

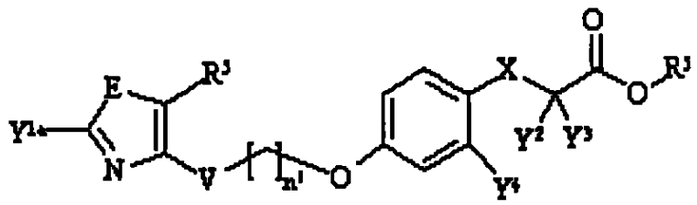
arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, un grupo alifático, un grupo alifático ramificado y alquilo (C1-C10) sustituido; y

n^1 are 2, 3, 4 ó 5.

3. El compuesto de la reivindicación 1, en el que Y^{1a} se selecciona entre el grupo compuesto por: arilo, heteroarilo, cicloalquilo, heterocicloalquilo, ariloxi,

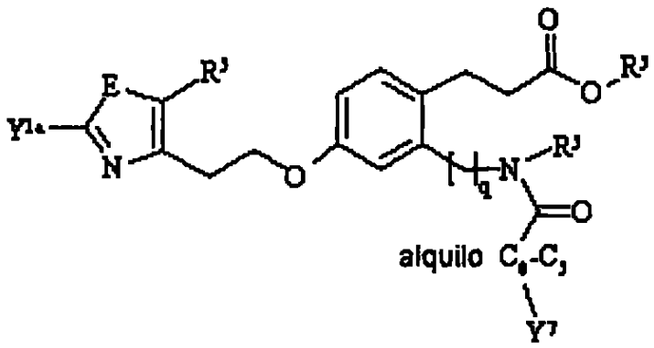


4. El compuesto de la reivindicación 1 ó 2, donde el compuesto se representa por la siguiente fórmula estructural,



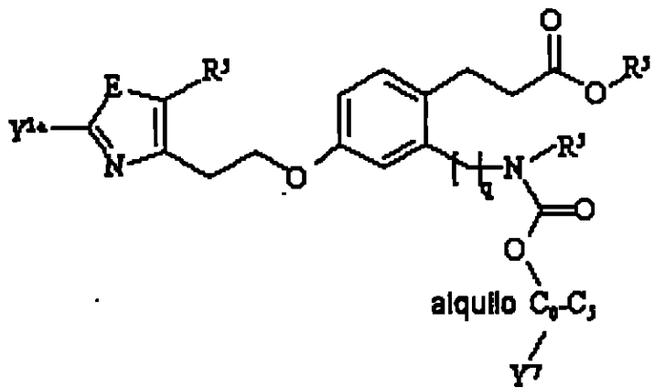
donde E es O o S.

5. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



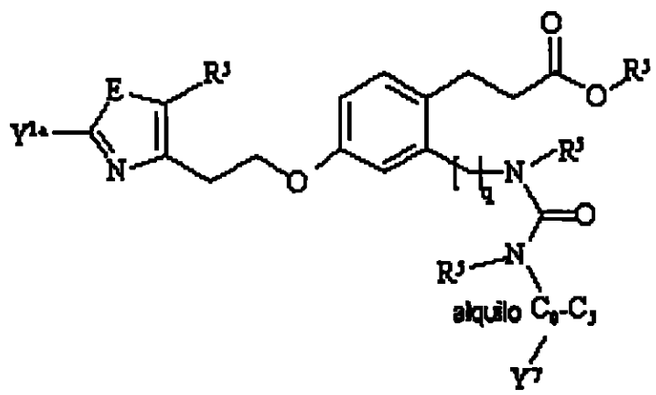
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

6. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



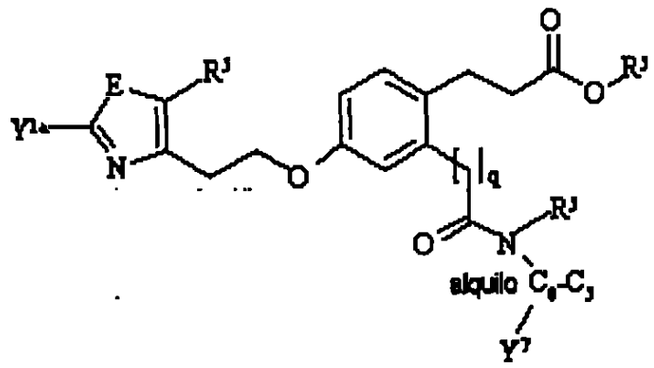
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

7. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



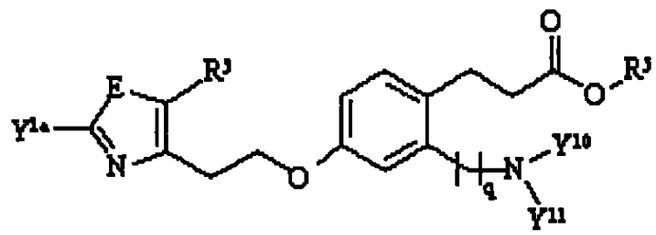
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

8. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



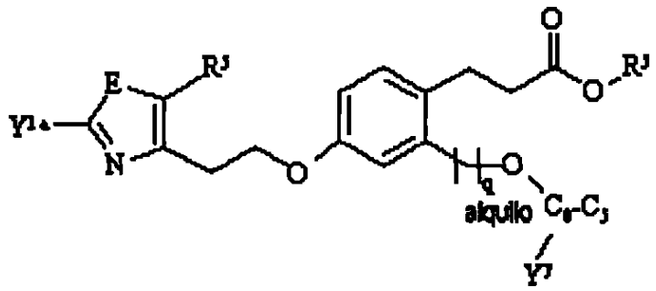
donde q es 0 ó 1; y cada R^5 es independientemente hidrógeno o metilo.

9. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



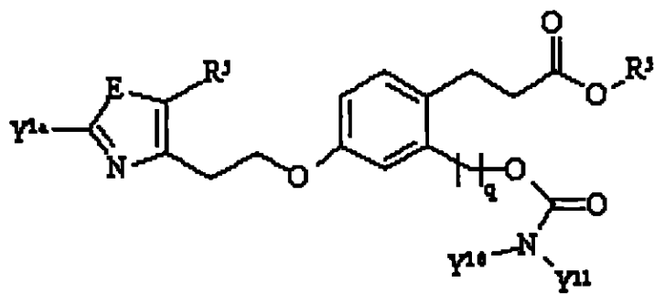
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

10. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



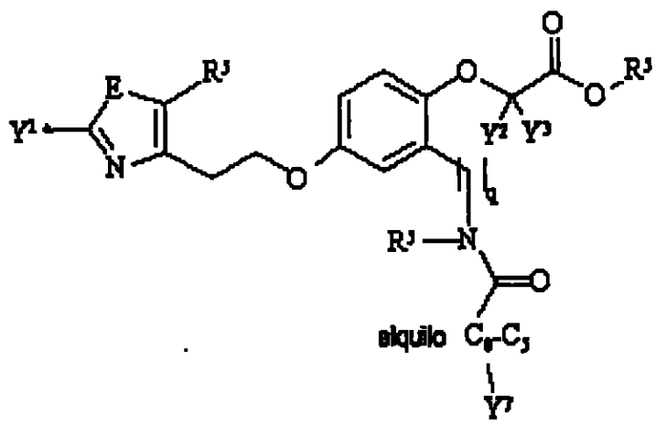
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

11. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



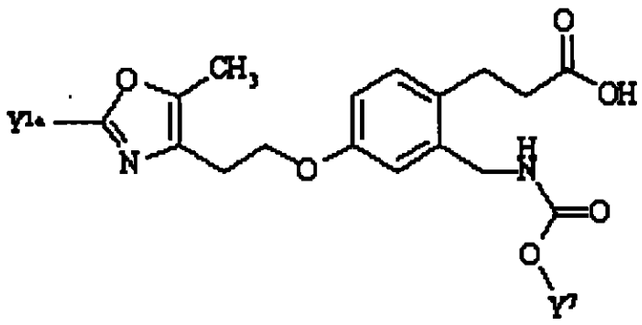
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

12. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



donde q es 1 ó 2; y cada R^5, Y^2 y Y^3 are independientemente hidrógeno o metilo.

13. El compuesto de la reivindicación 4 representado por la siguiente fórmula,

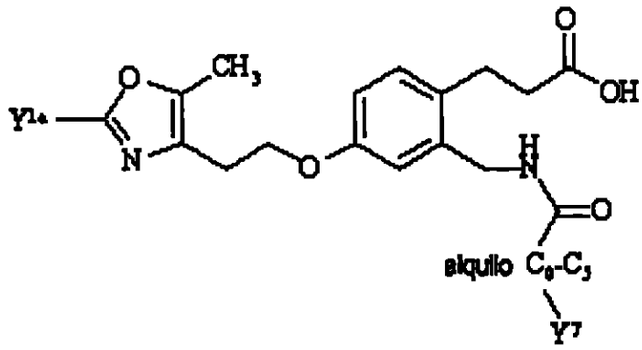


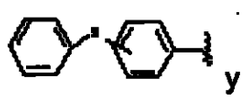
donde Y^{1a} es fenilo opcionalmente sustituido, naftilo,



y Z es un enlace, oxígeno, -NH-, -N(CH_3)-, -NHC(O)- o -C(O)NH-.

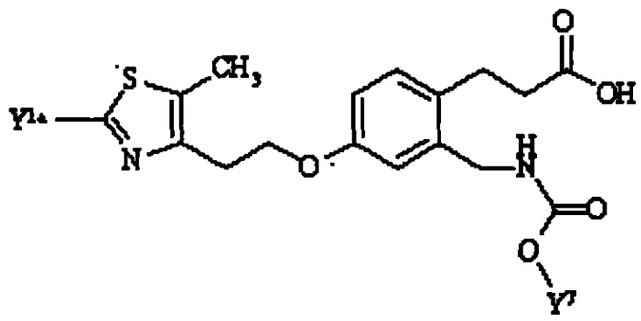
14. El compuesto de la reivindicación 4 representado por la siguiente fórmula,



donde Y^{1a} es fenilo opcionalmente sustituido, naftilo o  y

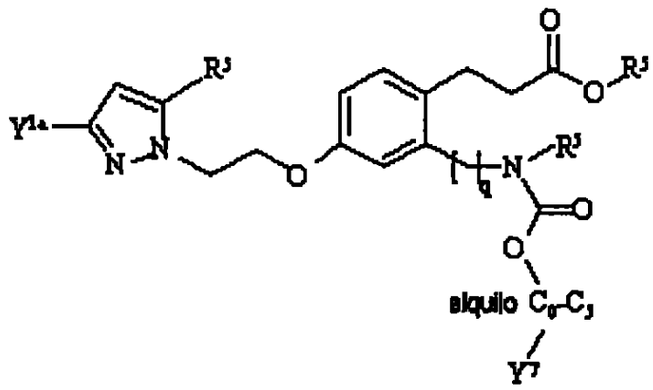
Z es un enlace, oxígeno, -NH-, -N(CH_3)-, -NHC(O)- o -C(O)NH-.

15. El compuesto de la reivindicación 4 representado por la siguiente fórmula,



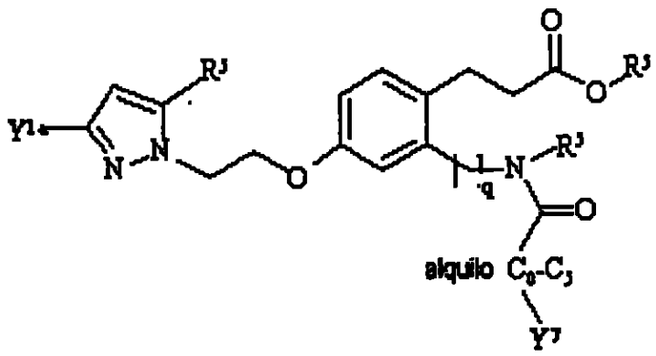
donde Y^{1a} arilo opcionalmente sustituido, heteroarilo, heterocicloalquilo, heteroaril-Z-heterocicloalquilo o heteroaril-Z-arilo.

16. El compuesto de la reivindicación 1 representado por la siguiente fórmula,



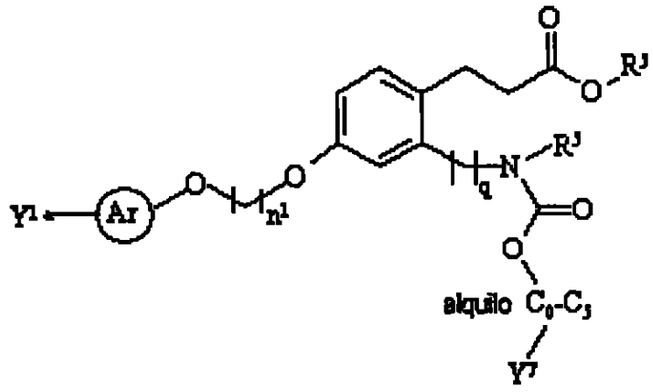
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

17. El compuesto de la reivindicación 1 representado por la siguiente fórmula,



donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

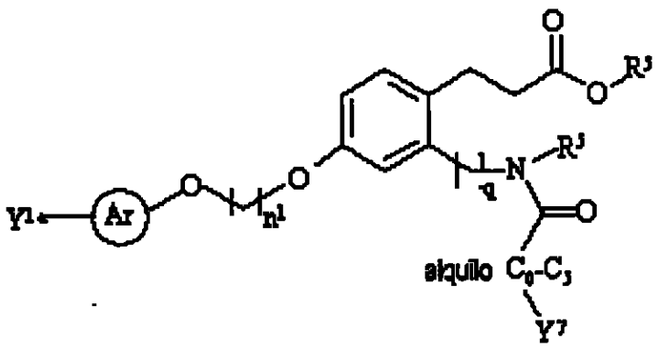
18. El compuesto de la reivindicación 1 representado por la siguiente fórmula,



donde,

Y^{1a} es hidrógeno, arilo, heteroarilo, o ariloxi; q es 1 ó 2; y n^1 es 2, 3, ó 4.

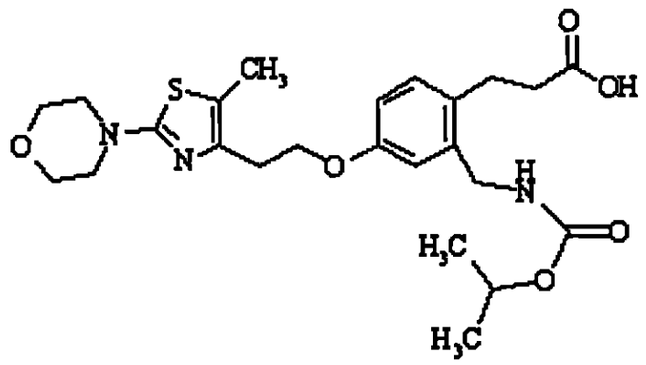
19. El compuesto de la reivindicación 1 representado por la siguiente fórmula,



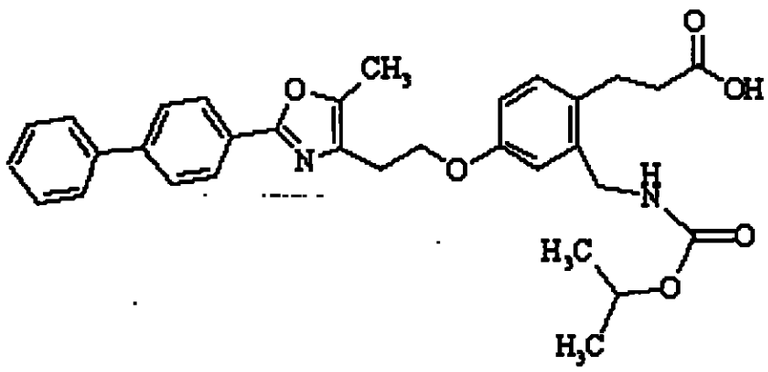
donde,

Y^{1a} es hidrógeno, arilo, heteroarilo o ariloxi; q es 1 ó 2; y n^1 es 2, 3, ó 4.

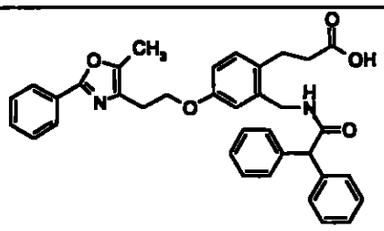
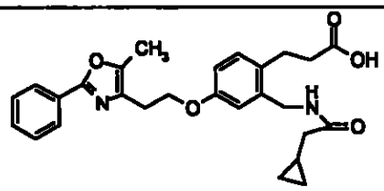
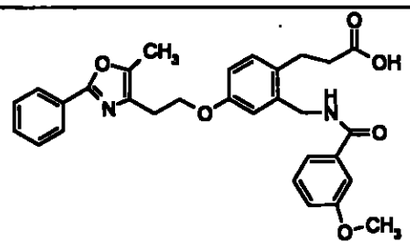
20. El compuesto de la reivindicación 1 ó 2, representado por la siguiente fórmula estructural,

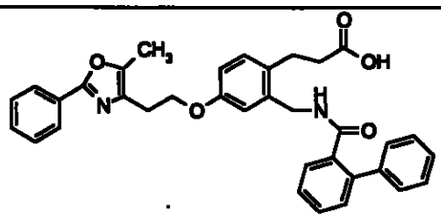
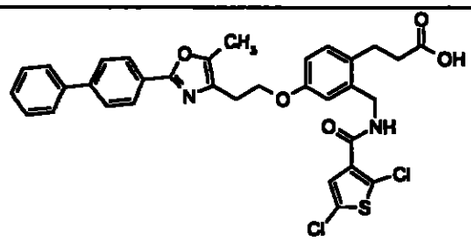
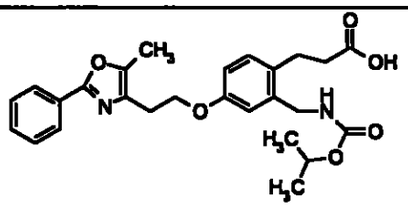
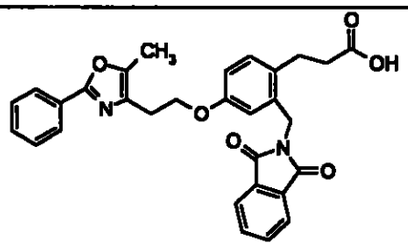
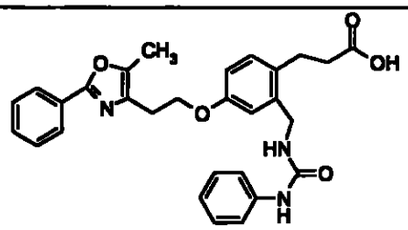


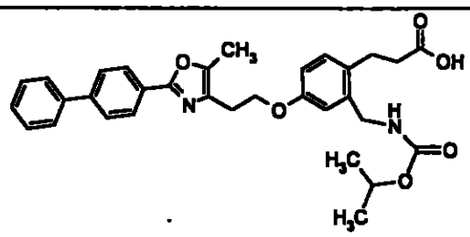
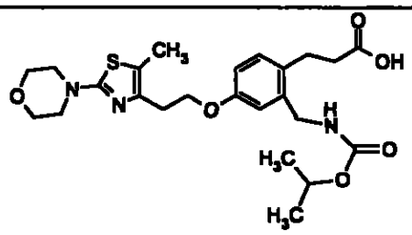
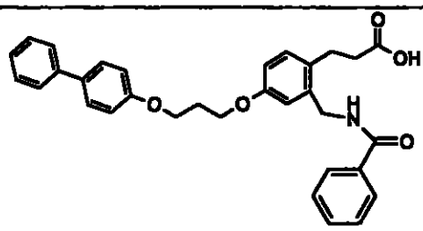
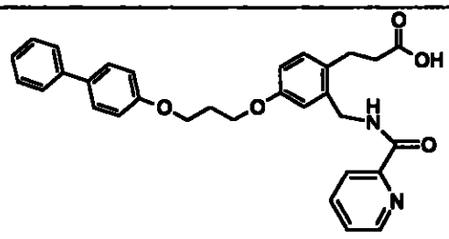
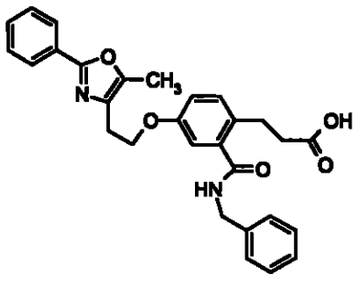
21. El compuesto de la reivindicación 1 ó 2 representado por la siguiente fórmula estructural,

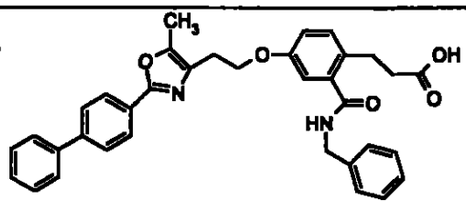
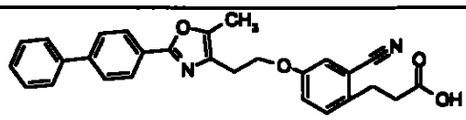
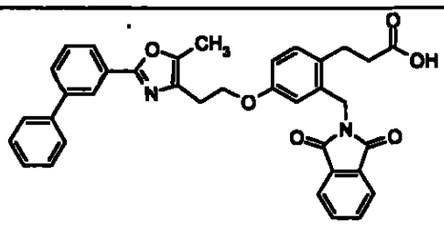
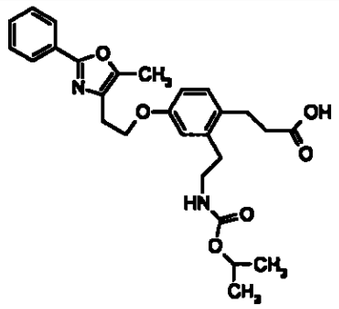
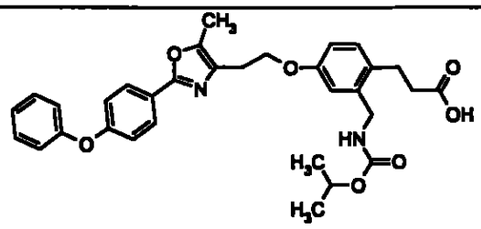


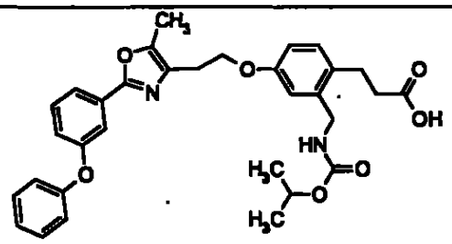
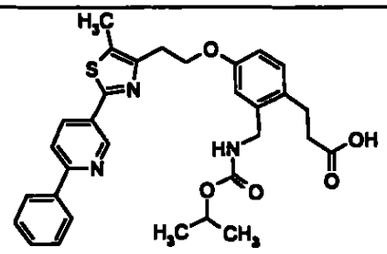
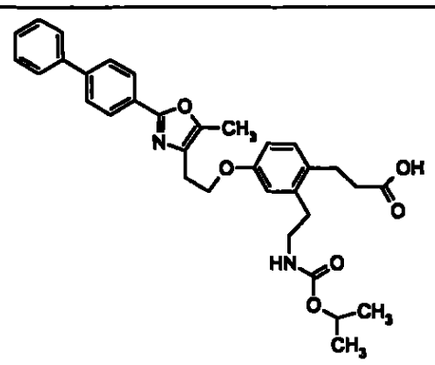
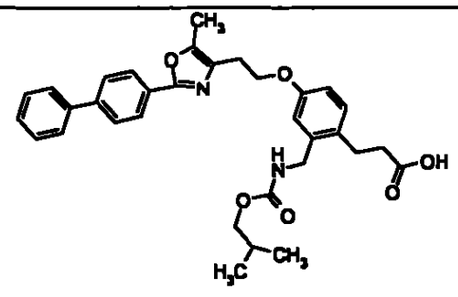
22. Un compuesto seleccionado entre el grupo compuesto por:

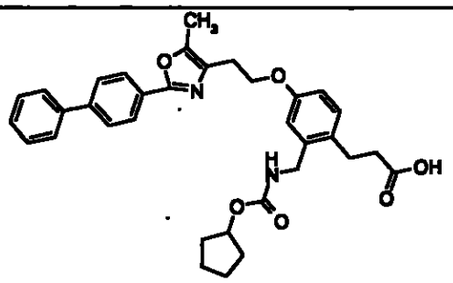
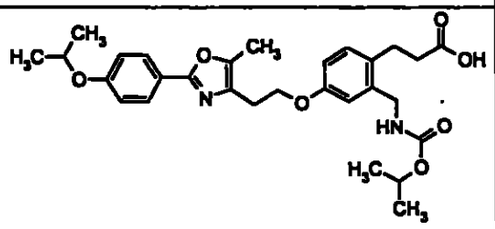
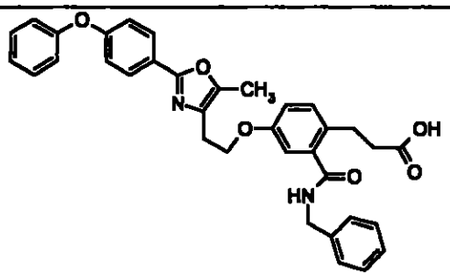
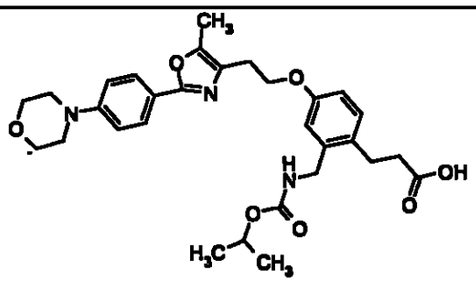
No.	Compuesto	nombre
1		ácido 3-{2-(difenilacetil-aminometil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
2		Ácido 3-{2-[(2-ciclopropilacetilamino) metil]-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
3		Ácido 3-{2-[(3-metoxibenzoilamino) metil]-4-[2-(5-metil-2-feniloxazol-4-il)etoxi] fenil} propiónico

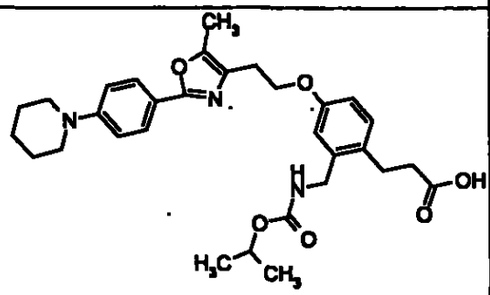
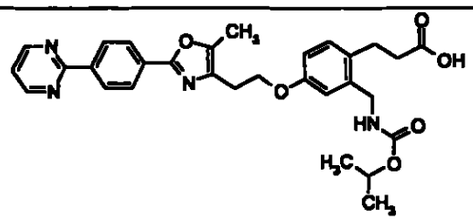
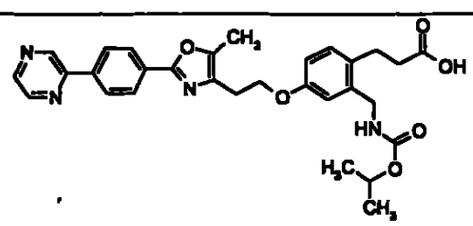
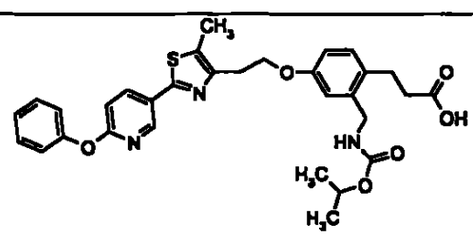
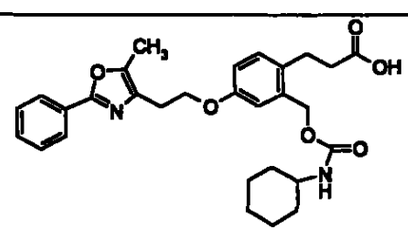
No.	Compuesto	nombre
4		Ácido 3-{2-{[(bifenil-2-carbonil) amino]metil}-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
5		Ácido 3-(4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-{[(2,5-diclorotiofeno-3-carbonil)amino]metil}fenil) propiónico
6		Ácido 3-{2-(isopropoxicarbonil-aminometil)-4-[2-(5-metil-2-feniloxazol-4-il) etoxi] fenil} propiónico
7		Ácido 3-{2-(1,3-dioxo-1,3-dihidroisoindol-2-ilmetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
8		Ácido 3-{4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-[(3-fenilureido)metil] fenil} propiónico

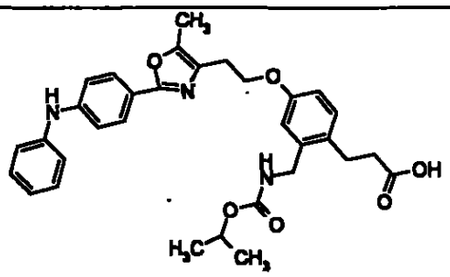
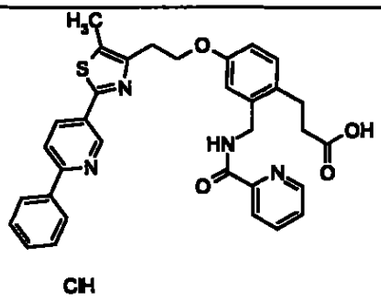
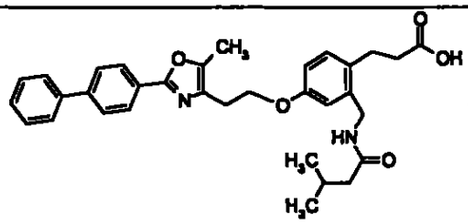
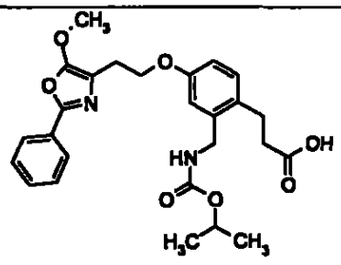
No.	Compuesto	nombre
9		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(isopropoxicarbonilaminometil)fenil] propiónico
10		Ácido 3-{2-(isopropoxicarbonil-aminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il) etoxi]fenil} propiónico
11		Ácido 3-{2-(benzoilaminometil)-4-[3-(bifenil-4-iloxi)propoxi] fenil} propiónico
12		Ácido 3-(4-[3-(bifenil-4-iloxi) propoxi]-2-{[(piridina-2-carbonil)amino]metil}fenil) propiónico
13		Ácido 3-{2-bencilcarbamoil-4-[2-(5-metil-2-feniloxazol-4-il) etoxi]fenil} propiónico

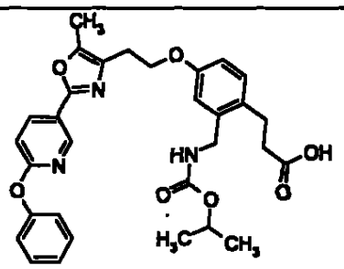
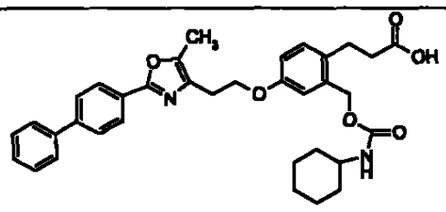
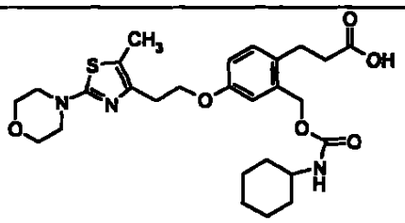
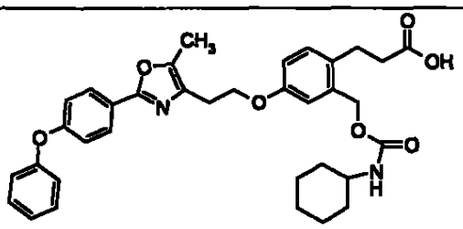
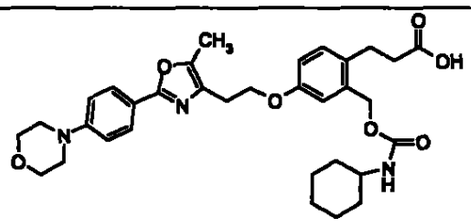
No.	Compuesto	nombre
14		Ácido 3-{2-bencilcarbamoil-4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]fenil} propiónico
15		Ácido 3-{4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-cianofenil} propiónico
16		Ácido 3-[4-[2-(2-bifenil-3-il-5-metiloxazol-4-il)etoxi]-2-(1,3-dioxo-1,3-dihidroisoindol-2-ilmetil)fenil] propiónico
17		Ácido 3-{2-(2-isopropoxicarbonil-aminoetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
18		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico

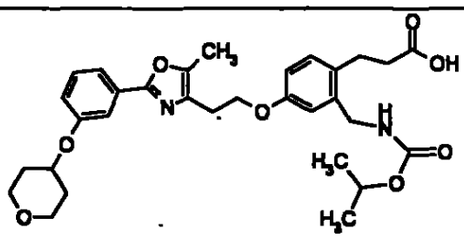
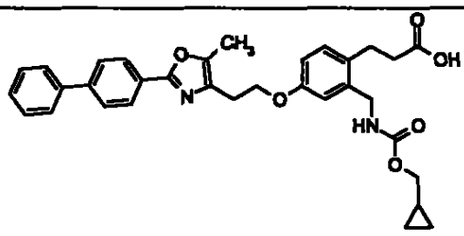
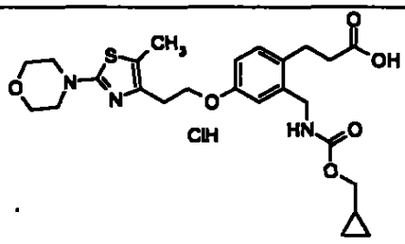
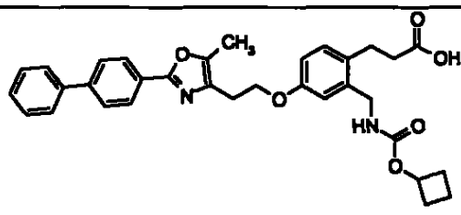
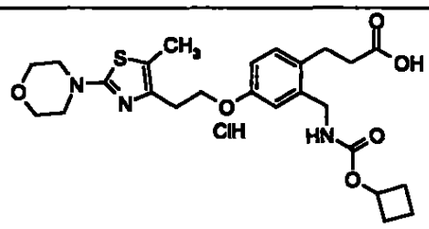
No.	Compuesto	nombre
19		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(3-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico
20		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(6-fenilpiridin-3-il)tiazol-4-il]etoxi}fenil) propiónico
21		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(2-isopropoxicarbonilaminoetil) fenil] propiónico
22		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(isobutoxicarbonilaminometil) fenil] propiónico

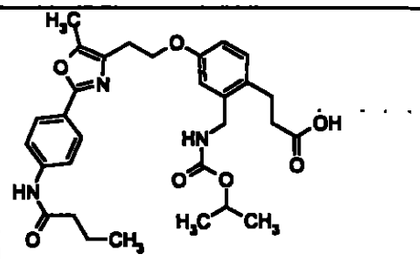
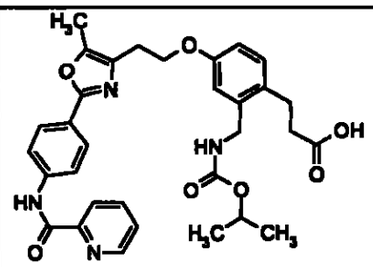
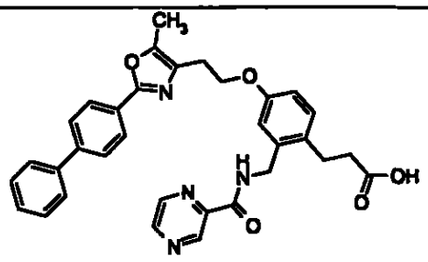
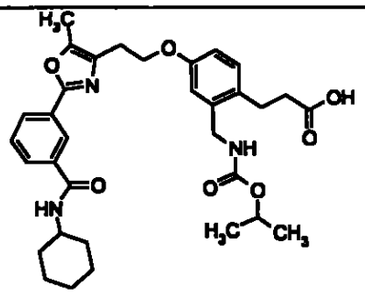
No.	Compuesto	nombre
23		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(ciclopentiloxicarbonil-aminometil)fenil] propiónico
24		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[2-(4-isopropoxifenil)-5-metiloxazol-4-il]etoxi} fenil) propiónico
25		Ácido 3-(2-bencilcarbamoil-4-{2-[5-metil-2-(4-fenoxifenil) oxazol-4-il]etoxi}fenil) propiónico
26		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-morfolin-4-ilfenil)oxazol-4-il]etoxi}fenil) propiónico

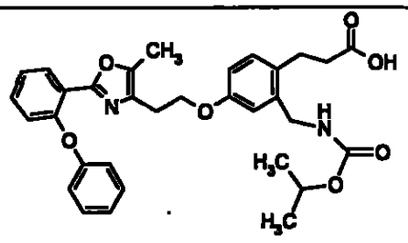
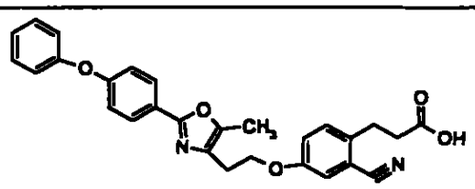
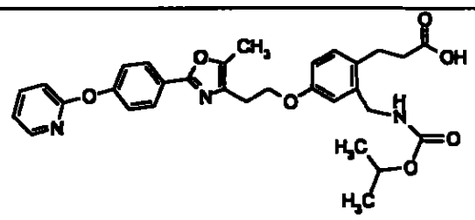
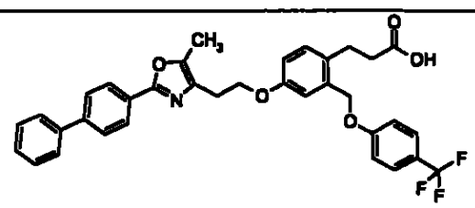
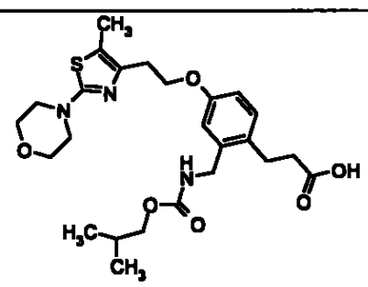
No.	Compuesto	nombre
27		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-piperidin-1-ilfenil)oxazol-4-il]etoxi}fenil) propiónico
28		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-pirimidin-2-ilfenil)oxazol-4-il]etoxi}fenil) propiónico
29		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-pirazin-2-ilfenil)oxazol-4-il]etoxi}fenil) propiónico
30		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(6-fenoxipiridin-3-il)tiazol-4-il]etoxi}fenil) propiónico
31		Ácido 3-{2-ciclohexilcarbamoil-oximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico

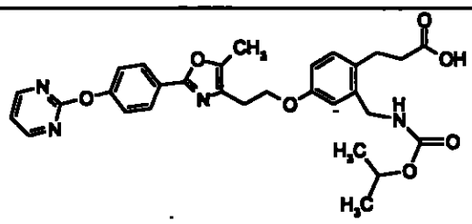
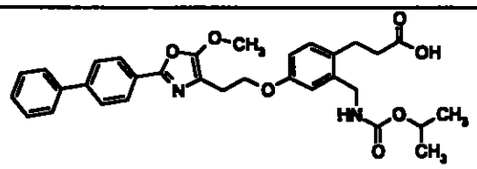
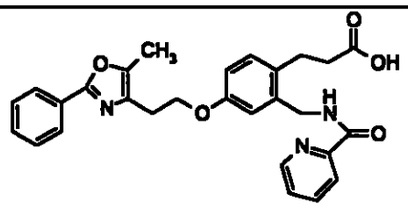
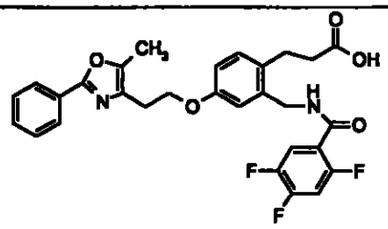
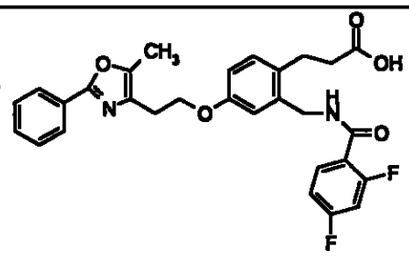
No.	Compuesto	nombre
32		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-fenilaminofenil)oxazol-4-il]etoxi}fenil) propiónico
33		Sal HCl del ácido 3-(4-{2-[5-metil-2-(6-fenilpiridin-3-il)tiazol-4-il]etoxi}-2-{[(piridina-2-carbonil)amino]metil}fenil) propiónico
34		Ácido 3-(4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-[(3-metilbutirilamino) metil]fenil} propiónico
35		Ácido 3-{2-(isopropoxicarbonil-aminometil)-4-[2-(5-metoxi-2-feniloxazol-4-il)etoxi] fenil} propiónico

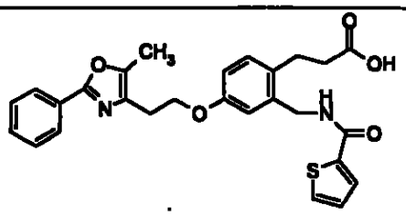
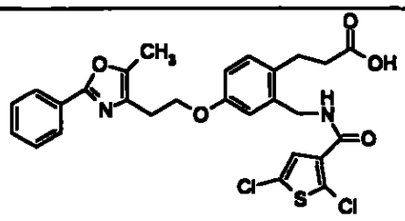
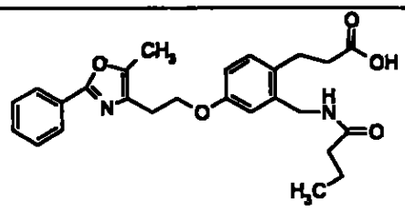
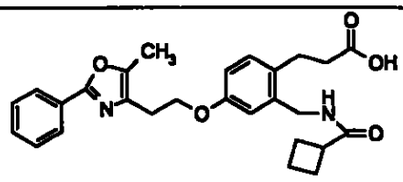
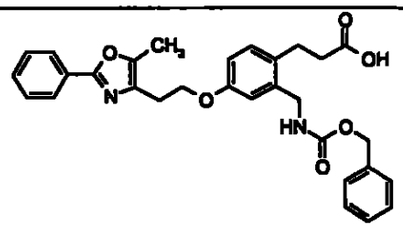
No.	Compuesto	nombre
36		Ácido 3-(2-(Isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(6-fenoxipiridin-3-il)oxazol-4-il]etoxi}fenil) propiónico
37		Ácido 3-(4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-ciclohexilcarbamoiloxi-metilfenil} propiónico
38		Ácido 3-{2-ciclohexilcarbamoil-oximetil-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil} propiónico
39		Ácido 3-(2-ciclohexilcarbamoil-oximetil-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico
40		Ácido 3-(2-ciclohexilcarbamoil-oximetil-4-{2-[5-metil-2-(4-morfolin-4-ilfenil)oxazol-4-il]etoxi}fenil) propiónico

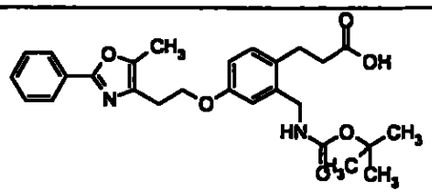
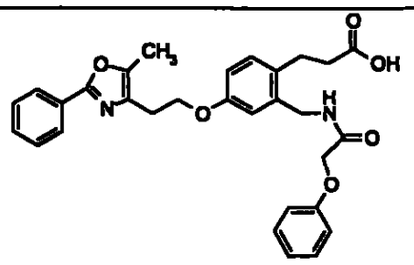
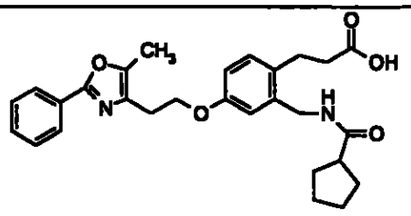
No.	Compuesto	nombre
41		Ácido 3-[2-(isopropoxicarbonil-aminometil)-4-(2-{5-metil-2-[3-(tetrahidropiran-4-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico
42		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(ciclopropilmetoxicarbonilamino metil)fenil] propiónico
43		Sal HCl del ácido 3-[2-(ciclopropilmetoxi-carbonilaminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil} propiónico
44		Sal HCl del ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(ciclobutoxicarbonil-aminometil)fenil]propiónico
45		Sal HCl del ácido 3-{2-(ciclobutoxicarbonil-aminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il) etoxi]fenil} propiónico

No.	Compuesto	nombre
46		Ácido 3-[4-{2-[2-(4-butirilaminofenil)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)-fenil] propiónico
47		Ácido 3-{2-(isopropoxicarbonil-amino-metil)-4-[2-(5-metil-2-{4-[(piridina-2-carbonil)-amino]-fenil}-oxazol-4-il)-etoxi]-fenil}-propiónico
48		Ácido 3-(4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-{[(pirazina-2-carbonil) amino]metil}fenil) propiónico
49		Ácido 3-[4-{2-[2-(3-ciclohexilcarbamoilfenil)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)-fenil] propiónico

No.	Compuesto	nombre
50		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(2-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico
51		Ácido 3-(2-ciano-4-{2-[5-metil-2-(4-fenoxi-fenil)-oxazol-4-il]-etoxi}-fenil) propiónico
52		Ácido 3-[2-(isopropoxicarbonil-aminometil)-4-(2-{5-metil-2-[4-(piridin-2-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico
53		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(4-trifluorometilfenoximetil) fenil] propiónico
54		Ácido 3-(2-(isobutoxicarbonil-aminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil} propiónico

No.	Compuesto	nombre
55		Ácido 3-[2-(isopropoxicarbonil-aminometil)-4-(2-{5-metil-2-[4-(pirimidin-2-iloxi) fenil] oxazol-4-il}etoxi)fenil] propiónico
56		Ácido 3-[4-[2-(2-bifenil-4-il-5-metoxioxazol-4-il)etoxi]-2-(isopropoxicarbonilaminometil)-fenil] propiónico
57		Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico
58		Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(2,4,5-trifluoro-benzoilamino)-metil]-fenil}-propiónico
59		Ácido 3-{2-[(2,4-difluoro-benzoilamino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

No.	Compuesto	nombre
60		ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{[(tiofeno-2-carbonil)-amino]-metil}-fenil)-propiónico
61		Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{[(tiofeno-2-carbonil)-amino]-metil}-fenil)-propriónico
62		Ácido 3-{2-(butirilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico
63		Ácido 3-{2-[(ciclobutanocarbonil-amino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico
64		Ácido 3-{2-(benciloxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

No.	Compuesto	nombre
65		Ácido 3-{2-(terc-butoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico
66		Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(2-fenoxi-acetilamino)-metil]-fenil}-propiónico
67		Ácido 3-{2-[(ciclopentanocarbonil-amino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

23. Una composición farmacéutica que comprende un vehículo farmacéuticamente aceptable y al menos un compuesto de las reivindicaciones 1-22 o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

24. Una composición farmacéutica que comprende (1) un compuesto de la reivindicación 1 ó 2, o una sal, solvato, hidrato o estereoisómero farmacéuticamente aceptable del mismo; (2) un segundo agente terapéutico seleccionado entre el grupo compuesto por sensibilizadores de insulina, sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de la a-glucosidasa,

secretagogos de insulina, insulina, agentes antihiperlipidémicos, agentes que elevan las HDL en plasma, inhibidores de la HMG-CoA reductasa, estatinas, inhibidores de la acril CoA:colesterol aciltransferasa, compuestos antiobesidad, agentes antihipercolesterolémicos, fibratos, vitaminas y aspirina; y (3) un vehículo farmacéuticamente aceptable.

25. Un procedimiento para modular un receptor activado por el proliferador de peroxisomas (PPAR), que comprende la etapa de poner en contacto el receptor con al menos un compuesto de las reivindicaciones 1-22, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

26. El procedimiento de la reivindicación 25, en el que el receptor activado por el proliferador de peroxisomas es un receptor alfa.

27. El procedimiento de la reivindicación 25, en el que el receptor activado por el proliferador de peroxisomas es un receptor gamma.

28. Un procedimiento para tratar o prevenir una enfermedad o afección mediada por el receptor gamma activado por el proliferador de peroxisomas, que comprende la etapa de administrar una cantidad eficaz de al menos un compuesto de la reivindicación 1 ó 2.

29. Un procedimiento para reducir la glucosa en sangre, que comprende la etapa de administrar una cantidad eficaz de al menos un compuesto de la reivindicación 1 ó 2.

30. Un método para tratar o prevenir una enfermedad o afección seleccionada entre el grupo compuesto por hiperglucemia, dislipidemia, diabetes de tipo II, diabetes de tipo I, hipertrigliceridemia, síndrome X, resistencia a la insulina, insuficiencia cardíaca, dislipidemia diabética, hiperlipidemia, hipercolesterolemia, hipertensión, obesidad, bulimia, anorexia nerviosa, enfermedad cardiovascular y otras enfermedades donde la resistencia a la insulina es un componente, que comprende la etapa de administrar una cantidad eficaz de al menos un compuesto de la reivindicación 1 ó 2.

31. Un procedimiento para tratar o prevenir la diabetes mellitus en un mamífero, que comprende la etapa de administrar a un mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de la reivindicación 1 ó 2.

32. Un procedimiento para tratar o prevenir una enfermedad cardiovascular en un mamífero, que comprende la etapa de administrar a un mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de la reivindicación 1 ó 2, o una sal, solvato, hidrato o estereoisómero farmacéuticamente aceptable del mismo.

33. Un procedimiento para tratar o prevenir el síndrome X en un mamífero, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de la reivindicación 1 ó 2, o una sal, solvato, hidrato o estereoisómero farmacéuticamente aceptable del

mismo.

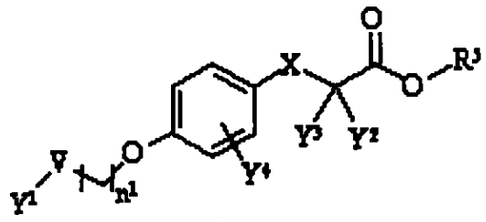
34. Un procedimiento para tratar o prevenir una enfermedad o afección seleccionada entre el grupo compuesto por hiperglucemia, dislipidemia, diabetes de tipo II, diabetes de tipo I, hipertrigliceridemia, síndrome X, resistencia a insulina, insuficiencia cardíaca, dislipidemia diabética, hiperlipidemia, hipercolesterolemia, hipertensión, obesidad, bulimia, anorexia nerviosa, enfermedad cardiovascular y otras enfermedades donde la resistencia a la insulina es un componente, que comprende la etapa de administrar una cantidad eficaz de al menos un compuesto de la reivindicación 1 ó 2 y una cantidad eficaz de un segundo agente terapéutico seleccionado entre el grupo compuesto por: sensibilizadores de insulina, sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de α-glucosidasa, secretagogos de insulina, insulina, agentes antihiperlipidémicos, agentes que aumentan el HDL en plasma, inhibidores de la HMG-CoA reductasa, estatinas, inhibidores de acril CoA:colesterol aciltransferasa, compuestos antiobesidad, agentes antihipercolesterolémicos, fibratos, vitaminas y aspirina.

35. Uso de un compuesto de un compuesto de la reivindicación 1 ó 2 y una sal, solvato, hidrato o estereoisómero farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para el tratamiento de una afección modulada por un PPAR.

RESUMEN DE LA DESCRIPCIÓN

MODULADORES DE RECEPTORES ACTIVADOS POR EL PROLIFERADOR DE PEROXISOMAS

La presente invención se refiere a un compuesto de fórmula I,



I

y sales, solvatos, hidratos o estereoisómeros farmacéuticamente aceptables del mismo, que son útiles en el tratamiento del Síndrome X, diabetes de tipo II, hiperglucemia, hiperlipidemia, obesidad, coagulopatía, hipertensión, arteriosclerosis, y otros trastornos relacionados con el Síndrome X así como enfermedades cardiovasculares.

TRATADO DE COOPERACIÓN DE PATENTES

Procedente de la
AUTORIDAD DEL EXAMEN PRELIMINAR INTERNACIONAL

A:	Fecha de envío (*día/mes/año*) 23.09.2003
Jang, Soonhee ELI LILLY AND COMPANY P.O. Box 6288 Indianapolis, IN 46206-6288 ESTADOS UNIDOS DE AMÉRICA	

Referencia del archivo del solicitante o agente	NOTIFICACIÓN IMPORTANTE
X-14528	

Solicitud Internacional Nº	Fecha de presentación internacional (*día/mes/año*)	Fecha de prioridad (*día/mes/año*)
PCT/US02/15143	24.05.2002	07.06.2001

Solicitante
ELI LILLY AND COMPANY

1. Por la presente, el solicitante notifica que esta Autoridad del Examen Preliminar Internacional transmite con la presente el informe de examen preliminar internacional y sus anexos, si los hubiera, establecidos en esta solicitud internacional.

2. Está siendo transmitida una copia del informe y sus anexos, si los hubiera, a la Agencia Internacional para la comunicación a todas las Oficinas elegidas.

3. Cuando se requiera por parte de cualquiera de las Oficinas elegidas, la Agencia Internacional preparará una traducción en inglés del informe (pero no de los anexos) y transmitirá tal traducción a esas Oficinas.

4. **AVISO**
El solicitante debe participar en la fase nacional ante cada Oficina elegida realizando ciertas actuaciones (completar traducciones y pagar las tasas nacionales) en un plazo de 30 meses desde la fecha de prioridad (o después en algunas Oficinas) (Artículo 39(1)) (véase también el aviso mandado por la Agencia Internacional con el formulario PCT/IB/301).

Cuando deba proporcionarse una traducción de la solicitud internacional a una Oficina elegida, dicha traducción debe contener una traducción de cualquiera de los anexos al informe de examen preliminar internacional. Es responsabilidad del solicitante preparar y proporcionar dicha traducción directamente a cada Oficina elegida implicada.

Para más detalles sobre los plazos aplicables y sobre los requerimientos de las Oficinas elegidas, véase el Volumen II de la Guía del solicitante PCT.

Se llama la atención del solicitante en el Artículo 33(5), que establece que los criterios de novedad, etapa inventiva y aplicabilidad industrial descritos en el Artículo 33(2) a (4) cumplen simplemente los propósitos del examen preliminar internacional y que "cualquier Estado Contratante puede aplicar criterios adicionales o diferentes con respecto a los propósitos de decidir si, en ese Estado, las invenciones reivindicadas pueden patentarse o no" (véase también el Artículo 27(5)). Tales criterios adicionales pueden referirse, por ejemplo, a exenciones de la patentabilidad, requerimientos para permitir la descripción, claridad y apoyo para las reivindicaciones.

Nombre y dirección de correo de la Autoridad del examen preliminar internacional:	Funcionario autorizado
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ambroa, J.R. Tlf. +49 89 2399-8012

Formulario PCT/IPEA/416 (Julio de 1994)

TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(PCT Artículo 36 y Norma 70)

Referencia del archivo del solicitante o agente X-14528	**PARA UNA ACCIÓN ADICIONAL**	Véase la Notificación de transmisión del Informe de Examen Preliminar Internacional (Formulario PCT/IPEA/416)

Solicitud Internacional Nº PCT/US02/15143	Fecha de presentación internacional (*día/mes/año*) 24.05.2002	Fecha de prioridad (*día/mes/año*) 07.06.2001

Clasificación de Patente Internacional (IPC) o tanto clasificación nacional como IPC
A61K31/42, A61K31/42

Solicitante
ELI LILLY AND COMPANY

1. Este informe de examen preliminar internacional se ha sido preparado por esta Autoridad del Examen Preliminar Internacional y se transmite al solicitante de acuerdo con el Artículo 36.
2. Este INFORME consta de un total de 6 hojas, incluyendo esta hoja de portada.

☒ Este informe también se acompaña de ANEXOS, es decir, hojas de la descripción, reivindicaciones y/o dibujos que se han corregido y son la base para este informe y/o hojas que contienen rectificaciones hechas ante esta Autoridad (véase Norma 70.16 y Sección 607 de las Instrucciones Administrativas según el PCT.

Estos anexos constan de un total de 29 hojas.

3. Este informe contiene indicaciones relacionadas con las siguientes cuestiones:

I	☒	Bases de la opinión
II	☐	Prioridad
III	☒	Opinión sin establecer con respecto a la novedad, etapa inventiva y aplicabilidad industrial
IV	☐	Falta de unidad de invención
V	☒	Afirmación razonada según la Norma 66.2(a)(ii) con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citaciones y explicaciones que apoyan dicha afirmación
VI	☐	Algunos documentos citados
VII	☐	Algunos defectos en la solicitud internacional
VIII	☐	Algunas observaciones en la solicitud internacional

Fecha de entrega de la demanda 17.12.2002	Fecha de terminación de este informe 23.09.2003
Nombre y dirección de correo de la Autoridad del examen preliminar internacional: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Funcionario autorizado Kollmannsberger, M Teléfono Nº +49 89 2399-7364

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL Solicitud internacional N° PCT/US02/15143

I. Bases del informe

1. Con respecto a los **elementos** de la solicitud internacional *(las hojas de sustitución que se han proporcionado a la Oficina receptora en respuesta a una invitación según el Artículo 14, en el presente informe se designan como "presentadas originalmente" y no se adjuntan a este informe ya que no contienen modificaciones (Normas 70.16 y 70.17)*:
Descripción, páginas:

1-406 como presentadas originalmente

Reivindicaciones, N° :

1-34 presentadas con telefax el 13.03.2003

2. Con respecto al **idioma**, todos los elementos marcados anteriormente estaban disponibles o se proporcionaron a esta Autoridad en el idioma en el que se presentó la solicitud internacional, a menos que se indique otra cosa en este apartado.

Estos elementos estaban disponibles o se proporcionaron a esta Autoridad en el siguiente idioma: , que es:

☐ el idioma de una traducción proporcionada para los fines de investigación internacional (de acuerdo con la Norma 23.1 (b)).

☐ el idioma de publicación de la solicitud internacional (según la Norma 48.3(b)).

☐ el idioma de una traducción proporcionada para los fines del examen preliminar internacional (según la Norma 55.2 y/o 55.3).

3. Con respecto a cualquier **secuencia de nucleótidos y/o de aminoácidos** descrita en la solicitud internacional, el examen preliminar internacional se realizó basándose en la lista de secuencias:

☐ contenida en la solicitud internacional en forma escrita.
☐ presentada junto con la solicitud internacional en forma legible por ordenador.
☐ proporcionada con posterioridad a esta Autoridad en forma escrita.
☐ proporcionada con posterioridad a esta Autoridad en forma legible por ordenador.
☐ Se ha proporcionado la declaración de que la lista de secuencias escrita proporcionada posteriormente no va más allá de la descripción de la solicitud internacional según se presentó.
☐ Se ha proporcionado la declaración de que la información guardada en forma legible por ordenador es idéntica a la lista de secuencias escrita.

4. Las modificaciones han dado como resultado la anulación de:

☐ la descripción, páginas:

☐ las reivindicaciones, N°s:

☐ los dibujos, hojas:

5. ☐ Este informe se ha establecido como si (algunas de) las modificaciones no se hubieran realizado, ya que se ha considerado que van más allá de la descripción según se presentó (Norma 70.2(c)):

(Cualquier hoja de sustitución que contenga tales modificaciones deberá mencionarse en el punto 1 y adjuntarse en este informe.)

6. Observaciones adicionales en caso de que sea necesario:

III. Opinión no establecida con respecto a la novedad, paso de la invención y aplicabilidad industrial

1. Las cuestiones de si la invención reivindicada parece ser nueva, implicar una etapa inventiva (no ser evidente) o aplicarse industrialmente no se han examinado respecto a:

☐ la solicitud internacional entera.

☒ las reivindicaciones Nº 25-34

porque:

☒ dicha solicitud internacional o dichas reivindicaciones Nº 24-34 se refieren a la siguiente materia objeto que no requiere ningún examen preliminar internacional (*especificar*):
Véase la hoja separada

☐ de esta forma la descripción, reivindicaciones o dibujos *(indicar los elementos particulares más adelante)* o dichas reivindicaciones Nº no están claros de forma que no puede formarse una opinión significativa (*especificar*):

☐ de esta forma, las reivindicaciones, o dichas reivindicaciones Nº están apoyadas de forma inadecuada por la descripción de que no puede formarse ninguna opinión significativa.

☐ no se ha establecido ningún informe de búsqueda internacional para dichas reivindicaciones Nº

2. No puede realizarse un examen preliminar internacional significativo debido a que la lista de secuencias de nucleótidos y/o aminoácidos no cumple con la norma proporcionada en el Anexo C de las Instrucciones Administrativas:

☐ La forma escrita no se ha proporcionado o no cumple con la norma.

☐ La forma legible por ordenador no se ha proporcionado o no cumple con la norma.

V. Declaración razonada según el Artículo 35(2) con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citaciones y explicaciones que apoyan tal declaración

1. Declaración

Novedad (N)	Sí:	Reivindicaciones 1-34
	No:	Reivindicaciones
Etapa inventiva (IS)	Sí:	Reivindicaciones 1-34
	No:	Reivindicaciones
Aplicabilidad industrial (IA)	Sí:	Reivindicaciones 1-24
	No:	Reivindicaciones

2. Citaciones y explicaciones

Véase la hoja separada

9587
992

Re Punto III

Las reivindicaciones 25-33 se refieren a una materia objeto que esta Autoridad considera que están cubiertas por las disposiciones de la Norma 67.1(iv) del PCT. Por lo tanto, no se formulará ninguna opinión con respecto a la aplicabilidad industrial de la materia objeto de estas reivindicaciones (Artículo 34(4)(a)(i) del PCT).

Re Punto V

V-1. Técnica anterior

Los siguientes documentos se consideran relevantes:

D1: WO 02 18355 A (BROOKS DAWN ALISA; CONNOR SCOTT EUGENE (US); DOMINIANNI SAMUEL JAM) 7 de marzo de 2002 (07-03-2002)

D2: WO 02 16332 A (BROOKS DAWN ALISA; GODFREY ALEXANDER GLENN (US); MANTLO NATHAN BRY) 28 de febrero de 2002 (28-02-2002)

D3: WO 01 16120 A (DOMINIANNI SAMUEL J: MATTHEWS DONALD P (US); MICHELLYS PIERRE YVES) 8 de marzo de 2001 (08-03-2001)

D4: WO 01 00566 A (ZANDT MICHAEL C VAN; INST FOR PHARMACEUTICAL DISCOV (US)) 4 de enero de 2001 (04-01-2001)

D5: EP-A-1 216 980 (EISAI CO LTD) 26 de junio de 2002 (26-06-2002)

D6: WO 01 25181

D1 y D2 son documentos P y no se consideran en la presente etapa de los procedimientos. D5 se ha publicado después de la fecha de presentación de la presente solicitud pero se considera una traducción de D6 que se ha publicado antes de la fecha de prioridad de la presente solicitud.

V-2. Novedad (Art. 33(2) del PCT)

Los compuestos de D3 difieren de las presentes reivindicaciones a causa del sustituyente Y4 (nomenclatura de la presente solicitud, véase R2/R3 en D3) que se requiere que presente una sustitución del heteroátomo en el resto alquilo en las presentes reivindicaciones mientras que en D3 sólo se reivindican y se ejemplifican alquilo, arilo y los sustituyentes de hidrocarburo relacionados (véase, por ejemplo, el ejemplo 60).

D4 describe (véase reivindicación 1 para R3 = fenoxi o R3 = OR7 y R7 = bencilo) compuestos que se han excluido de las presentes reivindicaciones por la definición de n = 2-5 (de esta forma, los compuestos en D4 presentan n = 0 y 1).

D5 describe compuestos (véase la reivindicación 1 y por ejemplo los ejemplos 771-785 en las páginas 135-137) para Y1 = alquilo, mientras que en la presente reivindicación 1 se requiere que Y1 sea un sustituyente de arilo.

De esta forma, se cumple el Art. 33(2) del PCT para las reivindicaciones 1-34.

9886
993

V-3. Etapa inventiva (Art. 33(2) del PCT)

Se dice que los compuestos de la presente solicitud se unen al receptor PPAR-γ y que de esta forma pueden usarse para la disminución del nivel de azúcar en sangre y, por consiguiente, pueden ser útiles en el tratamiento de diabetes i. a.

Se considera que D3 representa el estado más cercano de la técnica ya que también se dice que los compuestos descritos en éste se unen al receptor ppar-γ y pueden usarse para tratar la diabetes. La diferencia de los compuestos reivindicados con respecto a los descritos en D3 reside en el hecho de que los sustituyentes en el anillo fenilo incluyen un heteroátomo (por ejemplo, alquilo sustituido con amidas, amida o CN directamente unido al anillo fenilo, etc, veánse las definiciones de Y4 en la presente reivindicación 1) mientras que en D3 sólo se describen los grupos alquilo/arilo no sustituidos y relacionados para el sustituyente respectivo en el grupo fenilo central (veánse las definiciones de R2/R3). Las otras definiciones se solapan (en particular, el oxazol fenil-sustituido de D3 se incluye en las definiciones de Y1 de la presente reivindicación 1 y también está presente en cualquiera de los compuestos ejemplo de la presente solicitud).

De esta forma, el problema a resolver en vista de D3 podría observarse en la disposición de compuestos adicionales que presentan la actividad reivindicada.

D4 describe compuestos estructuralmente muy parecidos como los inhibidores de aldosa reductasa para inhibir el nivel de azúcar en sangre. Como el efecto fisiológico así como el mecanismo de acción parecen ser diferentes, D4 no se considera con respecto a la etapa inventiva.

Los compuestos de D5 presentan la misma actividad moduladora de ppar-γ que las reivindicadas y únicamente difieren en la definición de Y1 como alquilo (opuesto a arilo en la presente reivindicación 1). Por otro lado, la sustitución de restos alquilo en los anillos fenilo centrales con amidas etc (véase por ejemplo los ejemplos 125-132, párrafos 771-785; la cadena propoxi corresponde a δ-[CH2]n-V-Y1 para n = 2 y V = unido, por lo que la diferencia reside en la definición de Y1 como arilo en las presentes reivindicaciones mientras que en estos ejemplos, es un grupo metilo), es decir, el sustituyente Y4 en el anillo fenilo que distingue la presente reivindicación 1 de D3, está claramente demostrado. Sin embargo, no existe una equivalencia directa demostrada entre el arilo y el alquilo amida-sustituido en D5. De esta forma, los compuestos reivindicados no parece que puedan derivare de una combinación de D3 y D5.

De esta forma, se cumple el Art. 33(2) del PCT para las presentes reivindicaciones.

En una fase regional posterior, el solicitante debe ser requerido para demostrar si los compuestos reivindicados muestran realmente la actividad alegada puesto que la solicitud no contiene ningún dato de ensayo verificable.

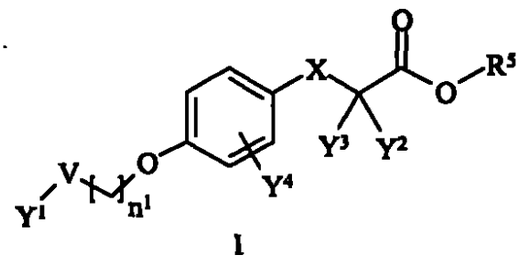
V-4. Aplicabilidad industrial (Art. 33(4) del PCT)

994

No surge ninguna objeción para las reivindicaciones 1-24 (en parte). Para la evaluación de las presentes reivindicaciones 25-34 sobre la cuestión de si son aplicables industrialmente, no existe ningún criterio unificado en los Estados contratantes del PCT. La patentabilidad también puede depender de la formulación de las reivindicaciones. El EPO, por ejemplo, no reconoce como industrialmente aplicable la materia objeto de las reivindicaciones para el uso de un compuesto en el tratamiento médico, pero, sin embargo, puede permitir reivindicaciones a un compuesto conocido para el primer uso en el tratamiento médico y el uso de tal compuesto para la fabricación de un medicamento para un nuevo tratamiento médico.

REIVINDICACIONES

1. Un compuesto de fórmula I,



I

y sales, solvatos, hidratos o estereoisómeros farmacéuticamente aceptables de los mismos, donde:

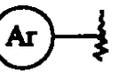
n^1 es 2, 3, 4 ó 5;

V es un enlace o O;

X es CH_2 o O;

p es 0 ó 1;

m es 1-4;

Y^1 es:  donde,

 es: arilo o heteroarilo,

donde arilo y heteroarilo están opcionalmente sustituidos con uno o más grupos seleccionados independientemente entre el grupo compuesto por:

hidrógeno, alquilo C_1-C_6, alcoxi C_1-C_6, halo, haloalquilo y haloalquiloxi;

Y^{1a} es: hidrógeno,

alquilo (C_0-C_3)-arilo,

C(O)-arilo,

heteroarilo,

cicloalquilo,

heterocicloalquilo,

ariloxi,

$NR^5(CH_2)_mOR^5$,

aril-Z-arilo,

aril-Z-heteroarilo,

aril-Z-cicloalquilo,

aril-Z-heterocicloalquilo,

heteroaril-Z-arilo,

heteroaril-Z-heterocicloalquilo o

heterocicloalquil-Z-arilo,

donde arilo, cicloalquilo, ariloxi, heteroarilo, y heterocicloalquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre el grupo compuesto por:

halo,

hidroxilo,

nitro,

ciano,

alquilo C_1-C_6,

alcoxi C_1-C_8 opcionalmente sustituido con $N(R^5)_2$,

haloalquilo,

$N(R^5)_2$,

$N[C(O)R^5]_2$,

$N[S(O)_2R^5]_2$,

$NR^5S(O)_2R^5$,

$NR^5C(O)R^5$,

$NR^5C(O)OR^5$,

$C(O)N(R^5)_2$,

$C(O)OR^5$ y

$C(O)R^5$;

Z es: un enlace,

-oxígeno-

$-C(O)NR^5-$

$-NR^5C(O)-$,

$-NR^5C(O)O-$,

-C(O)-,

$-NR^5-$,

$-[O]_p(CH_2)_m-$,

$-(CH_2)_m[O]_p-$,

$-NR^5(CH_2)_m-$ o

$-(CH_2)_m NR^5-$;

cada uno de Y^2 e Y^3 es independientemente:

hidrógeno,

alquilo C_1-C_6 o

alcoxi C_1-C_6;

Y^4 es: alquil (C_1-C_3)-$NR^5C(O)$-alquil (C_0-C_{10})-Y^7,

alquil (C_1-C_3)-$NR^5C(O)$-alquenil (C_2-C_{10})-Y^7,

alquil (C_1-C_3)-$NR^5C(O)$-alquinil (C_2-C_{10})-Y^7;

alquil (C_1-C_3)-$NR^5C(O)O$-alquil (C_0-C_{10})-Y^7,

alquil (C_1-C_3)-$NR^5C(O)NR^5$-alquil (C_0-C_{10})-Y^7,

alquil (C_1-C_3)-$NR^5C(S)NR^5$-alquil (C_0-C_{10})-Y^7,

alquil (C_0-C_3)-$C(O)NR^5$-alquil (C_0-C_{10})-Y^7,

alquil (C_1-C_3)-$OC(O)NY^{10}Y^{11}$,

alquil (C_1-C_3)-$NY^{10}Y^{11}$,

alquil (C_1-C_3)-O-alquil (C_0-C_{10})-Y^7,

alquil (C_1-C_3)-S-alquil (C_0-C_{10})-Y^7 o

CN;

Y^7 es: hidrógeno,

arilo,

heteroarilo,

alquilo C_1-C_{12},

alcoxi C_1-C_6,

cicloalquilo,

heterocicloalquilo,

ariloxi,

C(O)-heteroarilo o

SR^6,

donde alquilo, arilo, ariloxi, alcoxi, heteroarilo, cicloalquilo, y heterocicloalquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre R^7:

cada uno de Y^{10} e Y^{11} es independientemente:

hidrógeno,

arilo,

heteroarilo,

alquilo C_1-C_{10},

cicloalquilo,

$SO_2(R^6)$; o

Y^{10} e Y^{11} conjuntamente son un anillo heterocicloalquilo de 5 a 10 miembros o un anillo heterocicloalquilo condensado con arilo, y el anillo heterocicloalquilo contiene opcionalmente uno o más heteroátomos seleccionados entre N, O o S; y donde,

arilo, heteroarilo, heterocicloalquilo y alquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre R^7;

R^5 es: hidrógeno o alquilo C_1-C_6;

R^6 es: hidrógeno,

alquilo C_1-C_{10},

cicloalquilo,

arilo, o

heteroarilo,

donde alquilo, cicloalquilo, arilo y heteroarilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre R^7;

R^7 es: halo,

nitro,

oxo,

ciano,

hidroxilo,

bencilo,

fenilo,

fenoxi,

heteroarilo,

$C(O)R^6$,

alquilo C_1-C_{10},

alcoxi C_1-C_6,

haloalquilo C_1-C_6,

haloalquiloxi C_1-C_6,

$O(CH_2)_m$-fenilo,

$(CH_2)_mOC(O)$-arilo,

$C(O)OR^5$,

$S(O)_2R^5$,

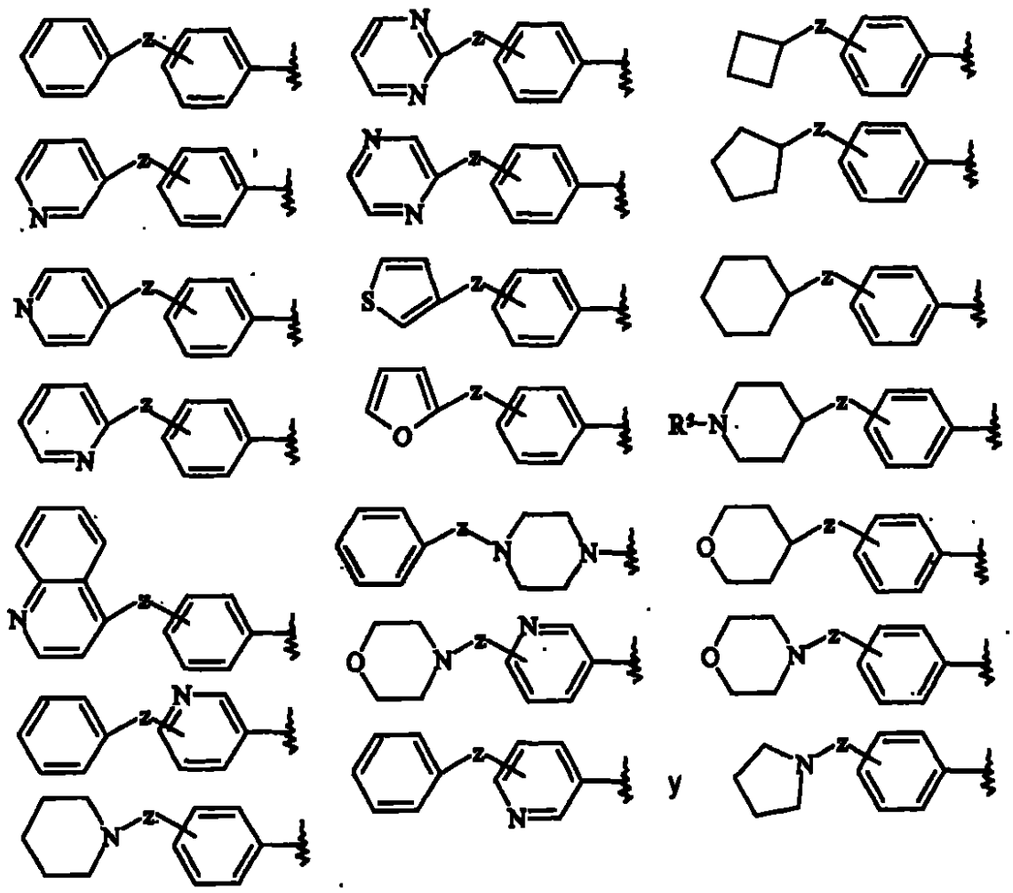
$S(O)_2N(R^5)_2$,

SR^5 o

$N(R^5)_2$,

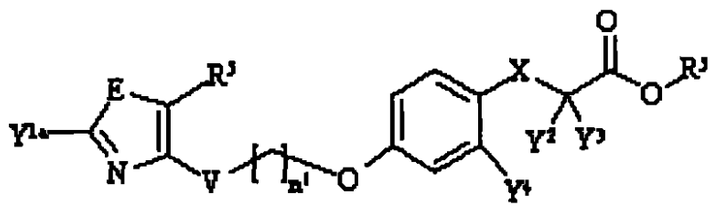
donde fenilo y fenoxi están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre halo o trifluorometilo.

2. El compuesto de la reivindicación 1, en el que Y^{1a} se selecciona entre el grupo compuesto por: arilo, heteroarilo, cicloalquilo, heterocicloalquilo, ariloxi,



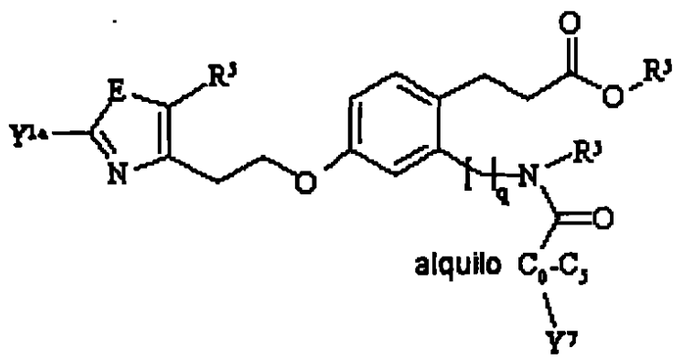
y

3. El compuesto de la reivindicación 1, donde el compuesto se representa por la siguiente fórmula estructural,



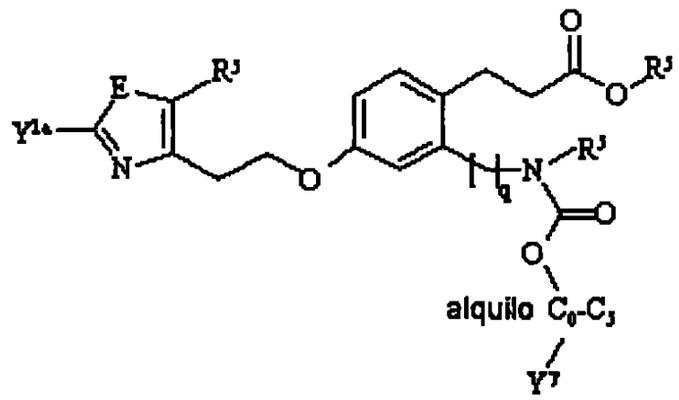
donde E es O o S.

4. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



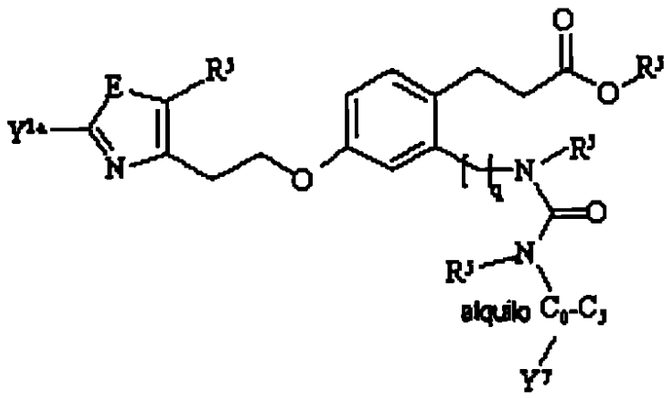
donde q es 0 ó 1; y cada R^5 es independientemente hidrógeno o metilo.

5. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



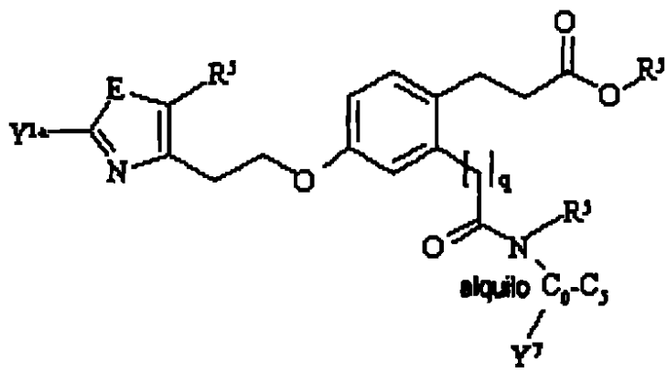
donde q es 0 ó 1; y cada R^5 es independientemente hidrógeno o metilo.

6. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



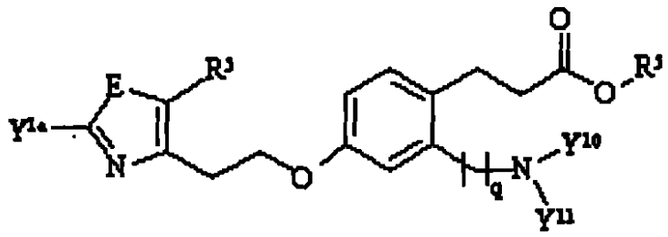
donde q es 0 ó 1; y cada R^5 es independientemente hidrógeno o metilo.

7. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



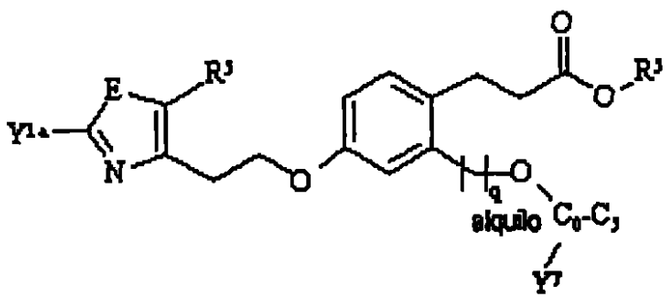
donde q es 0 ó 1; y cada R^5 es independientemente hidrógeno o metilo.

8. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



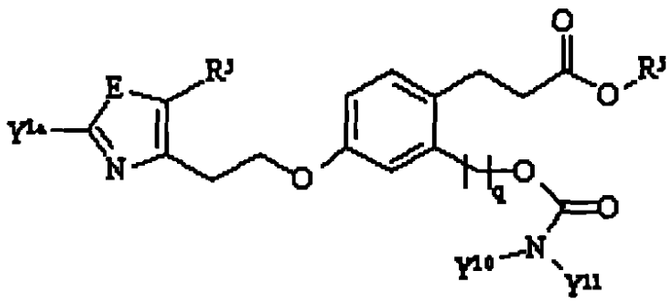
donde q es 0 ó 1; y cada R^5 es independientemente hidrógeno o metilo.

9. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



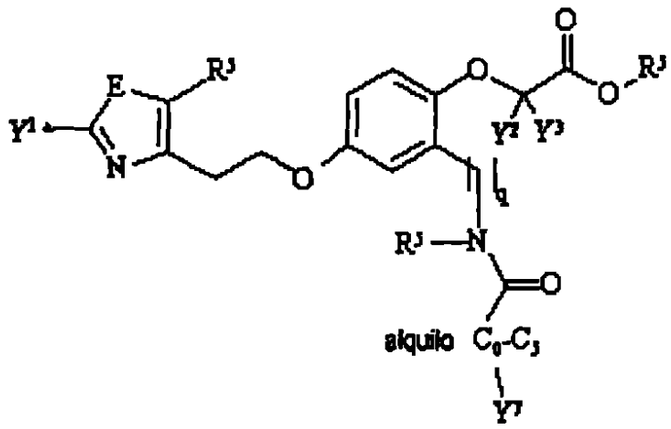
donde q es 0 ó 1; y cada R^5 es independientemente hidrógeno o metilo.

10. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



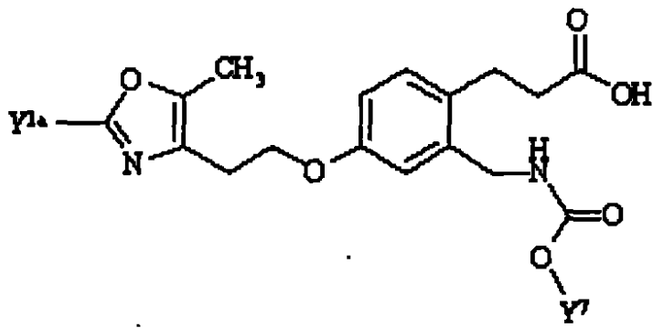
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

11. El compuesto de la reivindicación 4, donde el compuesto se representa por la siguiente fórmula estructural,



donde q es 1 ó 2; y cada R^5, Y^2 y Y^3 are independientemente hidrógeno o metilo.

12. El compuesto de la reivindicación 4 representado por la siguiente fórmula,

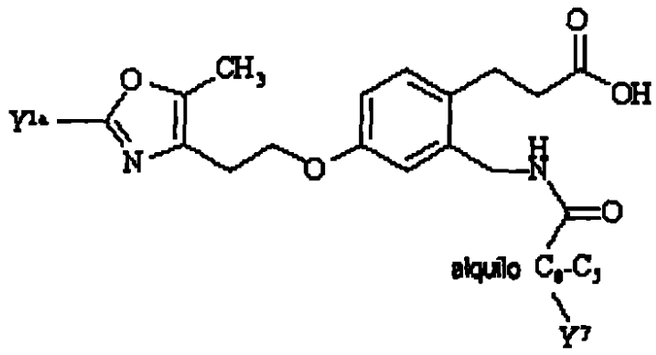


donde Y^{1a} es fenilo opcionalmente sustituido, naftilo,



y Z es un enlace, oxígeno, -NH-, -N(CH_3)-, -NHC(O)- o -C(O)NH-.

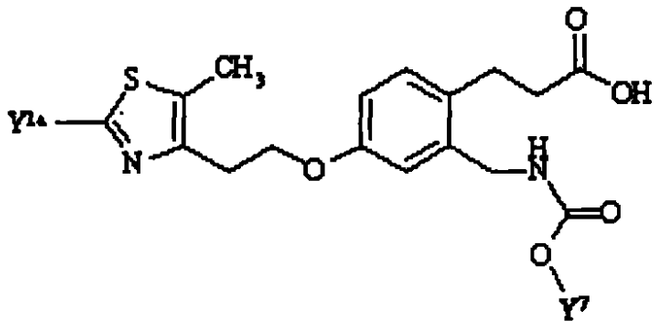
13. El compuesto de la reivindicación 4 representado por la siguiente fórmula,



donde Y^{1a} es fenilo opcionalmente sustituido, naftilo o  y

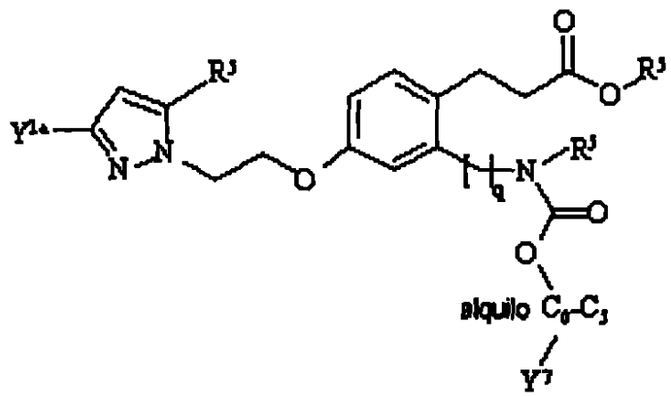
Z es un enlace, oxígeno, -NH-, -N(CH_3)-, -NHC(O)- o -C(O)NH-.

14. El compuesto de la reivindicación 4 representado por la siguiente fórmula,



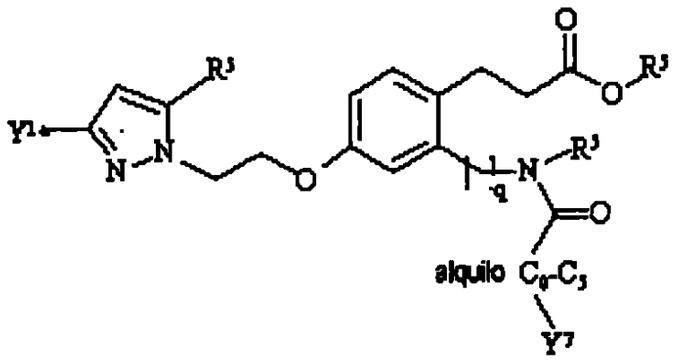
donde Y^{1a} es arilo opcionalmente sustituido, heteroarilo, heterocicloalquilo, heteroaril-Z-heterocicloalquilo o heteroaril-Z-arilo.

15. El compuesto de la reivindicación 1 representado por la siguiente fórmula,



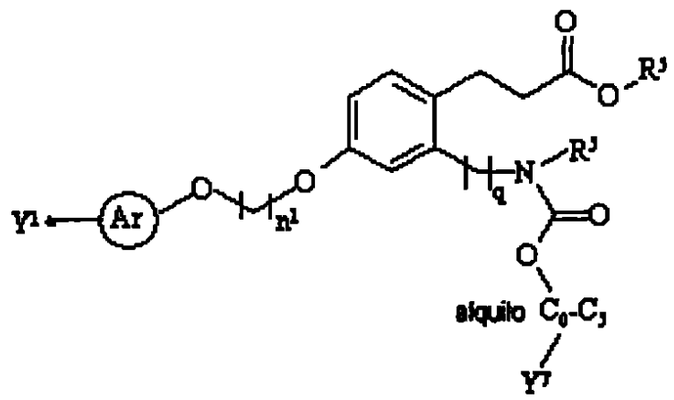
donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

16. El compuesto de la reivindicación 1 representado por la siguiente fórmula,



donde q es 1 ó 2; y cada R^5 es independientemente hidrógeno o metilo.

17. El compuesto de la reivindicación 1 representado por la siguiente fórmula,

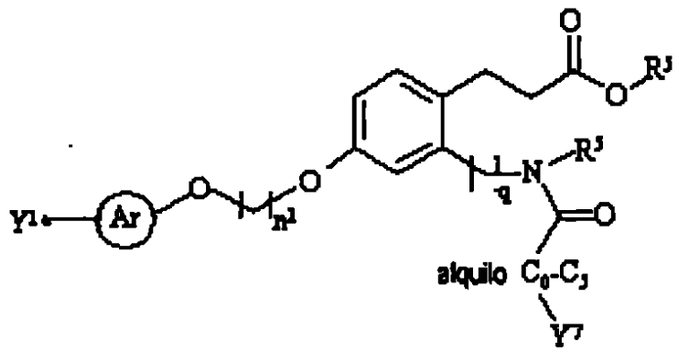


donde,

Y^{1a} es hidrógeno, arilo, heteroarilo, o ariloxi; q es 1 ó 2; y n^1 es 2, 3, ó 4.

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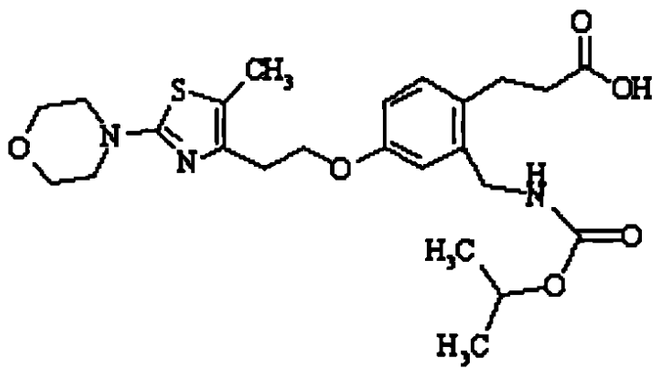
18. El compuesto de la reivindicación 1 representado por la siguiente fórmula,



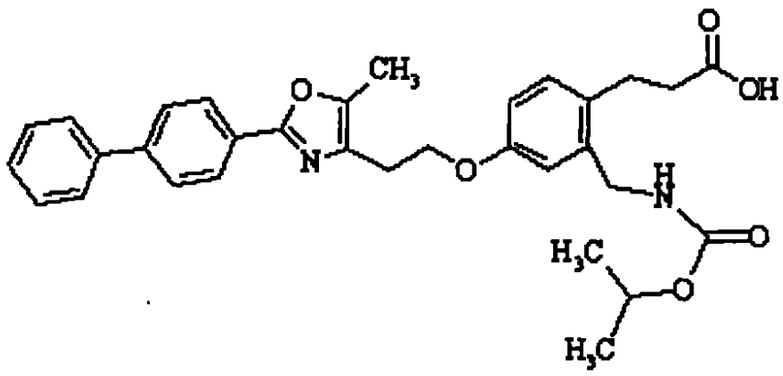
donde,

Y^{1a} es hidrógeno, arilo, heteroarilo o ariloxi; q es 1 ó 2; y n^1 es 2, 3, ó 4.

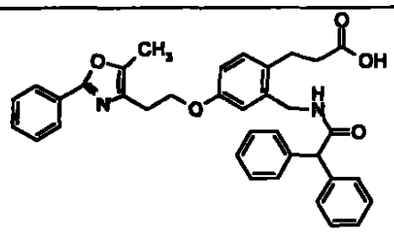
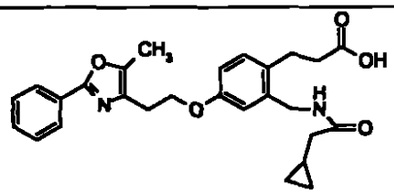
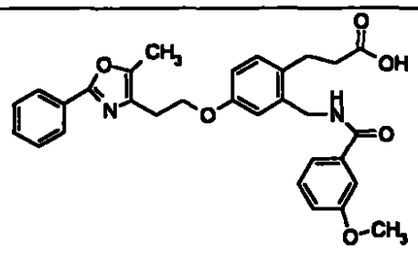
19. El compuesto de la reivindicación 1, representado por la siguiente fórmula estructural,

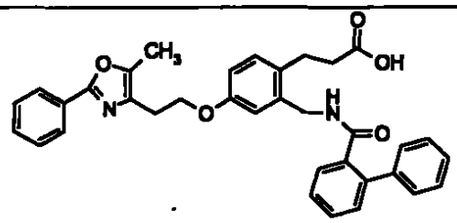
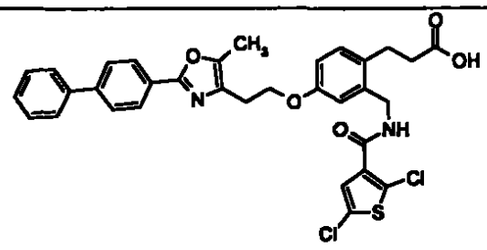
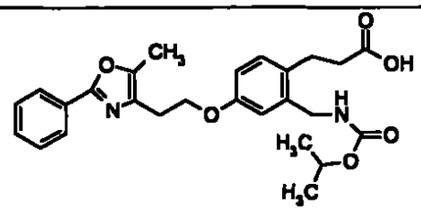
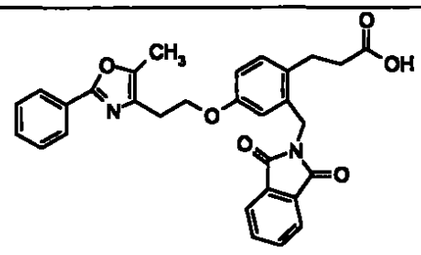


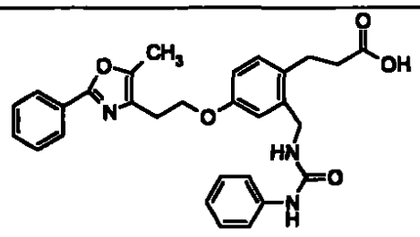
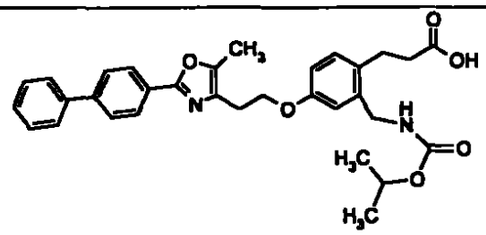
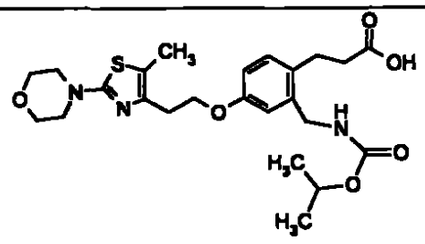
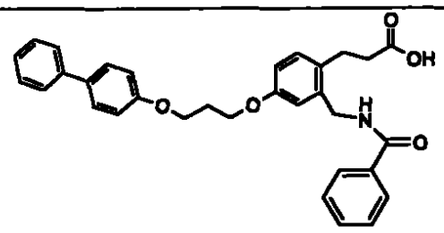
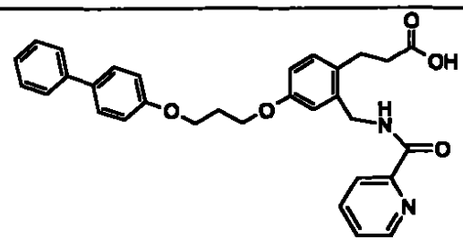
20. El compuesto de la reivindicación 1, representado por la siguiente fórmula estructural,

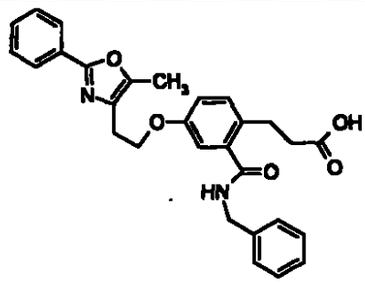
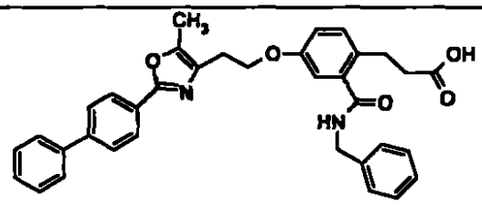
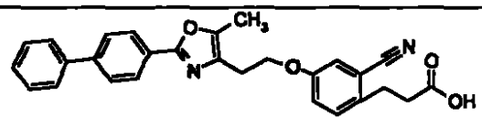
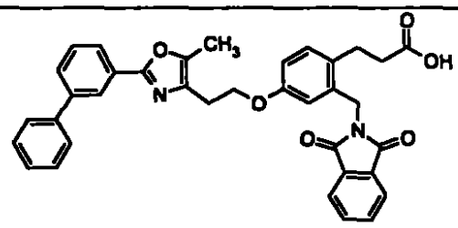
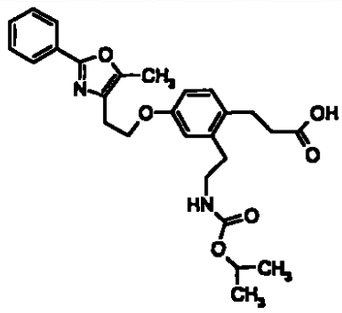


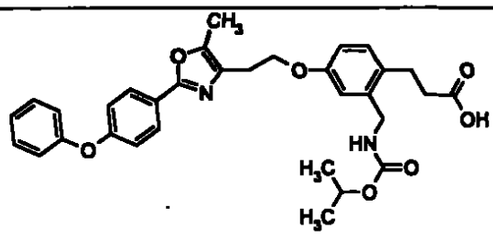
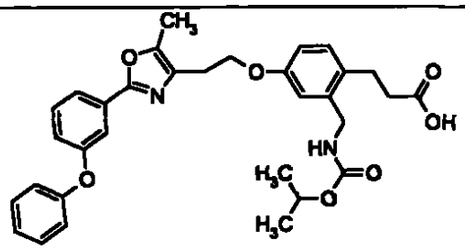
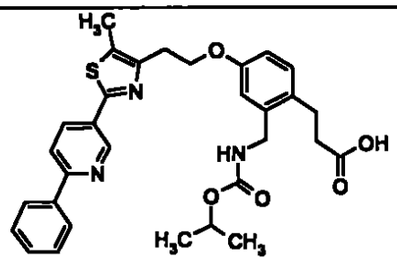
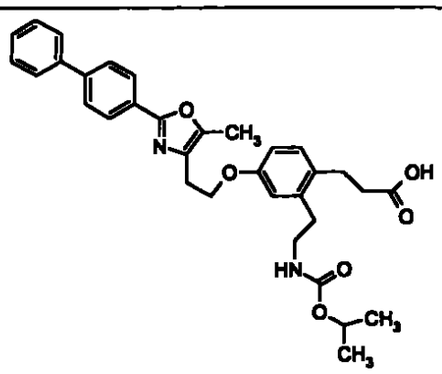
21. Un compuesto seleccionado entre el grupo compuesto por:

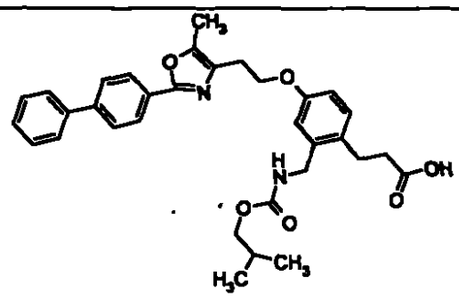
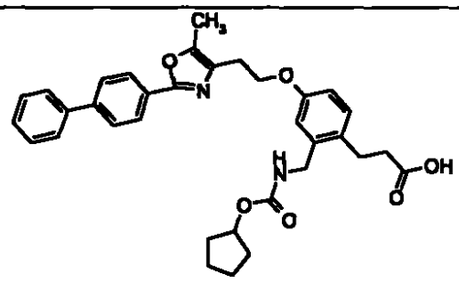
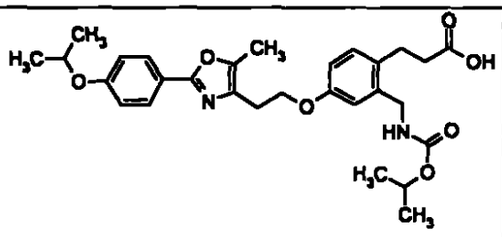
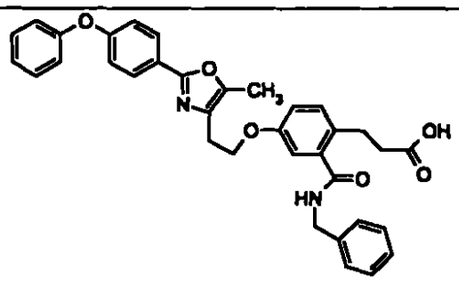
No.	Compuesto	nombre
1		ácido 3-{2-(difenilacetil-aminometil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
2		Ácido 3-{2-[(2-ciclopropilacetilamino) metil]-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
3		Ácido 3-{2-[(3-metoxibenzoilamino) metil]-4-[2-(5-metil-2-feniloxazol-4-il)etoxi] fenil} propiónico

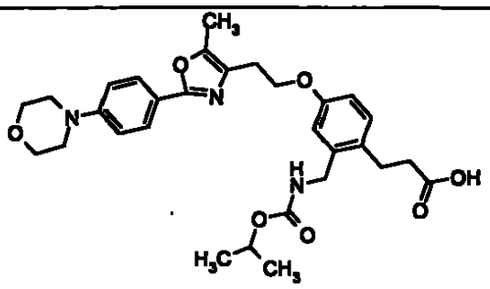
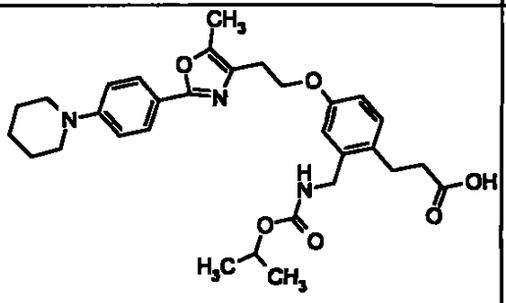
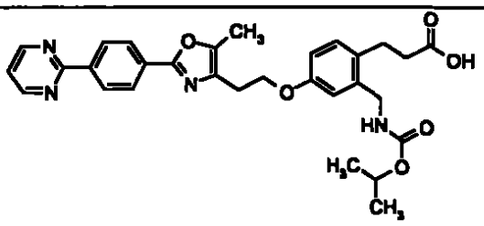
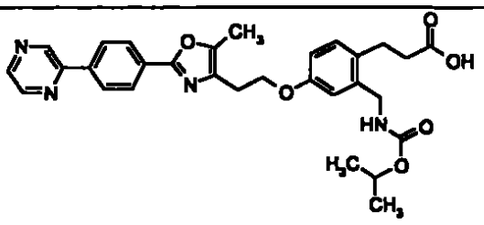
No.	Compuesto	nombre
4		Ácido 3-{2-{[(bifenil-2-carbonil) amino]metil}-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
5		Ácido 3-(4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-{[(2,5-diclorotiofeno-3-carbonil)amino]metil}fenil) propiónico
6		Ácido 3-{2-(isopropoxicarbonil-aminometil)-4-[2-(5-metil-2-feniloxazol-4-il) etoxi] fenil} propiónico
7		Ácido 3-{2-(1,3-dioxo-1,3-dihidroisoindol-2-ilmetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico

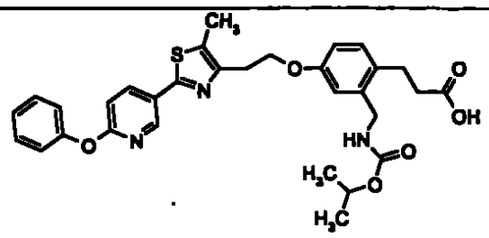
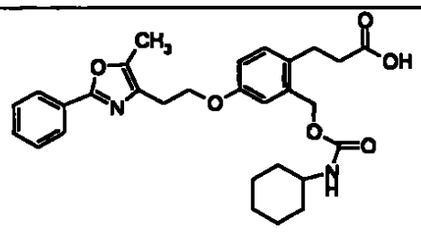
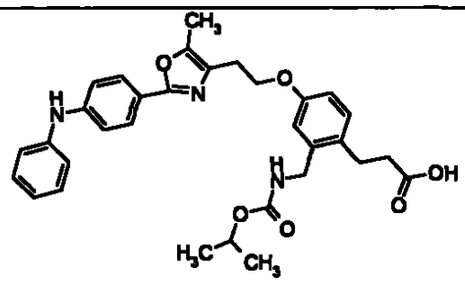
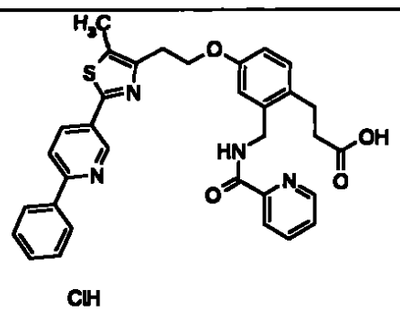
No.	Compuesto	nombre
8		Ácido 3-{4-[2-(5-metil-2-feniloxazol-4-il)etoxi]-2-[(3-fenilureido)metil] fenil} propiónico
9		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(isopropoxicarbonilaminometil)fenil] propiónico
10		Ácido 3-{2-(isopropoxicarbonil-aminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il) etoxi]fenil} propiónico
11		Ácido 3-{2-(benzoilaminometil)-4-[3-(bifenil-4-iloxi)propoxi] fenil} propiónico
12		Ácido 3-(4-[3-(bifenil-4-iloxi) propoxi]-2-{[(piridina-2-carbonil)amino]metil}fenil) propiónico

No.	Compuesto	nombre
13		Ácido 3-{2-bencilcarbamoil-4-[2-(5-metil-2-feniloxazol-4-il) etoxi]fenil} propiónico
14		Ácido 3-{2-bencilcarbamoil-4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]fenil} propiónico
15		Ácido 3-{4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-cianofenil} propiónico
16		Ácido 3-[4-[2-(2-bifenil-3-il-5-metiloxazol-4-il)etoxi]-2-(1,3-dioxo-1,3-dihidroisoindol-2-ilmetil)fenil] propiónico
17		Ácido 3-{2-(2-isopropoxicarbonil-aminoetil)-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico

No.	Compuesto	nombre
18		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico
19		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(3-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico
20		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(6-fenilpiridin-3-il)tiazol-4-il]etoxi}fenil) propiónico
21		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(2-isopropoxicarbonilaminoetil) fenil] propiónico

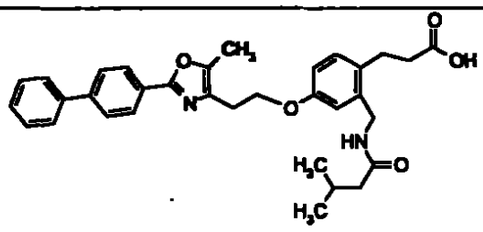
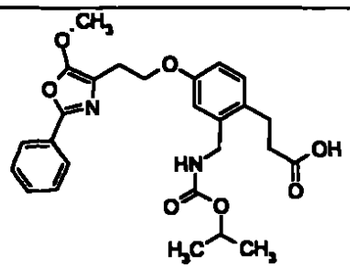
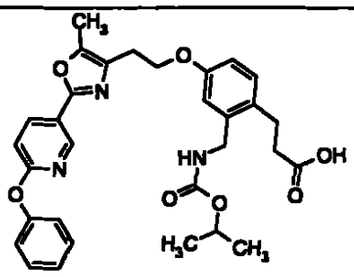
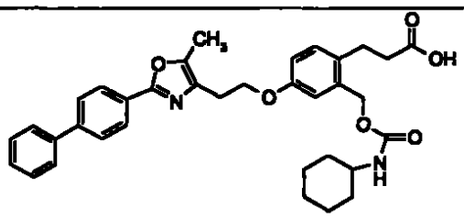
No.	Compuesto	nombre
22		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(isobutoxicarbonilaminometil) fenil] propiónico
23		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(ciclopentiloxicarbonil-aminometil)fenil] propiónico
24		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[2-(4-isopropoxifenil)-5-metiloxazol-4-il]etoxi} fenil) propiónico
25		Ácido 3-(2-bencilcarbamoil-4-{2-[5-metil-2-(4-fenoxifenil) oxazol-4-il]etoxi}fenil) propiónico

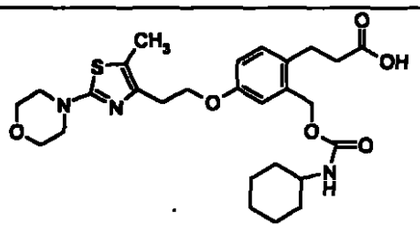
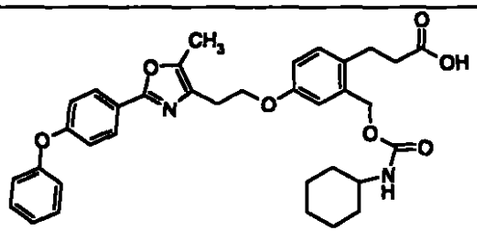
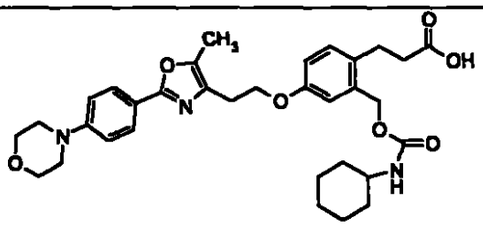
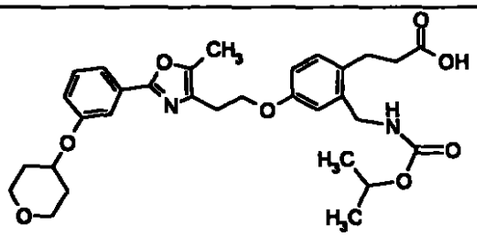
No.	Compuesto	nombre
26		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-morfolin-4-ilfenil)oxazol-4-il]etoxi}fenil) propiónico
27		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-piperidin-1-ilfenil)oxazol-4-il]etoxi}fenil) propiónico
28		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-pirimidin-2-ilfenil)oxazol-4-il]etoxi}fenil) propiónico
29		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-pirazin-2-ilfenil)oxazol-4-il]etoxi}fenil) propiónico

No.	Compuesto	nombre
30		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(6-fenoxipiridin-3-il)tiazol-4-il]etoxi}fenil) propiónico
31		Ácido 3-{2-ciclohexilcarbamoil-oximetil-4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil} propiónico
32		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(4-fenilaminofenil)oxazol-4-il]etoxi}fenil) propiónico
33		Sal HCl del ácido 3-(4-{2-[5-metil-2-(6-fenilpiridin-3-il)tiazol-4-il]etoxi}-2-{[(piridina-2-carbonil)amino]metil}fenil) propiónico

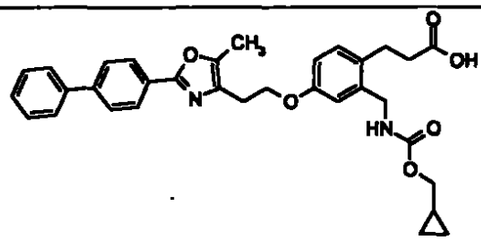
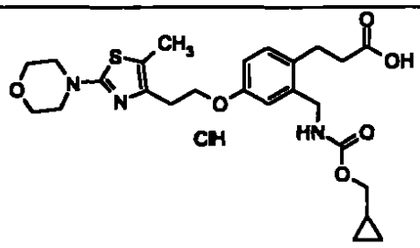
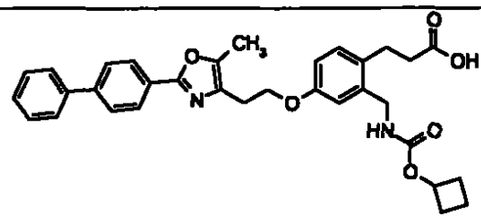
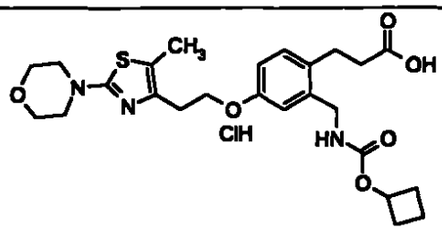
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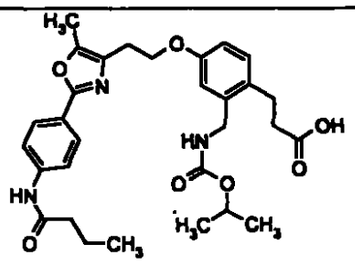
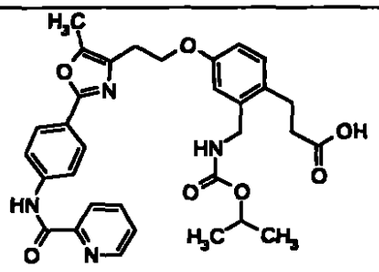
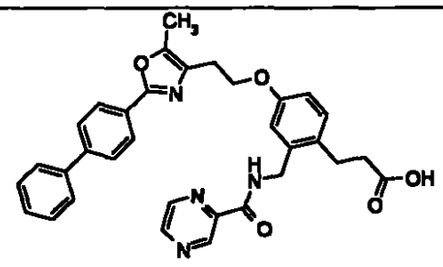
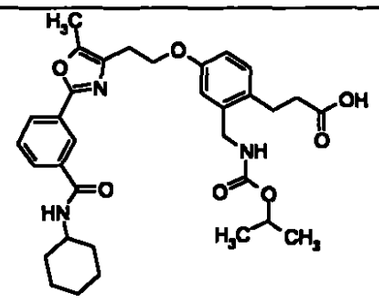
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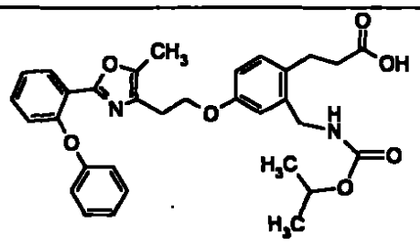
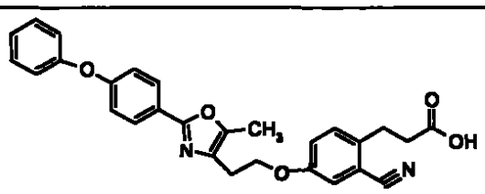
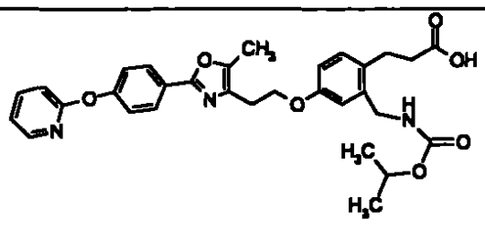
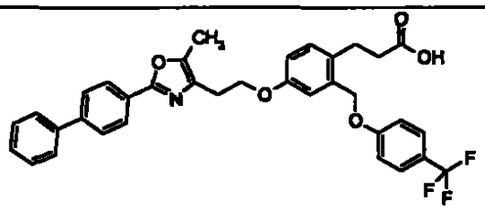
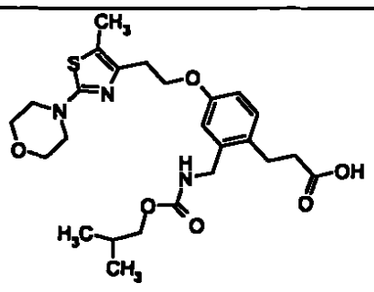
No.	Compuesto	nombre
34		Ácido 3-{4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-[(3-metilbutirilamino) metil]fenil} propiónico
35		Ácido 3-{2-(isopropoxicarbonil-aminometil)-4-[2-(5-metoxi-2-feniloxazol-4-il)etoxi] fenil} propiónico
36		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(6-fenoxipiridin-3-il)oxazol-4-il]etoxi}fenil) propiónico
37		Ácido 3-{4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-ciclohexilcarbamoiloxi-metilfenil} propiónico

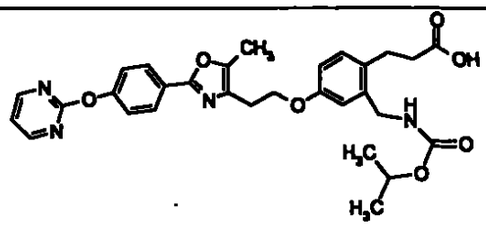
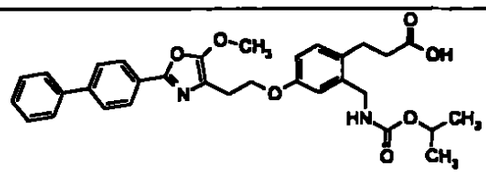
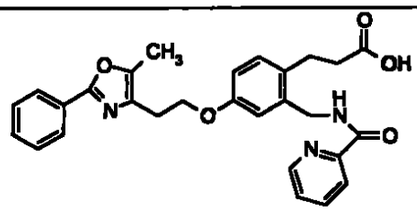
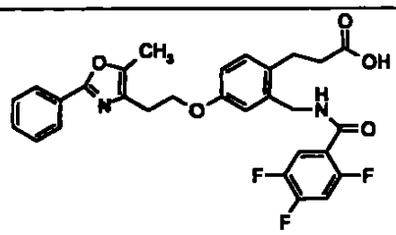
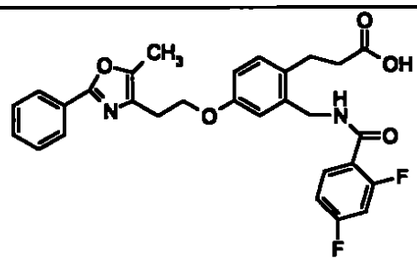
No.	Compuesto	nombre
38		Ácido 3-{2-ciclohexilcarbamoil-oximetil-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil} propiónico
39		Ácido 3-(2-ciclohexilcarbamoil-oximetil-4-{2-[5-metil-2-(4-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico
40		Ácido 3-(2-ciclohexilcarbamoil-oximetil-4-{2-[5-metil-2-(4-morfolin-4-ilfenil)oxazol-4-il]etoxi}fenil) propiónico
41		Ácido 3-[2-(isopropoxicarbonil-aminometil)-4-(2-{5-metil-2-[3-(tetrahidropiran-4-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico

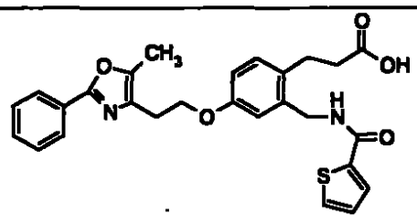
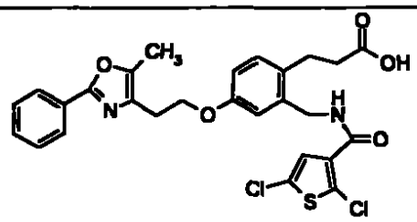
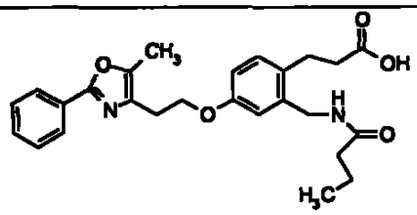
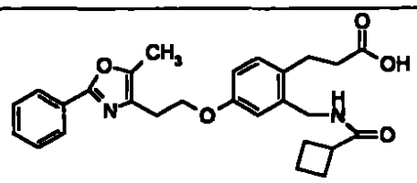
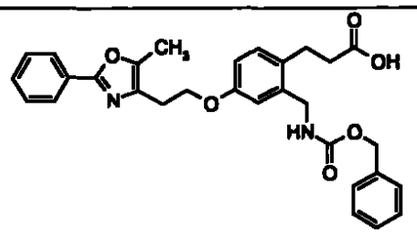
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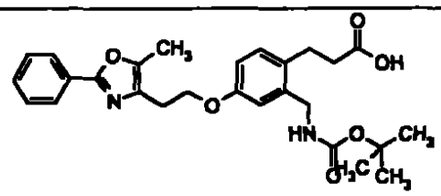
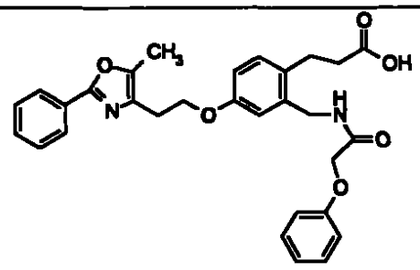
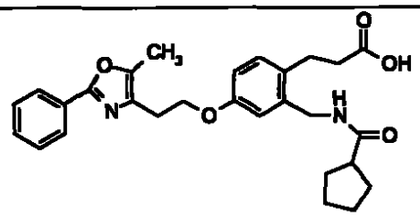
No.	Compuesto	nombre
42		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(ciclopropilmetoxicarbonilamino metil)fenil] propiónico
43		Sal HCl del ácido 3-{2-(ciclopropilmetoxi-carbonilaminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil} propiónico
44		Sal HCl del ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(ciclobutoxicarbonil-aminometil)fenil]propiónico
45		Sal HCl del ácido 3-{2-(ciclobutoxicarbonil-aminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il) etoxi]fenil} propiónico

No.	Compuesto	nombre
46		Ácido 3-[4-[2-[2-(4-butirilaminofenil)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)-fenil] propiónico
47		Ácido 3-{2-(Isopropoxicarbonil-amino-metil)-4-[2-(5-metil-2-{4-[(piridina-2-carbonil)-amino]-fenil}-oxazol-4-il)-etoxi]-fenil}-propiónico
48		Ácido 3-(4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-{[(pirazina-2-carbonil) amino]metil}fenil) propiónico
49		Ácido 3-[4-[2-[2-(3-ciclohexilcarbamoilfenil)-5-metiloxazol-4-il]etoxi}-2-(isopropoxicarbonilaminometil)-fenil] propiónico

No.	Compuesto	nombre
50		Ácido 3-(2-(isopropoxicarbonil-aminometil)-4-{2-[5-metil-2-(2-fenoxifenil)oxazol-4-il]etoxi}fenil) propiónico
51		Ácido 3-(2-ciano-4-{2-[5-metil-2-(4-fenoxi-fenil)-oxazol-4-il]-etoxi}-fenil) propiónico
52		Ácido 3-[2-(isopropoxicarbonil-aminometil)-4-(2-{5-metil-2-[4-(piridin-2-iloxi)fenil]oxazol-4-il}etoxi)fenil] propiónico
53		Ácido 3-[4-[2-(2-bifenil-4-il-5-metiloxazol-4-il)etoxi]-2-(4-trifluorometilfenoximetil) fenil] propiónico
54		Ácido 3-{2-(isobutoxicarbonil-aminometil)-4-[2-(5-metil-2-morfolin-4-iltiazol-4-il)etoxi]fenil} propiónico

No.	Compuesto	nombre
55		Ácido 3-[2-(isopropoxicarbonil-aminometil)-4-(2-{5-metil-2-[4-(pirimidin-2-iloxi) fenil] oxazol-4-il}etoxi)fenil] propiónico
56		Ácido 3-[4-[2-(2-bifenil-4-il-5-metoxioxazol-4-il)etoxi]-2-(isopropoxicarbonilaminometil)-fenil] propiónico
57		Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{[(piridina-2-carbonil)-amino]-metil}-fenil)-propiónico
58		Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(2,4,5-trifluoro-benzoilamino)-metil]-fenil}-propiónico
59		Ácido 3-{2-[(2,4-difluoro-benzoilamino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

No.	Compuesto	nombre
60		ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{[(tiofeno-2-carbonil)-amino]-metil}-fenil)-propiónico
61		Ácido 3-(4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-{[(tiofeno-2-carbonil)-amino]-metil}-fenil)-propriónico
62		Ácido 3-{2-(butirilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico
63		Ácido 3-{2-[(ciclobutanocarbonil-amino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico
64		Ácido 3-{2-(benciloxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

No.	Compuesto	nombre
65		Ácido 3-{2-(terc-butoxicarbonilamino-metil)-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico
66		Ácido 3-{4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-2-[(2-fenoxi-acetilamino)-metil]-fenil}-propiónico
67		Ácido 3-{2-[(ciclopentanocarbonil-amino)-metil]-4-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-fenil}-propiónico

22. Una composición farmacéutica que comprende un vehículo farmacéuticamente aceptable y al menos un compuesto de las reivindicaciones 1-21 o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

23. Una composición farmacéutica que comprende (1) un compuesto de la reivindicación 1, o una sal, solvato, hidrato o estereoisómero farmacéuticamente aceptable del mismo; (2) un segundo agente terapéutico

seleccionado entre el grupo compuesto por sensibilizadores de insulina, sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de la a-glucosidasa, secretagogos de insulina, insulina, agentes antihiperlipidémicos, agentes que elevan las HDL en plasma, inhibidores de la HMG-CoA reductasa, estatinas, inhibidores de la acril CoA:colesterol aciltransferasa, compuestos antiobesidad, agentes antihipercolesterolémicos, fibratos, vitaminas y aspirina; y (3) un vehículo farmacéuticamente aceptable.

24. Un procedimiento para modular un receptor activado por el proliferador de peroxisomas (PPAR), que comprende la etapa de poner en contacto el receptor con al menos un compuesto de las reivindicaciones 1-21, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

25. El procedimiento de la reivindicación 24, en el que el receptor activado por el proliferador de peroxisomas es un receptor alfa.

26. El procedimiento de la reivindicación 24, en el que el receptor activado por el proliferador de peroxisomas es un receptor gamma.

27. Un procedimiento para tratar o prevenir una enfermedad o afección mediada por el receptor gamma activado por el proliferador de peroxisomas,

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que comprende la etapa de administrar una cantidad eficaz de al menos un compuesto de la reivindicación 1-21.

28. Un procedimiento para reducir la glucosa en sangre, que comprende la etapa de administrar una cantidad eficaz de al menos un compuesto de las reivindicaciones 1-21.

29. Un método para tratar o prevenir una enfermedad o afección seleccionada entre el grupo compuesto por hiperglucemia, dislipidemia, diabetes de tipo II, diabetes de tipo I, hipertrigliceridemia, síndrome X, resistencia a la insulina, insuficiencia cardíaca, dislipidemia diabética, hiperlipidemia, hipercolesterolemia, hipertensión, obesidad, bulimia, anorexia nerviosa, enfermedad cardiovascular y otras enfermedades donde la resistencia a la insulina es un componente, que comprende la etapa de administrar una cantidad eficaz de al menos un compuesto de las reivindicaciones 1-21.

30. Un procedimiento para tratar o prevenir la diabetes mellitus en un mamífero, que comprende la etapa de administrar a un mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de las reivindicaciones 1-21.

31. Un procedimiento para tratar o prevenir una enfermedad cardiovascular en un mamífero, que comprende la etapa de administrar a un mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de las reivindicaciones 1-21, o una sal, solvato, hidrato o estereoisómero farmacéuticamente aceptable del mismo.

32. Un procedimiento para tratar o prevenir el síndrome X en un mamífero, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de las reivindicaciones 1-21, o una sal, solvato, hidrato o estereoisómero farmacéuticamente aceptable del mismo.

33. Un procedimiento para tratar o prevenir una enfermedad o afección seleccionada entre el grupo compuesto por hiperglucemia, dislipidemia, diabetes de tipo II, diabetes de tipo I, hipertrigliceridemia, síndrome X, resistencia a insulina, insuficiencia cardíaca, dislipidemia diabética, hiperlipidemia, hipercolesterolemia, hipertensión, obesidad, bulimia, anorexia nerviosa, enfermedad cardiovascular y otras enfermedades donde la resistencia a la insulina es un componente, que comprende la etapa de administrar una cantidad eficaz de al menos un compuesto de las reivindicaciones 1-21 y una cantidad eficaz de un segundo agente terapéutico seleccionado entre el grupo compuesto por: sensibilizadores de insulina,

sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de α-glucosidasa, secretagogos de insulina, insulina, agentes antihiperlipidémicos, agentes que aumentan el HDL en plasma, inhibidores de la HMG-CoA reductasa, estatinas, inhibidores de acril CoA:colesterol aciltransferasa, compuestos antiobesidad, agentes antihipercolesterolémicos, fibratos, vitaminas y aspirina.

34. Uso de un compuesto de un compuesto de las reivindicaciones 1-21 y una sal, solvato, hidrato o estereoisómero farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para el tratamiento de una afección modulada por un PPAR.

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PATENT COOPERATI N TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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To:

Jang, Soonhee ✓
ELI LILLY AND COMPANY
P.O. Box 6288
Indianapolis, IN 46206-6288
ETATS-UNIS D'AMERIQUE

ELI LILLY & COMPANY
NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	23.09.2003
Applicant's or agent's file reference X-14528 ✓	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US02/15143 ✓	24.05.2002 ✓	07.06.2001

Applicant
ELI LILLY AND COMPANY

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 invention 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 international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ambroa, J.R. Tel. +49 89 2399-8012

Form PCT/IPEA/416 (July 1992)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATI N REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-14528	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/15143	International filing date *(day/month/year)* 24.05.2002	Priority date *(day/month/year)* 07.06.2001
International Patent Classification (IPC) or both national classification and IPC A61K31/42, A61K31/42		
Applicant ELI LILLY AND COMPANY		

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 6 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 consist of a total of 29 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - 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 Rule 66.2(a)(ii) 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	Date of completion of this report
17.12.2002	23.09.2003
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Kollmannsberger, M Telephone No. +49 89 2399-7364

Form PCT/IPEA/409 (Cover Sheet) (January 1994)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US02/15143

I. Basis of the report

1. With regard to the elements of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-406 as originally filed

Claims, Numbers

1-34 filed with telefax on 13.03.2003

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/US02/15143

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 25-34

   because:

   ☒ the said international application, or the said claims Nos. 25-34 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-34
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-34
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Claims 25-33 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

V-1. Prior art

The following documents are considered to be relevant:

D1: WO 02 18355 A (BROOKS DAWN ALISA ;CONNOR SCOTT EUGENE (US); DOMINIANNI SAMUEL JAM) 7 March 2002 (2002-03-07)
D2: WO 02 16332 A (BROOKS DAWN ALISA ;GODFREY ALEXANDER GLENN (US); MANTLO NATHAN BRY) 28 February 2002 (2002-02-28)
D3: WO 01 16120 A (DOMINIANNI SAMUEL J ;MATTHEWS DONALD P (US); MICHELLYS PIERRE YVES) 8 March 2001 (2001-03-08)
D4: WO 01 00566 A (ZANDT MICHAEL C VAN ;INST FOR PHARMACEUTICAL DISCOV (US)) 4 January 2001 (2001-01-04)
D5: EP-A-1 216 980 (EISAI CO LTD) 26 June 2002 (2002-06-26)
D6: WO 01 25181

D1 and D2 are P-documents and are disregarded at the present stage of the proceedings. D5 has been published after the filing date of the present application but is taken as a translation of D6 which has been published before the priority date of the present application.

V-2. Novelty (Art 33(2) PCT)

The compounds in D3 differ from the present claims on account of the substituent Y4 (nomenclature of the present application, see R2/R3 in D3) which is required to present a heteroatom substitution at the alkyl moiety in the present claims whereas in D3 only alkyl, aryl and related hydrocarbon substituents are claimed and

exemplified (see e. g. example 60).

D4 discloses (see claim 1 for R3=phenoxy or R3=OR7 and R7=benzyl) compounds which have been excluded from the present claims by the definition of n=2-5 (the compounds in D4 thus presenting n=0 and 1).

D5 discloses compounds (see claim 1 and e. g. examples 771-785 on pages 135-137) for Y1=alkyl, whereas in present claim 1 Y1 is required to be an aryl substituent.

Art. 33(2) PCT is thus fulfilled for claims 1-34.

V-3. Inventive step (Art. 33(3) PCT)

The compounds of the present application are said to bind to the PPAR-γ receptor and may thus be used for the lowering of the blood sugar level and accordingly may be useful in the treatment of i. a. diabetes.

D3 is considered to represent the closest state of the art as the compounds disclosed therein also are said to bind to the ppar-γ receptor and may be used to treat diabetes. The difference of the claimed compounds to those disclosed in D3 lies in the fact that the the substituents at the phenyl ring include a hetero atom (e. g. alkyl substituted by amides, amide or CN directly bound to the phenyl ring etc., see definitions of Y4 in present claim 1) whereas in D3 only unsubstituted alkyl/aryl and related groups are disclosed for the respective substituent at the central phenyl group (see definitions of R2/R3 there). The other definitions overlap (in particular the phenyl substituted oxazole of D3 is included in the definitions of Y1 of present claim 1 and is also present in many of the example compounds of the present application).

The problem to be solved in view of D3 could thus be seen in the provision of further compounds that present the claimed activity.

D4 discloses structurally very close compounds as aldose reductase inhibitors for lowering the blood sugar level. Since the physiological effect as well as the mechanism of action appears to be different, D4 is disregarded with respect to inventive step.

The compounds of D5 present the same ppar-γ modulating activity as the claimed

ones and differ only in the definition of Y1 as alkyl (as opposed to aryl in present claim 1). On the other hand, the substitution of alkyl moieties at the central phenyl rings by amides etc. (see e. g. examples 125-132, paragraphs771-785; the propoxy chain corresponds to O-[CH2]n-V-Y1 for n=2 and V=bond, so the difference lies in the definition of Y1 as aryl in the present claims whereas in these examples it is a methyl group), i. e. the substituent Y4 at the phenyl ring that distinguishes present claim 1 from D3, is clearly demonstrated. There is however no direct equivalence shown between the alkyl and the amide-substituted alkyl in D5. The claimed compounds thus do not appear to be derivable from a combination of D3 and D5.

Art. 33(3) PCT is thus fulfilled for the present claims.

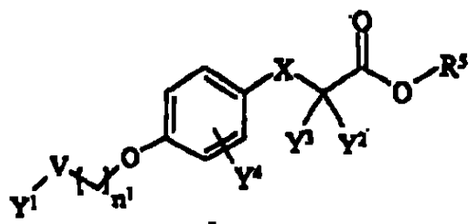
In a following regional phase the applicant might be requested to show whether the claimed compounds actually show the alledged activity since the application does not contain any verifiable test data.

V-4. Industrial applicability (Art. 33(4) PCT)

No objection arises for claims 1-24 (in part). For the assessment of the present claims 25-34 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

WHAT IS CLAIMED IS:

1. A compound of formula I,



I

and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof, wherein:

n^1 is 2, 3, 4 or 5;

V is a bond or O;

X is CH_2 or O;

p is 0 or 1;

m is 1-4;

Y^1 is:  wherein,

Ar is: aryl or heteroaryl,

wherein aryl and heteroaryl are optionally substituted with one or more groups independently selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, haloalkyl and haloalkyloxy;

Y^{1a} is: hydrogen,

$(C_0$-$C_3)$alkyl-aryl,

C(O)-aryl,

heteroaryl,

cycloalkyl,

heterocycloalkyl,

aryloxy,
$NR^5(CH_2)_mOR^5$,
aryl-Z-aryl,
aryl-Z-heteroaryl,
aryl-Z-cycloalkyl,
aryl-Z-heterocycloalkyl,
heteroaryl-Z-aryl,
heteroaryl-Z-heterocycloalkyl or
heterocycloalkyl-Z-aryl,
wherein aryl, cycloalkyl, aryloxy, heteroaryl, and heterocycloalkyl are optionally substituted with one or more substituents independently selected from the group consisting of:

halo,
hydroxyl,
nitro,
cyano,
C_1-C_4 alkyl,
C_1-C_4 alkoxy optionally substituted with $N(R^5)_2$,
haloalkyl,
$N(R^5)_2$,
$N[C(O)R^5]_2$,
$N[S(O)_2R^5]_2$,
$NR^5S(O)_2R^5$,
$NR^5C(O)R^5$,
$NR^5C(O)OR^5$,
$C(O)N(R^5)_2$,
$C(O)OR^5$ and
$C(O)R^5$;

Z is: a bond,
-oxygen-
$-C(O)NR^5-$

$-NR^5C(O)-$,
$-NR^5C(O)O-$,
$-C(O)-$,
$-NR^5-$,
$-[O]_p(CH_2)_m-$,
$-(CH_2)_m[O]_p-$,
$-NR^5(CH_2)_m-$ or
$-(CH_2)_m NR^5-$;

Y^2 and Y^3 are each independently:
hydrogen,
C_1-C_6 alkyl or
C_1-C_6 alkoxy;

Y^4 is: $(C_1–C_3)$alkyl-$NR^5C(O)$-$(C_0–C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(O)$-$(C_2–C_5)$alkenyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(O)$-$(C_2–C_5)$alkynyl-Y^7;
$(C_1–C_3)$alkyl-$NR^5C(O)O$-$(C_0–C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(O)NR^5$-$(C_0–C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-$NR^5C(S)NR^5$-$(C_0–C_5)$alkyl-Y^7,
$(C_0–C_3)$alkyl-$C(O)NR^5$-$(C_0–C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-$OC(O)NY^{10}Y^{11}$,
$(C_1–C_3)$alkyl-$NY^{10}Y^{11}$,
$(C_1–C_3)$alkyl-O-$(C_0–C_5)$alkyl-Y^7,
$(C_1–C_3)$alkyl-S-$(C_0–C_5)$alkyl-Y^7 or
CN;

Y^7 is: hydrogen,
aryl,
heteroaryl,
C_1-C_{12} alkyl,
C_1-C_6 alkoxy,

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cycloalkyl,
heterocycloalkyl,
aryloxy,
C(O)-heteroaryl or
SR^6,
wherein alkyl, aryl, aryloxy, alkoxy, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more groups independently selected from R^7;

Y^{10} and Y^{11} are each independently:
hydrogen,
aryl,
heteroaryl,
C_1-C_{10} alkyl,
cycloalkyl,
$SO_2(R^6)$; or
Y^{10} and Y^{11} together are a 5- to 10-membered heterocycloalkyl ring or heterocycloalkyl ring fused with aryl, and the heterocycloalkyl ring optionally containing one or more heteroatoms selected from N, O or S; and wherein, aryl, heteroaryl, heterocycloalkyl and alkyl are optionally substituted with one or more substituents independently selected from R^7;

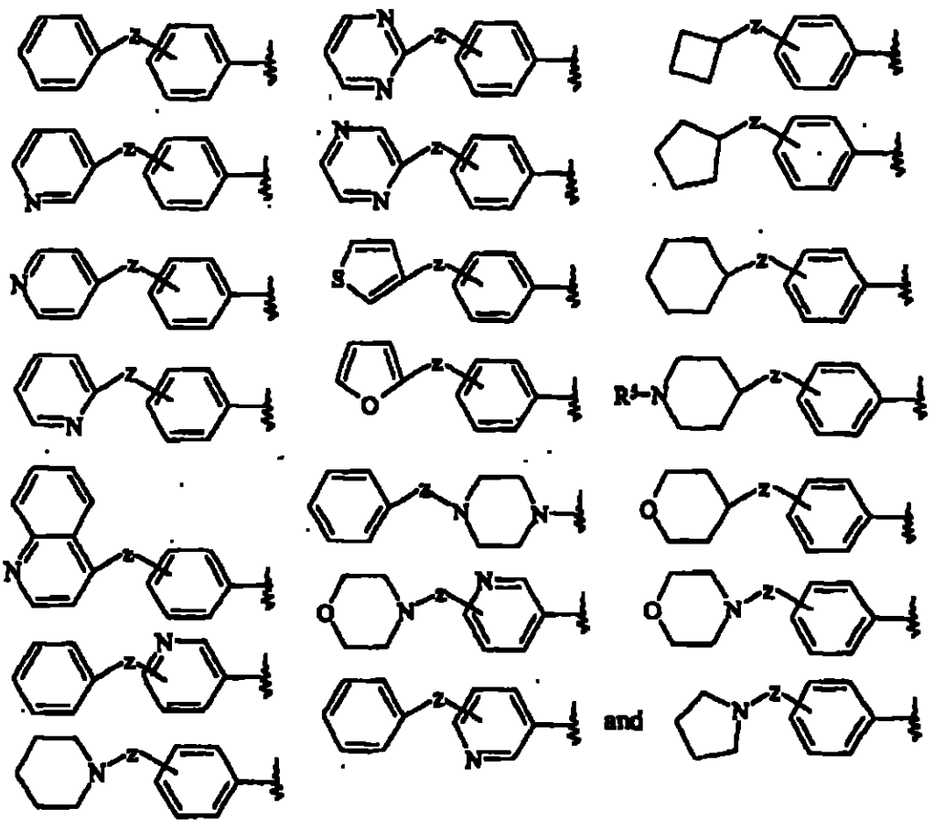
R^5 is: hydrogen or C_1-C_6 alkyl;

R^6 is: hydrogen,
C_1-C_{10} alkyl,
cycloalkyl,
aryl, or
heteroaryl,
wherein alkyl, cycloalkyl, aryl and heteroaryl are optionally substituted with one or more substituents independently selected from R^7;

R^7 is: halo,
nitro,
oxo,
cyano,
hydroxyl,
benzyl,
phenyl,
phenoxy,
heteroaryl,
$C(O)R^6$,
C_1-C_{10} alkyl,
C_1-C_6 alkoxy,
C_1-C_6 haloalkyl,
C_1-C_6 haloalkyloxy,
$O(CH_2)_m$-phenyl,
$(CH_2)_mOC(O)$-aryl,
$C(O)OR^5$,
$S(O)_2R^5$,
$S(O)_2N(R^5)_2$,
SR^5 or
$N(R^5)_2$,

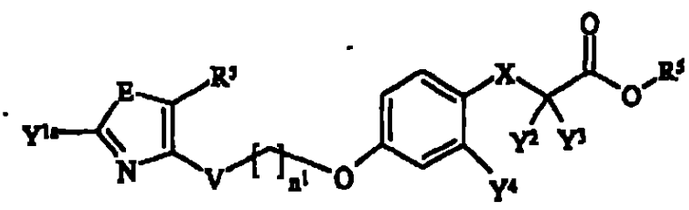
wherein phenyl and phenoxy are optionally substituted with one or more groups independently selected from halo or trifluoromethyl.

2. The compound of Claim 1, wherein Y^{1a} is selected from the group consisting of: aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aryloxy,



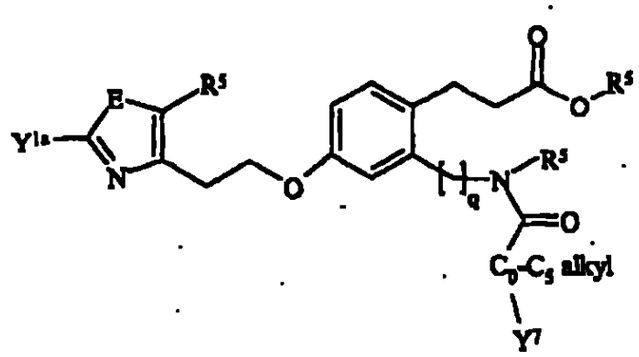
and

3. The compound of Claim 1, wherein the compound is represented by the following structural formula,



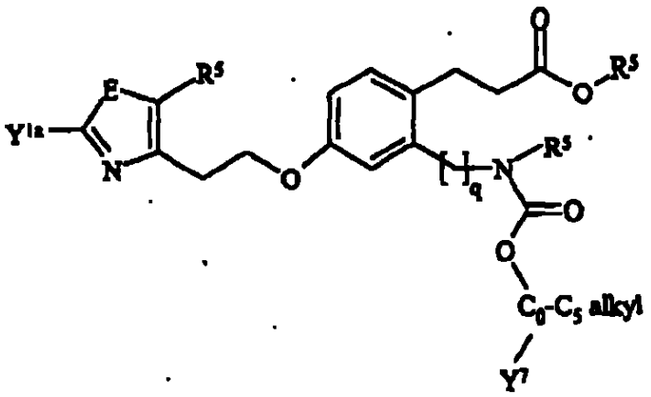
wherein B is O or S.

4. The compound of Claim 4, wherein the compound is represented by the following structural formula,



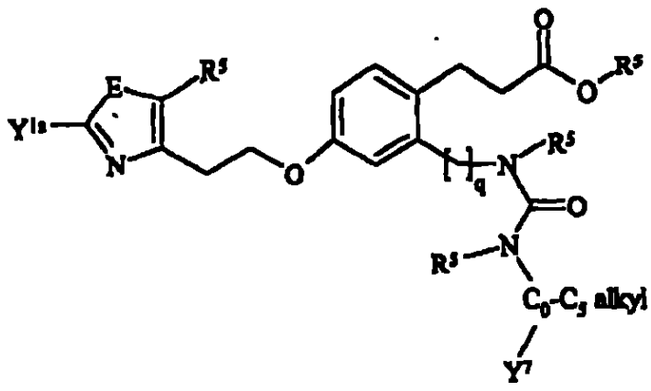
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

5. The compound of Claim 4, wherein the compound is represented by the following structural formula,



wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

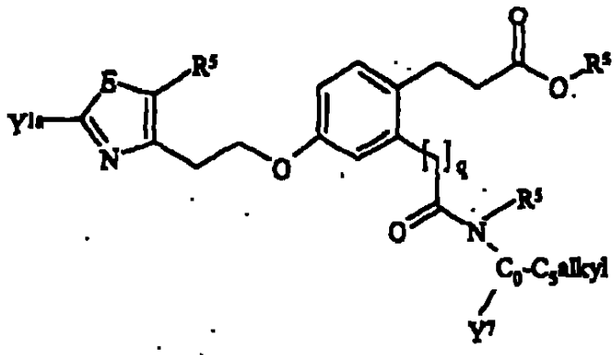
6. The compound of Claim 4, wherein the compound is represented by the following structural formula,



wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

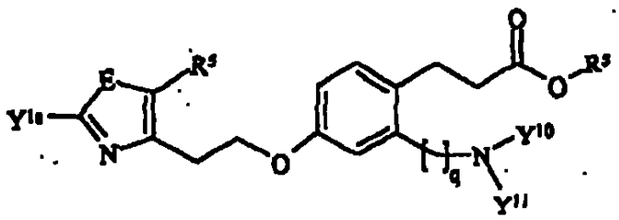
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7. The compound of Claim 4, wherein the compound is represented by the following structural formula,



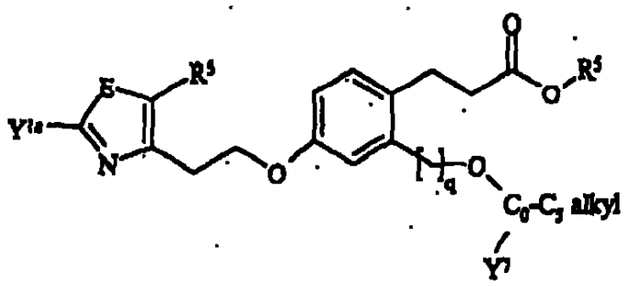
wherein q is 0 or 1; and each R^5 is independently hydrogen or methyl.

8. The compound of Claim 4, wherein the compound is represented by the following structural formula,



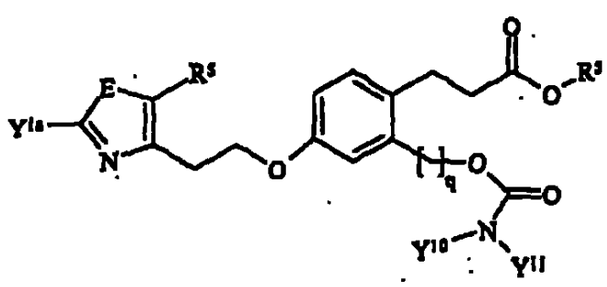
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

9. The compound of Claim 4, wherein the compound is represented by the following structural formula,



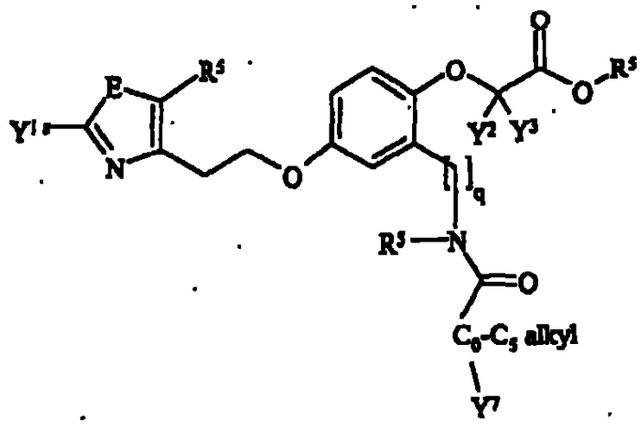
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

10. The compound of Claim 4, wherein the compound is represented by the following structural formula,



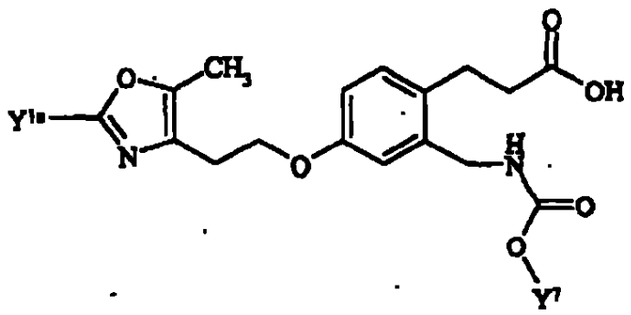
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

11. The compound of Claim 4, wherein the compound is represented by the following structural Formula,

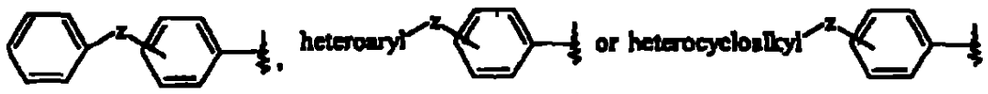


wherein q is 1 or 2; and each R^5, Y^2 and Y^3 are independently hydrogen or methyl.

12. The compound of Claim 4 represented by the following structural formula,



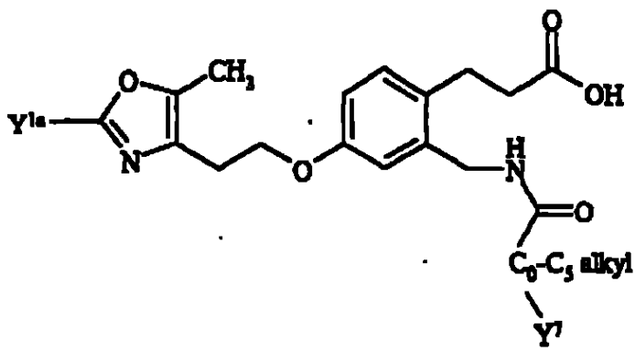
wherein Y^{1a} is optionally substituted phenyl, naphthyl,



and Z is a bond, oxygen, -NH-, -N(CH_3)-, -NHC(O)- or -C(O)NH-.

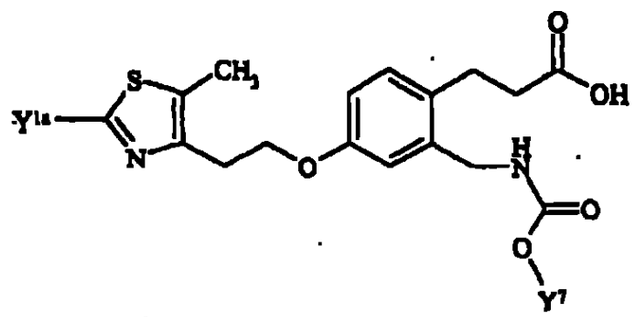
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13. The compound of Claim 4 represented by the following structural formula,



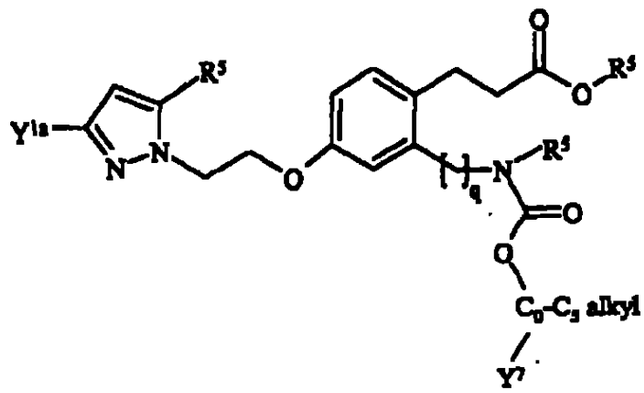
wherein Y^{1a} is optionally substituted phenyl, naphthyl or  and Z is a bond, oxygen, -NH-, -N(CH_3)-, -NHC(O)- or -C(O)NH-.

14. The compound of Claim 4 represented by the following structural formula,



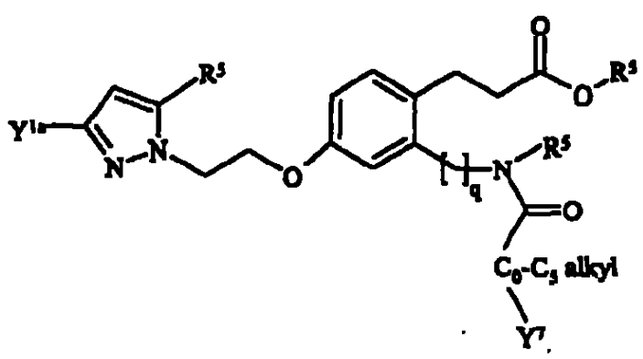
wherein Y^{1a} is optionally substituted aryl, heteroaryl, heterocycloalkyl, heteroaryl-Z-heterocycloalkyl or heteroaryl-Z-aryl.

15. The compound of Claim 1 represented by the following structural formula,



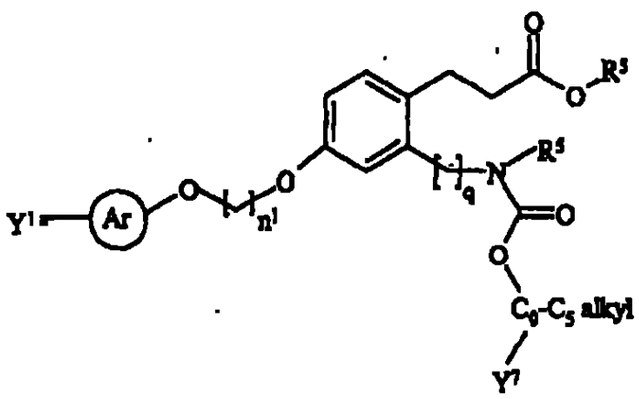
wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

16. The compound of Claim 1 represented by the following structural formula,



wherein q is 1 or 2; and each R^5 is independently hydrogen or methyl.

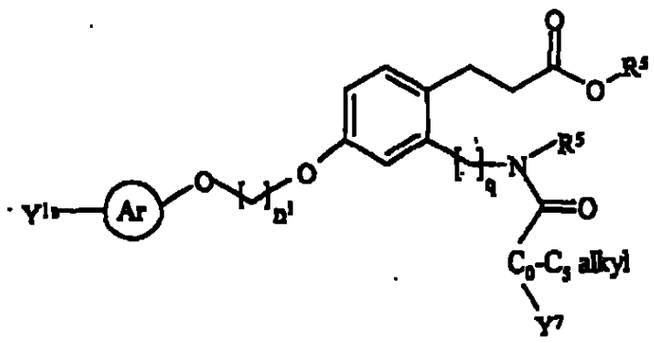
17. The compound of Claim 1 represented by the following structural formula,



wherein,

Y^{1a} is hydrogen, aryl, heteroaryl, or aryloxy; q is 1 or 2; and n^1 is 2, 3, or 4.

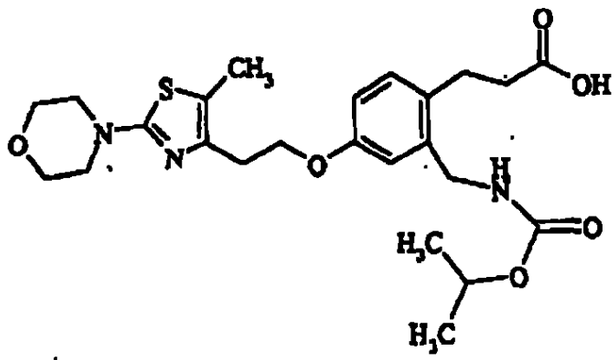
18. The compound of Claim 1 represented by the following structural formula,



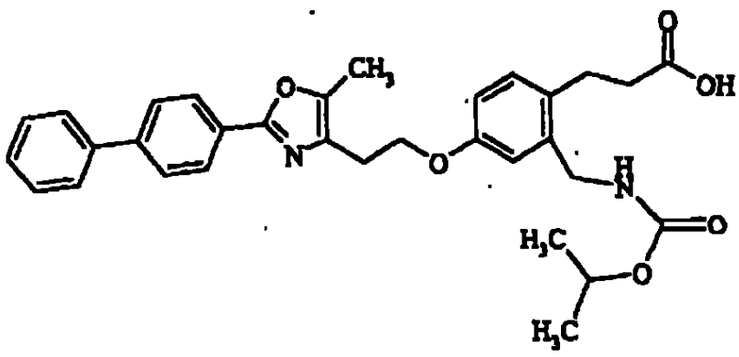
wherein,

Y^{1a} is hydrogen, aryl, heteroaryl or aryloxy; q is 1 or 2; and n^1 is 2, 3, or 4.

19. The compound of Claim 1 represented by a following structural formula,

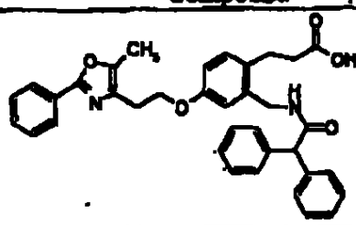
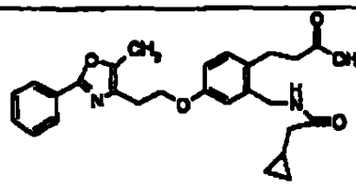
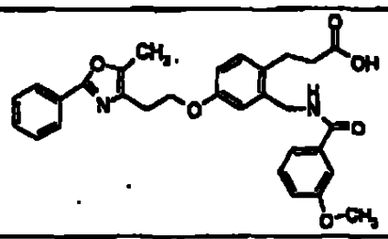
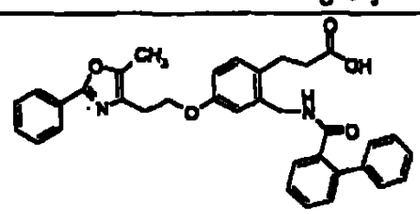
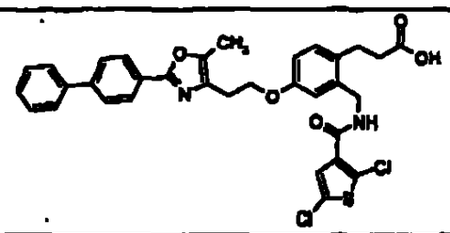
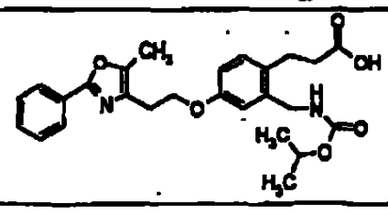


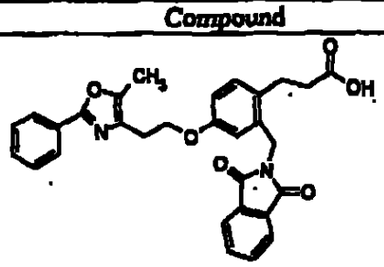
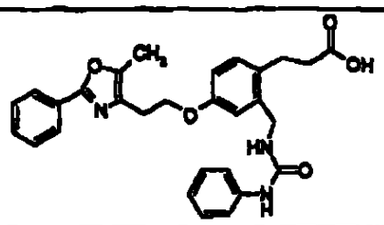
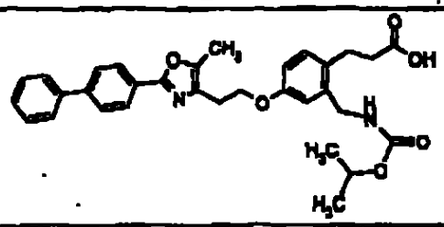
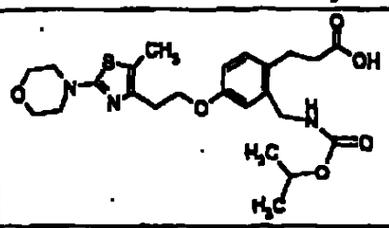
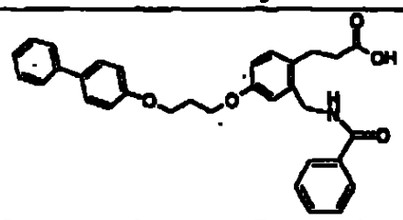
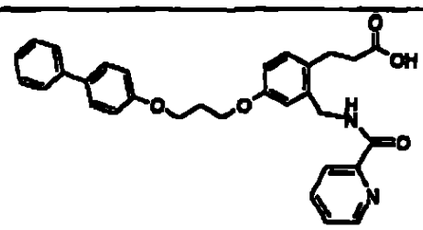
20. The compound of Claim 1 represented by a following structural formula,

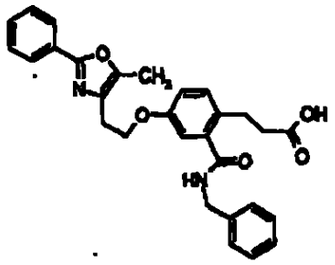
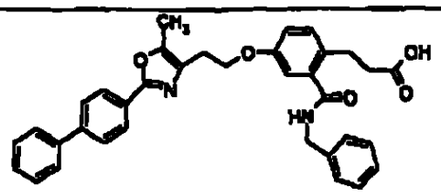
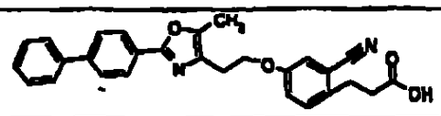
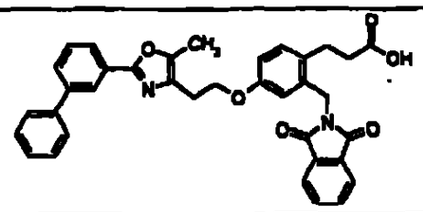
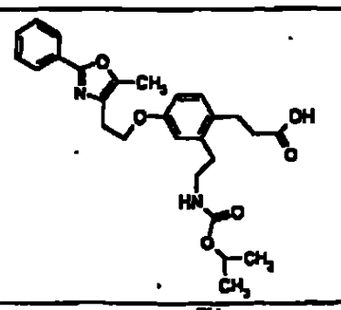
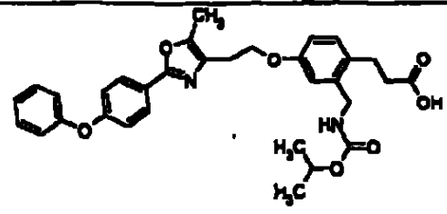


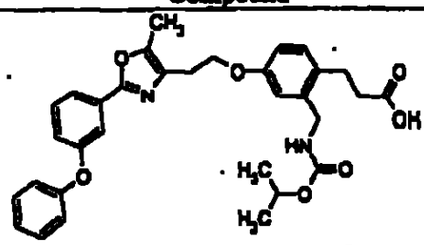
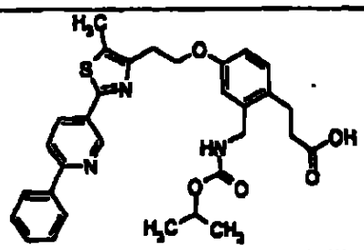
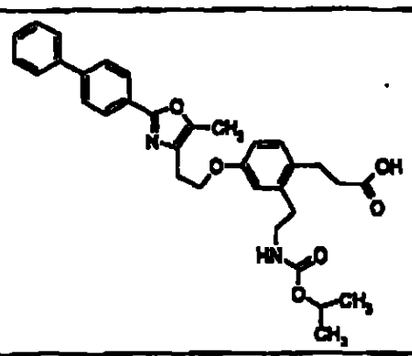
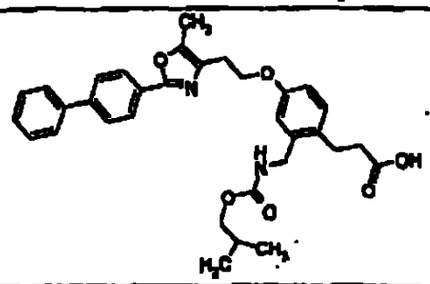
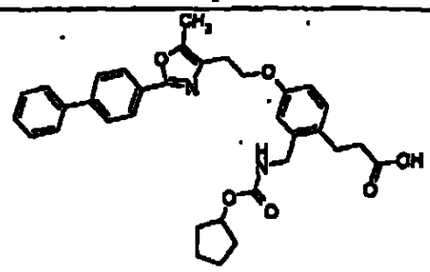
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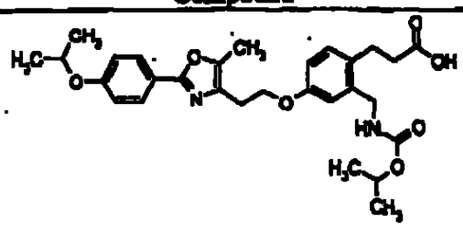
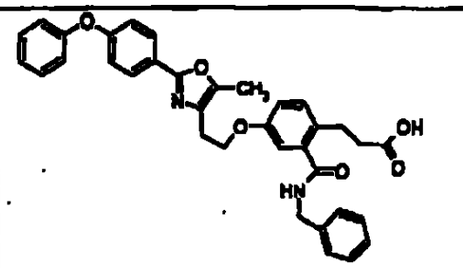
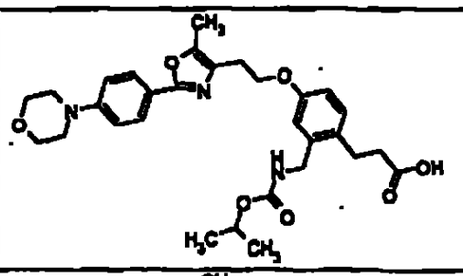
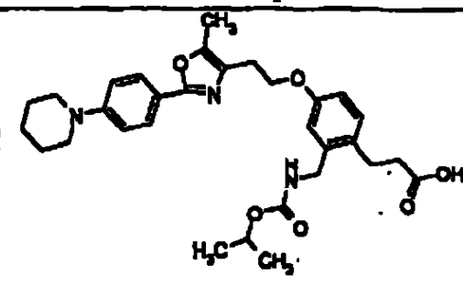
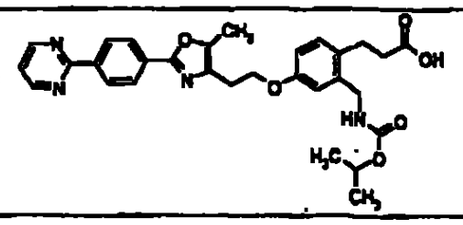
21. A compound selected from the group consisting of:

No.	Compound	Name
1		3-{2-(Diphenylacetyl-aminomethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
2		3-{2-[(2-Cyclopropylacetylamino)methyl] -4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid
3		3-{2-[(3-Methoxybenzoylamino) methyl]-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
4		3-{2-{[(Biphenyl-2-carbonyl) amino]methyl}-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
5		3-(4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-{[(2,5-dichlorothiophene-3-carbonyl)amino]methyl}phenyl) propionic acid
6		3-{2-(Isopropoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid

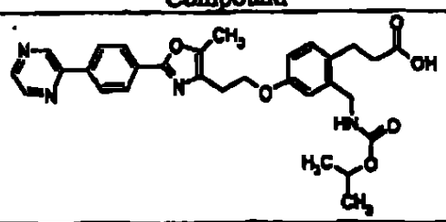
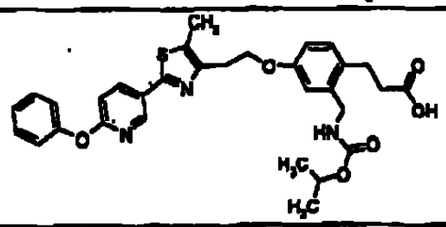
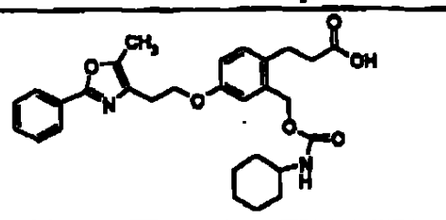
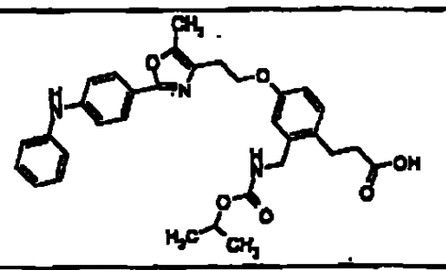
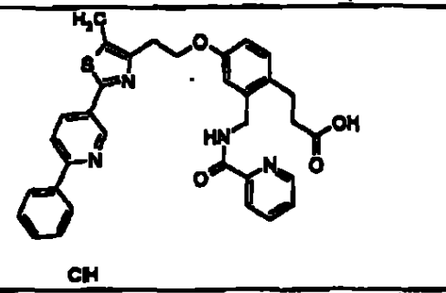
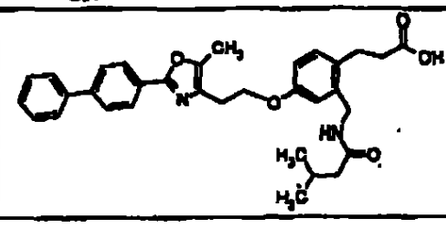
No.	Compound	Name
7		3-{2-(1,3-Dioxo-1,3-dihydroisoindol-2-ylmethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid
8		3-{4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-[(3-phenylureido)methyl] phenyl} propionic acid
9		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(isopropoxycarbonyl-aminomethyl)phenyl] propionic acid
10		3-{2-(Isopropoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl) ethoxy]phenyl} propionic acid
11		3-{2-(Benzoylaminomethyl)-4-[3-(biphenyl-4-yloxy)propoxy] phenyl} propionic acid
12		3-(4-[3-(Biphenyl-4-yloxy) propoxy]-2-{[(pyridine-2-carbonyl)amino]methyl}phenyl) propionic acid

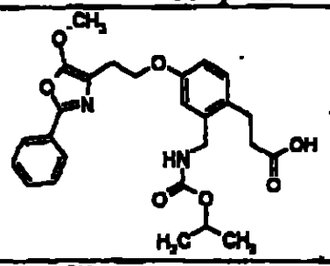
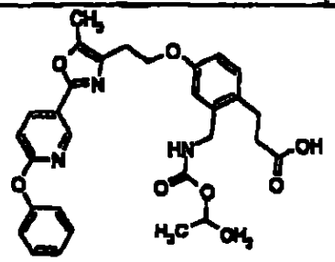
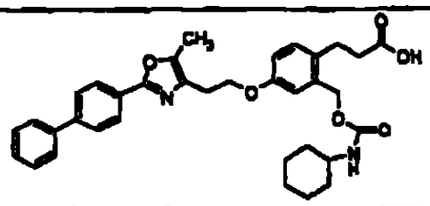
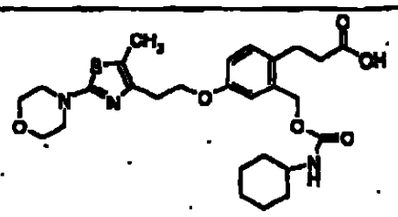
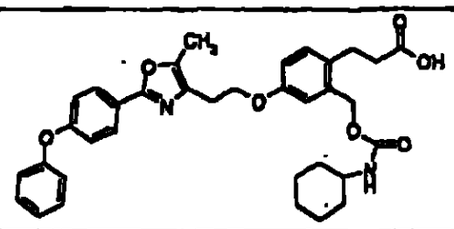
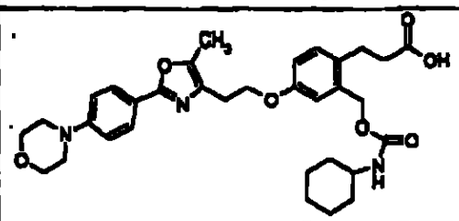
No.	Compound	Name
13		3-{2-Benzylcarbamoyl-4-[2-(5-methyl-2-phenyloxazol-4-yl) ethoxy]phenyl} propionic acid
14		3-{2-Benzylcarbamoyl-4-[2-(2-biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]phenyl} propionic acid
15		3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-cyanophenyl} propionic acid
16		3-[4-[2-(2-Biphenyl-3-yl-5-methyloxazol-4-yl)ethoxy]-2-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)phenyl] propionic acid
17		3-{2-(2-Isopropoxycarbonyl-aminoethyl)-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
18		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid

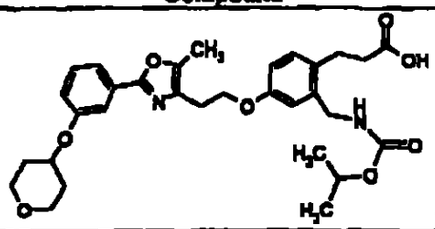
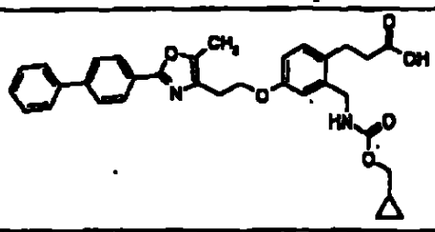
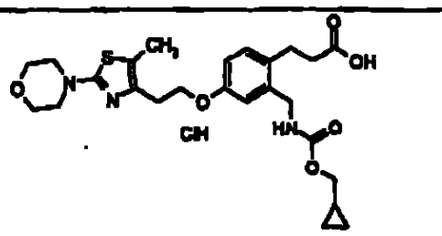
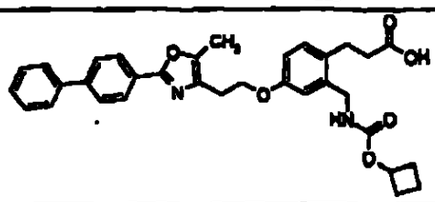
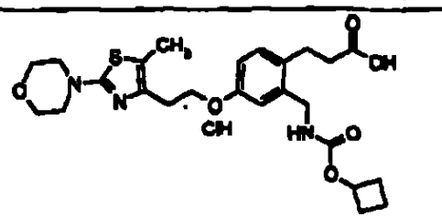
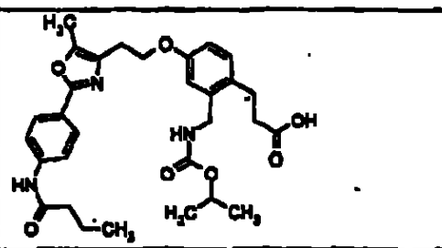
No.	Compound	Name
19		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(3-phenoxyphenyl)oxazol-4-yl] ethoxy}phenyl) propionic acid
20		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(6-phenylpyridin-3-yl)thiazol-4-yl]ethoxy}phenyl) propionic acid
21		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(2-isopropoxycarbonylaminoethyl) phenyl] propionic acid
22		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(isobutoxycarbonyl-aminomethyl)phenyl] propionic acid
23		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(cyclopentyloxycarbonyl-aminomethyl)phenyl] propionic acid

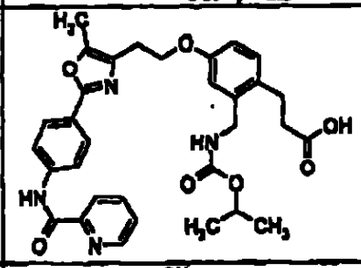
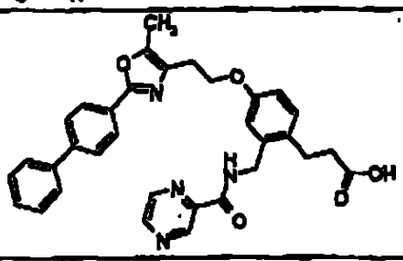
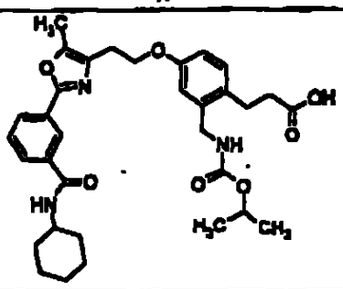
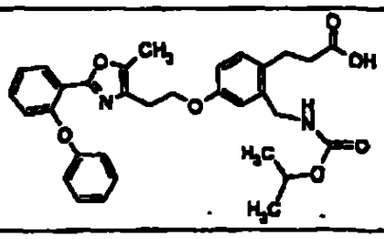
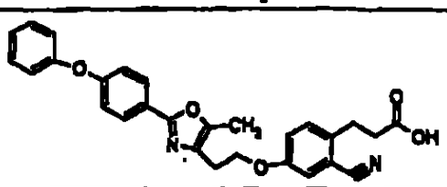
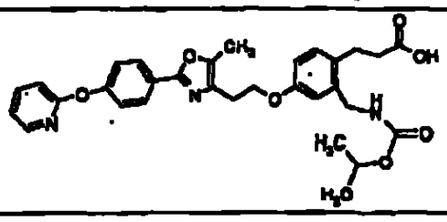
No.	Compound	Name
24		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[2-(4-isopropoxyphenyl)-5-methyloxazol-4-yl]ethoxy} phenyl) propionic acid
25		3-(2-Benzylcarbamoyl-4-{2-[5-methyl-2-(4-phenoxyphenyl) oxazol-4-yl]ethoxy}phenyl) propionic acid
26		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-morpholin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
27		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-piperidin-1-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
28		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-pyrimidin-2-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid

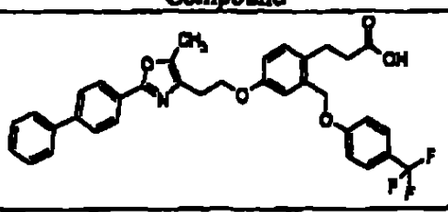
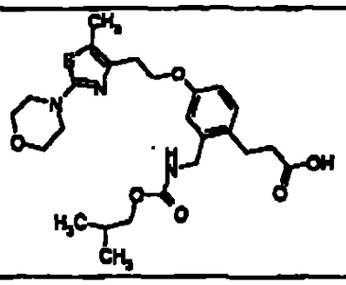
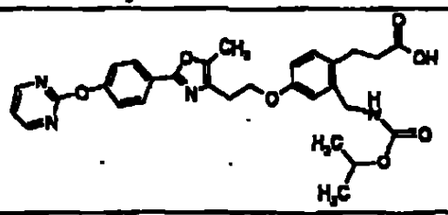
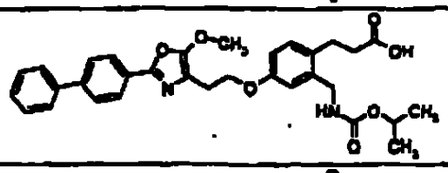
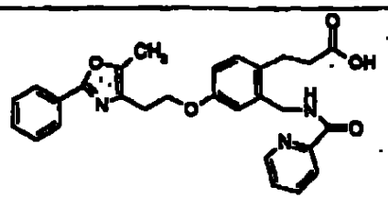
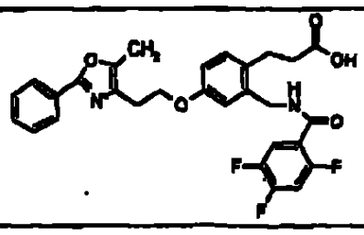
AMENDED SHEET

No.	Compound	Name
29		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-pyrazin-2-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
30		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(6-phenoxypyridin-3-yl)thiazol-4-yl]ethoxy}phenyl) propionic acid
31		3-{2-Cyclohexylcarbamoyl-oxymethyl-4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
32		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(4-phenylaminophenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
33		3-(4-{2-[5-Methyl-2-(6-phenylpyridin-3-yl)thiazol-4-yl]ethoxy}-2-{[(pyridine-2-carbonyl)amino]methyl}phenyl) propionic acid HCl salt
34		3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-[(3-methylbutyrylamino) methyl]phenyl} propionic acid

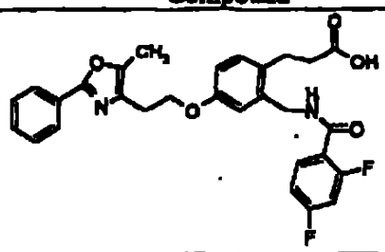
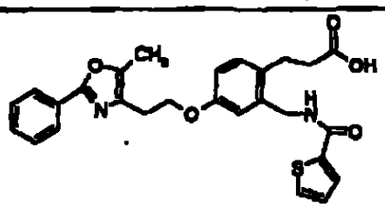
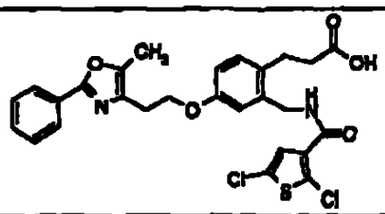
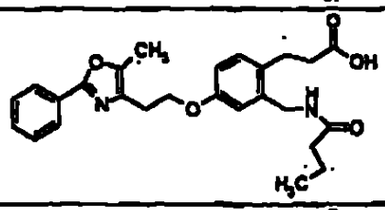
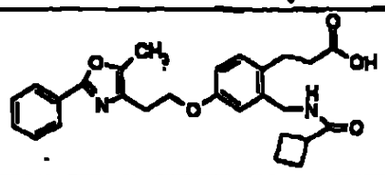
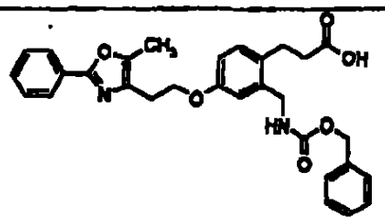
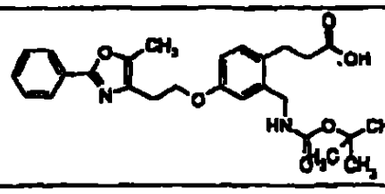
No.	Compound	Name
35		3-{2-(Isopropoxycarbonyl-aminomethyl)-4-[2-(5-methoxy-2-phenyloxazol-4-yl)ethoxy] phenyl} propionic acid
36		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(6-phenoxypyridin-3-yl)oxazol-4-yl]ethoxy}phenyl) propionic acid
37		3-{4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-cyclohexylcarbamoyloxymethyl phenyl} propionic acid
38		3-{2-Cyclohexylcarbamoyl-oxymethyl-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl) ethoxy]phenyl} propionic acid
39		3-(2-Cyclohexylcarbamoyl-oxymethyl-4-{2-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-yl] ethoxy}phenyl) propionic acid
40		3-(2-Cyclohexylcarbamoyl-oxymethyl-4-{2-[5-methyl-2-(4-morpholin-4-ylphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid

No.	Compound	Name
41		3-[2-(Isopropoxycarbonyl-aminomethyl)-4-(2-{5-methyl-2-[3-(tetrahydropyran-4-yloxy) phenyl]oxazol-4-yl} ethoxy) phenyl] propionic acid
42		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(cyclopropylmethoxycarbonylaminomethyl)phenyl] propionic acid
43		3-{2-(Cyclopropylmethoxy-carbonylaminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl)ethoxy]phenyl} propionic acid HCl salt
44		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(cyclobutoxycarbonylaminomethyl)phenyl]propionic acid HCl salt
45		3-{2-(Cyclobutoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl) ethoxy]phenyl} propionic acid HCl salt
46		3-[4-{2-[2-(4-Butyrylaminophenyl)-5-methyloxazol-4-yl]ethoxy)-2-(isopropoxycarbonyl-aminomethyl)phenyl] propionic acid

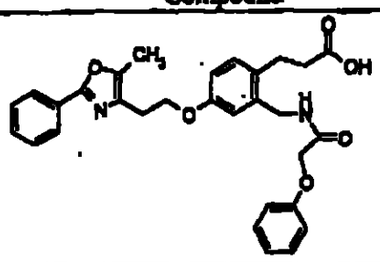
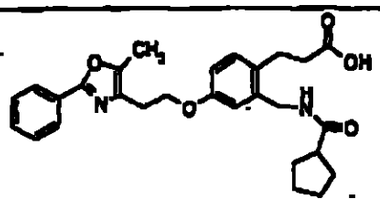
No.	Compound	Name
47		3-{2-(Isopropoxycarbonyl-amino-methyl)-4-[2-(5-methyl-2-{4-[(pyridine-2-carbonyl)-amino]-phenyl}-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
48		3-(4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-{[(pyrazine-2-carbonyl) amino]methyl}phenyl) propionic acid
49		3-[4-{2-[2-(3-Cyclohexylcarbamoylphenyl)-5-methyloxazol-4-yl]ethoxy}-2-(isopropoxycarbonyl-aminomethyl)phenyl] propionic acid
50		3-(2-(Isopropoxycarbonyl-aminomethyl)-4-{2-[5-methyl-2-(2-phenoxyphenyl)oxazol-4-yl]ethoxy}phenyl) propionic acid
51		3-(2-Cyano-4-{2-[5-methyl-2-(4-phenoxy-phenyl)-oxazol-4-yl]-ethoxy}-phenyl) propionic acid
52		3-[2-(Isopropoxycarbonyl-aminomethyl)-4-(2-{5-methyl-2-[4-(pyridin-2-yloxy)phenyl] oxazol-4-yl]ethoxy}phenyl] propionic acid

No.	Compound	Name
53		3-[4-[2-(2-Biphenyl-4-yl-5-methyloxazol-4-yl)ethoxy]-2-(4-trifluoromethylphenoxymethyl)phenyl] propionic acid
54		3-{2-(Isobutoxycarbonyl-aminomethyl)-4-[2-(5-methyl-2-morpholin-4-ylthiazol-4-yl) ethoxy]phenyl} propionic acid
55		3-[2-(Isopropoxycarbonyl-aminomethyl)-4-(2-{5-methyl-2-[4-(pyrimidin-2-yloxy)phenyl] oxazol-4-yl}ethoxy)phenyl] propionic acid
56		3-[4-[2-(2-Biphenyl-4-yl-5-methoxyoxazol-4-yl)ethoxy]-2-(isopropoxycarbonylaminomethyl)phenyl] propionic acid
57		3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{[(pyridine-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid
58		3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(2,4,5-trifluoro-benzoylamino)-methyl]-phenyl}-propionic acid

AMENDED SHEET

No.	Compound	Name
59		3-{2-[(2,4-Difluoro-benzoylamino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
60		3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{[(thiophene-2-carbonyl)-amino]-methyl}-phenyl)-propionic acid
61		3-(4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-{[(thiophene-2-carbonyl)-amino]-methyl}-phenyl)-proprionic acid
62		3-{2-(Butyrylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
63		3-{2-[(Cyclobutanecarbonyl-amino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
64		3-{2-(Benzyloxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid
65		3-{2-(tert-Butoxycarbonylamino-methyl)-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

 AMENDED SHEET

No.	Compound	Name
66		3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-2-[(2-phenoxy-acetylamino)-methyl]-phenyl}-propionic acid
67		3-{2-[(Cyclopentanecarbonyl-amino)-methyl]-4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

22. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one compound of Claims 1-21 or a pharmaceutically acceptable salt, solvate or hydrate thereof.

23. A pharmaceutical composition comprising (1) a compound of Claim 1, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof; (2) a second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acryl CoA:cholestrol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin; and (3) a pharmaceutically acceptable carrier.

24. A method of modulating a peroxisome proliferator activated receptor (PPAR), comprising the step of contacting the receptor with at least one compound of Claims 1-21, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

25. The method of Claim 24, wherein the peroxisome proliferator activated receptor is an alpha-receptor.

26. The method of Claim 24, wherein the peroxisome proliferator activated receptor is a gamma-receptor.

27. A method for treating or preventing a peroxisome proliferator activated receptor-gamma mediated disease or condition comprising the step of administering an effective amount of at least one compound of Claims 1-21.

28. A method for lowering blood-glucose comprising the step of administering an effective amount of at least one compound of Claims 1-21.

29. A method of treating or preventing disease or condition selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of at least one compound of Claims 1-21.

30. A method of treating or preventing diabetes mellitus in a mammal comprising the step of administering to a mammal a therapeutically effective amount of at least one compound of Claims 1-21.

31. A method of treating or preventing cardiovascular disease in a mammal comprising the step of administering to a mammal a therapeutically effective amount of at least one compound of Claims 1-21, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

32. A method of treating or preventing syndrome X in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of

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at least one compound of Claims 1-21, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

33. A method of treating or preventing disease or condition selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of at least one compound of Claims 1-21 and an effective amount of second therapeutic agent selected from the group consisting of: insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acryl CoA:cholestrol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin.

34. Use of a compound of Claims 1-21 and pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, for the manufacture of a medicament for the treatment of a condition modulated by a PPAR.

INTERNATIONAL SEARCH REPORT

Inte ial Application No
PCT/US 02/15143

1067 1061

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/42 C07D263/32 A61P3/10 C07D231/12 A61K31/422
A61K31/426 A61K31/427 C07D233/58 C07D277/24 C07D277/38
C07C271/24 C07C271/22 C07C233/87 C07C233/63 C07D413/12

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 C07C A61K A61P

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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 18355 A (BROOKS DAWN ALISA ;CONNOR SCOTT EUGENE (US); DOMINIANNI SAMUEL JAM) 7 March 2002 (2002-03-07) page 213; example 50	1-35
P,Y	WO 02 16332 A (BROOKS DAWN ALISA ;GODFREY ALEXANDER GLENN (US); MANTLO NATHAN BRY) 28 February 2002 (2002-02-28) claims definition of R2/R3	1-35
Y	WO 01 16120 A (DOMINIANNI SAMUEL J ;MATTHEWS DONALD P (US); MICHELLYS PIERRE YVES) 8 March 2001 (2001-03-08) claims definition of R2/R3	1-35

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[X] Further documents are listed in the continuation of box C. [X] 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 claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 2002	12/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kollmannsberger, M

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T062

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 02/15143

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 C07D413/14 C07D413/04 C07D413/10 C07D417/14
C07D417/04 C07D213/81 C07D307/83

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)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 00566 A (ZANDT MICHAEL C VAN ;INST FOR PHARMACEUTICAL DISCOV (US)) 4 January 2001 (2001-01-04) claim 1 see definition of R1-R4 and R7; page 77 -page 78; examples 43,44 page 1, line 16 - line 29	1-35
E	EP 1 216 980 A (EISAI CO LTD) 26 June 2002 (2002-06-26) page 135 -page 137; examples 771-785 page 1, paragraph 1 -page 2, paragraph 18 page 48 -page 50	1-35
Y	& WO 01 25181 A (EISAI CO LTD) 12 April 2001 (2001-04-12)	1-35

☐ 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 claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kollmannsberger, M

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INTERNATI NAL SEARCH REPORT

International application No.
PCT/US 02/15143 1069

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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[illegible]al Application No
PCT/US 02/15143

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10/64

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0218355 A	07-03-2002	AU 8465801 A	13-03-2002
		WO 0218355 A1	07-03-2002
WO 0216332 A	28-02-2002	AU 8466001 A	04-03-2002
		WO 0216332 A1	28-02-2002
WO 0116120 A	08-03-2001	AU 7073400 A	26-03-2001
		EP 1206457 A1	22-05-2002
		WO 0116120 A1	08-03-2001
		US 6417212 B1	09-07-2002
WO 0100566 A	04-01-2001	AU 5886900 A	31-01-2001
		BR 0011928 A	09-04-2002
		CN 1364153 T	14-08-2002
		CZ 20014637 A3	17-04-2002
		EP 1198451 A2	24-04-2002
		NO 20016272 A	17-01-2002
		WO 0100566 A2	04-01-2001
		US 6420426 B1	16-07-2002
EP 1216980 A	26-06-2002	AU 7449900 A	10-05-2001
		EP 1216980 A1	26-06-2002
		WO 0125181 A1	12-04-2001

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SUPERINTENDENCIA [illegible]
Radicacion : [illegible] Folios: 1064
Fecha (AMD): 2004-12-[illegible] 16:58:21
Tramite : [illegible]
Dependencia: [illegible]

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	(✓)
- Indicación de que se solicita la concesión de una patente.	( )	(✓)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(✓)
- Descripción de la invención.	( )	(✓)
- Dibujos de ser estos pertinentes.	( )	(✓)
Comprobante de Pago de las tasas establecidas.		
COMPLETA (✓)	INCOMPLETA ( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
- Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )

Firma Responsable:

Fecha:

Industria y Comercio
SUPERINTENDENCIA

Folio 1065 1072

2020
Bogotá DC

Doctor(a)
CARLOS R OLARTE
Apoderado(a)
ELI LILLY AND COMPANY

REFERENCIA:	Radicación No.	03 107405
	Solicitud Internacional	PCT/US2002/15143
	Fecha Inicio fase nacional	07/01/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	41
	Folios	001

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 Unica 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, 04 FEB. 2004

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

202055