Industria y Comercio

SUPERINTENDENCIA

PCT
CAPITULO II

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

07-55671

21 **EXPEDIENTE No.** _____

54 **TÍTULO** ANALOGOS DE 12-ARYL PROSTAGLANDINA

51 **CLASIFICACIÓN INTERNACIONAL** _____

71 **SOLICITANTE** ALLERGAN, INC

DOMICILIO IRVINE, CALIFORNIA, ESTADOS UNIDOS DE AMERICA

74 **APODERADO** JERONIMO CASTILLO BONILLA

22 **BOGOTÁ, D. C.,** _____

(FORMA P 10)

SS

PETITORIO

Industria y Comercio

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-055671- -00000-0000
Fecha: 2007-06-01 16:23:04 Dep. 2020 NUECREACIONI
Tra. 2 PATENTES Eve. 1 REGDEPOSITO
Act. 411 PRESENTACION Folios: 361

FORMULARIO ÚNICO DE
PI
ENTRADA EN F

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-055671- -00000-0000
Fecha: 2007-06-01 16:23:04 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 361

(1) SOLICITUD DE

[X] Patente de Invención.

[ ] Patente de Modelo de Utilidad,

[ ] Capítulo I. [X] Capítulo II

(2) SOLICITANTE (71)	Nombre: ALLERGAN, INC Dirección: 2525 Dupont Drive, Irvine, California, Estados Unidos de América Nacionalidad o Domicilio: estadounidense Lugar de Constitución: Delaware Teléfono: Fax: E-mail:	IDENTIFICACIÓN C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual ____ Número ____
(3) REPRESENTANTE O APODERADO	Nombre: JERÓNIMO CASTILLO BONILLA Dirección: Calle 93A N° 14-17, Ofc 311 Bogotá, D.C. Teléfono: 2 363493 Fax: 2 182351 E-mail: info@pcastillopineda.com	IDENTIFICACIÓN C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual ____ Número 79462057 TP 10415
(4) INVENTOR (ES) (72)	Nombre: Yariv DONDE Dirección: 24386 Antilles Way, Dana Point, California, E. U.A. Nacionalidad o Domicilio estadounidense	

(5) PCT (86)

Solicitud Internacional No. PCT/US2005/044501 Fecha Diciembre 8.2005

Publicación Internacional No. WO 2006/063179 A1 Fecha Junio 15,2006

(6) Título (54) ANALOGOS DE 12-ARYL PROSTAGLANDINA

(7) Clasificación Internacional (51) ____

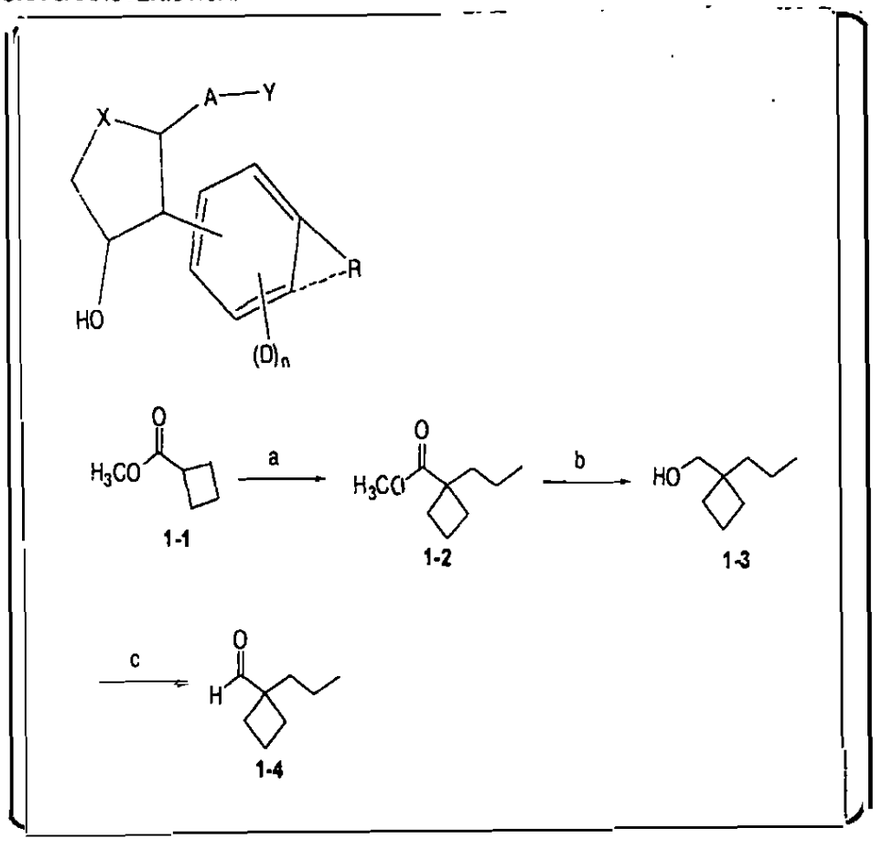
(8) Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] NO [ ]	US	10/12/2004	11/009.298

(9) Comprobante de pago No. 07 44530 Fecha 01-06-07

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de representación de la solicitud.
- [X] Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuera el caso.
- [ ] Documentos 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).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De se 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 se el caso, certificado de depósito del material biológico.
- [X] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el 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. Publicación Internacional

(11) FIGURA CARACTERÍSTICA:



(12) Solicito la concesión de la patente.

NOMBRE JERÓNIMO CASTILLO BONILLA

FIRMA:

C.C. 79462057 T.P. 104167

Instrucciones para la presentación del os anexos, ver reverso de esta pagina.

(Continuación Inventores)

Nombre : Jeremiah H. NGUYEN
Dirección : 16146 Bamboo Street, La Puente, California, Estados Unidos de América
Nacionalidad : estadounidense

SUPERINTENDENCIA

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S.A.

3

Item	Expediente No	07055671 No de unidades	No de Folio
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA X	1	✓
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones:

LAW OFFICES
PEDRO CASTILLO PINEDA &
ASSOCIATES
P.O. BOX 48362
Bogotá, Colombia / South America

IMPORTANT NOTE
The lodging of this GENERAL POWER with the Patent Office obviates the need of presenting special powers with each individual trade mark application.

FOR PATENTS AND TRADE MARKS IN
COLOMBIA

	Poder General	**General Power of Attorney**
1 Applicant's name	(1)	ALLERGAN, INC.
2 Applicant's address	domiciliado en (2)	domiciled in (2) 2525 Dupont Drive Irvine, CA 92612 USA

-1

nombra al Dr. JERONIMO CASTILLO BONILLA y/o Dra. XIMENA BONILLA PEREIRA, y/o Dr. ALVARO CASTILLO GRAU, Calle 93A N° 14-17 Oficina 311 en Bogotá, Colombia, como sus representantes con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades Colombianas, administrativas, judiciales o de policía, en primera o segunda instancia, la obtención de Patentes de Invención, Registro de Marcas, de Modelos y de Dibujos Industriales, de Nombres Comerciales y Enseñas, Lemas Comerciales y Denominaciones de Origen, lo mismo que traspasos, extensiones, renovaciones, cambios de nombre, registro de licencias de explotación y registro de licencias de uso referentes a tales actuaciones, cancelación de Registros de marca, a cuyo efecto les faculta para dar ante dichas autoridades todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, apelaciones y reclamos, solicitar la aplicación de medidas cautelares; solicitar la nulidad de Patentes de Invención, modelos de utilidad, diseños industriales, así como la de registros de marcas ante la autoridad nacional competente; aceptar en nuestro nombre y representación la Cesión de derechos de invención y de patente de invención que se nos haga por cualquier persona, abonar todos los impuestos, cuotas y pagos determinados por la ley, recibir todos los documentos y valores dando el descargo respectivo, llenar cualesquiera otros requisitos, desistir y tomar en fin todas las medidas que creyeren conducentes al resguardo de nuestros intereses y en caso de presentarse oposiciones y/o observaciones para que intervengan como demandantes o como demandados, con todas las demás facultades necesarias, así como iniciar y tramitar procesos jurisdiccionales relativos a competencia desleal. Este poder comprende además las facultades de recibir, desistir, transigir, comprometer, sustituir, revocar sustituciones, conciliar, recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

hereby appoint, JERONMO CASTILLO BONILLA and/or XIMENA BONILLA PEREIRA, and/or ALVARO CASTILLO GRAU, Calle 93A N° 14-17 Office 311 en Bogotá, Colombia, as our representatives with special, ample and sufficient power to obtain from the offices and Colombian authorities, administrative, judicial and police, in first or in second instance, Privileged Patents of invention, Registration of Trade Marks, of Models and Industrial Drawings, of Commercial Names and ensigns, Commercial slogans and Origin Denominations as well as assignments, extensions, renewals, changes of name, registration of license of exploitation and of license of use referred to said actions, Cancellation Actions against trademark Registrations, who are empowered to take before said authorities all of the necessary steps for the purposes indicated, to file applications, to formulate descriptions, corrections, protests, declarations, appeals, and claims, apply for precautionary measures; apply for the nullity of Patent Inventions, Utility Models, Industrial Designs, as well as for Trademark Registrations before the competent national authority; to accept on our behalf and representation the assignment of rights of inventions and titles of invention that may be done to us by any person, to pay all taxes, quotas and payments prescribed by law, to receive all the documents and proceeds giving the respective acquittance or receipt, to fulfill any other requisites to desist and take in fact any other measures that may be deemed conducive to the safeguard of our interests, and in case that oppositions and/or observations are presented to intervene as complainant and defendant, with all necessary legal faculties, as well as to file jurisdictional processes related to disloyal competition. This power of attorney includes the faculties to receive, desist, compromise, transact substitute it in all or in part, to revoke substitutions, to conciliate, to receive notifications and to appoint extra-judicial or judicial attorneys.

3 Date
4 Applicant's signature

Dado y firmado en (3).....
.....
.....

Given and signed in (3).....
Irvine, California
April 12, 2005

4)Signature (s)

M. A. Voet

Martin A. Voet
Assistant Secretary

OFICINAS DE ABOGADOS

PEDRO CASTILLO PINEDA & ASOCIADOS

Bogota, Colombia / Sur América

NOTA IMPORTANTE

Al registrar este PODER GENERAL en la Oficina de Patentes, no se necesita presentar poderes especiales con cada solicitud de marca registrada.

PARA PATENTES MARCAS REGISTRADAS EN

COLOMBIA

Poder General

1. Nombre del Solicitante (1): ALLERGAN, INC.

2. Dirección del solicitante (2): 2525 Dupont Drive Irvine, CA 92612 USA

Nombra al Dr. JERONIMO CASTILLO BONILLA y/o Dra. XIMENA BONILLA PEREIRA, y/o Dr. ALVARO CASTILLO GRAU, Calle 93A No. 14-17 Oficina 311 en Bogota, Colombia, como sus representantes con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades Colombianas, administrativas, judiciales o de policía, en primera o segunda instancia, la obtención de Patentes de Invención, Registro de Marcas, de Modelos y de Dibujos Industriales, de Nombres Comerciales y Enseñas, Lemas Comerciales y Denominaciones de Origen, lo mismo que traspasos, extensiones, renovaciones, cambios de nombre, registro de licencias de explotación y registro de licencias de uso referentes a tales actuaciones, cancelación de Registros de marca, a cuyo efecto les faculta para dar ante dichas autoridades todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, apelaciones y reclamos, solicitar la aplicación de medidas,

cautelares; solicitar la nulidad de Patentes de Invención, modelos de utilidad, diseños industriales, así como la de registros de marcas ante la autoridad nacional competente; aceptar en nuestro nombre y representación la Cesión de derechos de invención y de patente de invención que se nos haga por cualquier persona, abonar todos los impuestos, cuotas y pagos determinados por la ley, recibir todos los documentos y valores dando el descargo respectivo, llenar cualesquiera otros requisitos, desistir y tomar en fin todas las medidas que creyeren conducentes al resguardo de nuestros intereses y en caso de presentarse oposiciones y/o observaciones para que intervengan como demandantes o como demandados, con todas las demás facultades necesarias, así como iniciar y tramitar procesos jurisdiccionales relativos a competencia desleal. Este poder comprende además las facultades de recibir, desistir, transigir, comprometer, sustituir, revocar sustituciones, conciliar, recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

Dado y firmado en (3) Irvine, California – Abril 12 de 2005.

(Firmado)

Martin A. Voet

Secretario Encargado

NOTA DEL TRADUCTOR
YO, ROSALÍA MOGOLLÓN C., TRADUCTORA E INTÉRPRETE OFICIAL PARA LOS IDIOMAS ESPAÑOL – INGLÉS – ESPAÑOL, AUTORIZADA POR EL MINISTERIO DE JUSTICIA MEDIANTE RESOLUCIÓN # 2037 DE DICIEMBRE 1 DE 2003 CONFIRMO, POR MEDIO DE LA PRESENTE, QUE LA ANTERIOR TRADUCCIÓN CORRESPONDE CABALMENTE AL ORIGINAL ESCRITO EN INGLÉS.
MI DIRECCIÓN: CRA 15 # 99 - 13 OFICINA 306 TEL: 2188209–2766303 BOGOTÁ – COLOMBIA

State of California

SECRETARY OF STATE

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

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

CERTIFIED

5. *At Sacramento, California*
6. *the 21st day of April 2005*
7. *by Deputy Secretary of State, State of California*
8. *No. 236021*
9. *Seal/Stamp:*

10. *Signature*

BRUCE McPHERSON
Secretary of State

BY

NP-24 A (REV. 2-05)

OSP 05 88438

Estado de California

Secretaría de Estado

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. País: **Estados Unidos de América**

EL PRESENTE DOCUMENTO PÚBLICO

2. Ha sido firmado por: **TAMARA J. HALLEN**

3. Actuando en calidad de: **NOTARIO PÚBLICO, ESTADO DE CALIFORNIA**

4. Lleva el sello/estampilla de: **TAMARA J. HALLEN, Notario Público**

Certificado

3. En: **Sacramento, California**

4. El: **21 de Abril de 2005**

5. Por: **Secretario Encargado del Estado, Estado de California**

6. No.: **236021**

7. Sello /Estampilla

10. Firma : *(Firmado)*

BRUCE McPHERSON

Secretario de Estado

NOTA DEL TRADUCTOR

YO, ROSALÍA MOGOLLÓN C., TRADUCTORA E INTÉRPRETE OFICIAL PARA LOS IDIOMAS ESPAÑOL – INGLÉS – ESPAÑOL, AUTORIZADA POR EL MINISTERIO DE JUSTICIA MEDIANTE RESOLUCIÓN # 2037 DE DICIEMBRE 1 DE 2003 CONFIRMO, POR MEDIO DE LA PRESENTE, QUE LA ANTERIOR TRADUCCIÓN CORRESPONDE CABALMENTE AL ORIGINAL ESCRITO EN INGLÉS.

MI DIRECCIÓN: CRA 15 # 99 - 13 OFICINA 306 TEL: 2188209–2766303 BOGOTÁ – COLOMBIA

ROSALÍA MOGOLLÓN C. Ministry of Justice Res. No. 2037 December 1/03 OFFICIAL TRANSLATOR & INTERPRETER

MINISTERIO DE
RELACIONES EXTERIORES

358029
Rosalía Mogollón
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 MAY -2 P 2:21
mcs
JEFE DE LEGALIZACIONES
BOGOTA D.C.

CALIF RNIA ALL-PURPOSE ACKN WLEDGMENT

State of California
County of Orange } ss.

On April 12, 2005 (Date) before me, Tamara J. Hallen, Notary Public (Name and Title of Officer (e.g., "Jane Doe, Notary Public"))

personally appeared Martin A. Voet (Name(s) of Signer(s)),

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

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

TAMARA J. HALLEN
Commission # 1414872
Notary Public - California
Orange County
My Comm. Expires May 29, 2007

WITNESS my hand and official seal.

Tamara J. Hallen
Signature of Notary Public

OPTIONAL

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

Description of Attached Document

Title or Type of Document: General Power of Attorney - Colombia

Document Date: April 12, 2005 Number of Pages: 1

Signer(s) Other Than Named Above: none

Capacity(ies) Claimed by Signer

Signer's Name: Martin A. Voet

☐ Individual
☐ Corporate Officer — Title(s): Assistant Secretary
☐ Partner — ☐ Limited ☐ General
☐ Attorney-in-Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other:

Signer Is Representing: Allergan, Inc.

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

RECONOCIMIENTO PARA TODOS LOS EFECTOS LEGALES OTORGADO EN CALIFORNIA

Estado de California } **S.S.**

Condado **Orange**

A los 12 de Abril de 2005 ante mi Tamara J. Hallen. Notaria Pública compareció Martin A. Voet

☒ A quien conozco personalmente y sé que es la persona cuyo nombre aparece suscrito en el instrumento adjunto y reconoció ante mi haber otorgado dicho instrumento en virtud de su capacidad legal. Mediante su firma autorizó el presente instrumento en nombre propio o en nombre de la entidad en cuya representación está actuando.

EN TESTIMONIO DE LO ANTERIOR firmo y coloco mi sello oficial.

(Firma)

NOTARIO PÚBLICO

OPCIONAL

Aunque la información que aparece a continuación no es exigida por la ley, puede ser valiosa para las personas que se basen es este documento y puede ayudar para que no sea utilizado o anexado de manera fraudulenta a un documento distinto.

Descripción de Documento Adjunto

Nombre y tipo de documento: Poder general – Colombia

Fecha del documento: 12 de Abril de 2005 No. de hojas: 1

Signatario distinto al mencionado anteriormente: Ninguno

Capacidad legal del signatario

Nombre del signatario: Martin A. Voet

☐ Funcionario corporativo – cargo: Secretario encargado

el signatario representa a: Allergan, Inc.

TAMARA J. HALLEN

Licencia # 1414872

Notario Público – California

Condado de Orange

Mi licencia vence el 29 de mayo de 2007

Pedro Castillo Pineda Lawyers

AFFIDAVIT

I, (name), hereby solemnly and truly declare that I am (post of) for ALLERGAN, INC, domiciled at 2525 Dupont Drive, Irvine, California 92612, United States of America, Corporation organized in accordance with the laws of the State of ~~California~~ Delaware and that I am empowered to grant this declaration.

Signed this 19th day of July, 2006.

ALLERGAN, INC

By: (Signature)
Name

Martin A. Voet, Assistant Secretary

Note: Notarized and Legalized up by Apostille

State of California

SECRETARY OF STATE

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by Angel Cardenas*
3. *acting in the capacity of Deputy Clerk-Recorder, County of Orange, State of California*
4. *bears the seal/stamp of the County of Orange, State of California*

CERTIFIED

5. *At Sacramento, California*
6. *the 3rd day of August 2006*
7. *by Deputy Secretary of State, State of California*
8. *No. 297443*
9. *Seal/Stamp:*

10. *Signature*

Bruce McPherson

Secretary of State

BY Jaime Winkel

NP-24 A (REV. 4-05)

OSP 05 90772

STATE OF CALIFORNIA

County of Orange

I, TOM DALY, County Clerk-Recorder in and for said County, having by law a seal do hereby certify that MARY LOU MC NOWN whose name is subscribed to the attached certificate of acknowledgement, proof of affidavit, was at the time of taking such acknowledgment, proof or affidavit, a Notary Public IN AND FOR ORANGE COUNTY, duly commissioned and sworn and residing in said County, and was, as such, an officer of said State, duly authorized by the laws thereof to take and certify the same, as well as to take and certify the proof and acknowledgment of deeds and other instruments in writing to be recorded in said State, and that full faith and credit are and ought to be given to his official acts; that the impression of his official seal is not required by law to be filed in the office of the County Clerk-Recorder. I further certify that I am well acquainted with his hand writing and verily believe that the signature to the attached certificate is his genuine signature, and further that the annexed instrument is executed and acknowledged according to the laws of the State of California.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed the seal of said County Clerk-Recorder.

This 25th day of JULY 2006

TOM DALY
County Clerk-Recorder in and for
the County of Orange

By _____ Deputy
ANGEL CARDENAS

CALIF RNIA ALL-PURPOSE A KN WLEDGMENT

State of California
County of ORANGE } ss.

On JULY 19 2006 before me, MARY LOU MCNOWN, notary public
Date Name and Title of Officer (e.g., "Jane Doe, Notary Public")

personally appeared MARTIN A. VOET
Name(s) of Signer(s)

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

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

WITNESS my hand and official seal.

Mary Lou McNown
Signature of Notary Public

MARY LOU MC NOWN
Commission # 1431736
Notary Public - California
Orange County
My Comm. Expires Aug 16, 2007

OPTIONAL

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

Description of Attached Document

Title or Type of Document: _____

Document Date: _____

Signer(s) Other Than Named Above: _____

Capacity(ies) Claimed by Signer

Signer's Name: _____

☐ Individual
☐ Corporate Officer — Title(s): _____
☐ Partner — ☐ Limited ☐ General
☐ Attorney-in-Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____

Signer Is Representing: _____

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 17693PCTAP

Box No. I TITLE OF INVENTION

12-ARYL PROSTAGLANDIN ANALOGS

Box No. II APPLICANT ☐ This person is also inventor

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612
United States of America

Telephone No. (714) 246-4348

Facsimile No. (714) 246-4249

Teleprinter No. None

Applicant's registration No. with the Office 51,851

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DONDE, Yariv
24386 Antilles Way
Dana Point, CA 92629
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV 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 ☐ 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.)*

JOHNSON, Brent A.; BARAN, Robert J.; DONOVAN, Stephen; GERMAN, Joel; STATHAKIS, Dean G.; VOET, Martin A.
c/o Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612
United States of America

Telephone No. (714) 246-4348

Facsimile No. (714) 246-4249

Teleprinter No. None

Agent's registration No. with the Office 51,851

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

NGUYEN, Jeremiah H.
16146 Bamboo Street
La Puente, CA 91744
United States of America

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [X] the United States of America only [ ] the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

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This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany is not designated for any kind of national protection

☐ KR Republic of Korea is not designated for any kind of national protection

☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is: national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) (10.12.04) 10 December 2004	11/009,298	US		
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):*

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA / .... EP .....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) on paper, the following number of sheets:

request (including declaration sheets)	4	
description (excluding sequence listing and/or tables related thereto)	106	
claims	20	
abstract	1	
drawings	27	
Sub-total number of sheets	158	0
sequence listing		
tables related thereto		
(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)		
Total number of sheets	158	0

(b) ☐ only in electronic form (Section 801(a)(i))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

(c) ☐ also in electronic form (Section 801(a)(ii))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listing: .....
- ☐ tables related thereto: .....

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*: — Number of items

1. ☒ fee calculation sheet :
2. ☐ original separate power of attorney :
3. ☐ original general power of attorney :
4. ☐ copy of general power of attorney; reference number, if any: ..... :
5. ☐ statement explaining lack of signature :
6. ☐ priority document(s) identified in Box No. VI as item(s): ..... :
7. ☐ translation of international application into *(language)*: ..... :
8. ☐ separate indications concerning deposited microorganism or other biological material :
9. ☐ sequence listing in electronic form *(indicate type and number of carriers)*
   - (i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application) :
   - (ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter* :
   - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column :
10. ☐ tables in electronic form related to sequence listing *(indicate type and number of carriers)*
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    - (ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*) :
    - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :
11. ☒ other *(specify)*: Postcard; Transmittal Letter to US/RO Re Certification Under 37CFR1.10

Figure of the drawings which should accompany the abstract: 1

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

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).

Brent A. JOHNSON, Ph.D. Brent A. Johnson

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

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Date of receipt of the record copy by the International Bureau:

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

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's file reference

Applicant

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 300 [T]

2. SEARCH FEE . . . . . 1,877 [S]

International search to be carried out by ISA/EP

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FILING FEE

Where items (b) and/or (c) of Box No. IX apply, enter Sub-total number of sheets
Where items (b) and (c) of Box No. IX do not apply, enter Total number of sheets } 158

[i1] first 30 sheets . . . . . 1,102 [i1]

[i2] 128 (number of sheets in excess of 30) x $12 (fee per sheet) = 1,536 [i2]

[i3] additional component (only if a sequence listing and/or tables related thereto are filed in electronic form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):

400 x _____ (fee per sheet) = _____ [i3]

Add amounts entered at i1, i2 and i3 and enter total at I . . . . 2,638 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international filing fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the international filing fee.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . 20 [P]

5. TOTAL FEES PAYABLE . . . . . 4,835 USD

Add amounts entered at T, S, I and P, and enter total in the TOTAL box — TOTAL

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- [x] Authorization to charge the fee for priority document.

Receiving Office: RO/ US

Deposit Account No.: 01-0885

Date: December 5, 2005

Name: Brent A. JOHNSON, Ph.D.

Signature: Brent A. Johnson

See Notes to the fee calculation sheet

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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DONDE, Yariv [US/US]; 24386 Antilles Way, Dana Point, CA 92629 (US). NGUYEN, Jeremiah, H. [US/US]; 16145 Bamboo Street, La Puente, CA 91744 (US).

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

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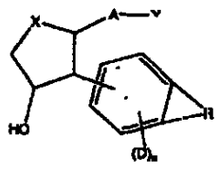
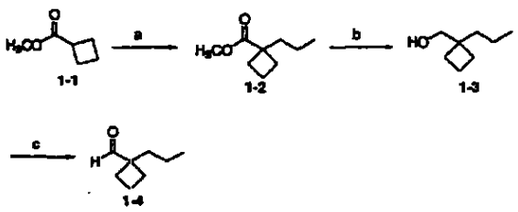
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

[Continued on next page]

(54) Title: 12-ARYL PROSTAGLANDIN ANALOGS



(I)



(57) Abstract: Compounds comprising the formula (I) are disclosed, wherein Y, A, X, R, D, and n are as described. A compound comprising a prostaglandin EP_2 selective agonist wherein the ω-chain comprises a substituted phenyl, wherein at least one substituent consists of hydrocarbyl or non-linear hydroxyhydrocarbyl is also disclosed herein. Methods, compositions, and medicaments related thereto are also disclosed.

WO 2006/063179 A1

12-ARYL PROSTAGLANDIN ANALOGS

By Inventors

Yariv Donde and Jeremiah H. Nguyen

FIELD OF THE INVENTION

This invention relates to compounds which are useful for treatment of diseases. In particular, the compounds related to the invention are useful for the treatment of diseases or conditions related to prostaglandins or to the activity of prostaglandin receptors.

BACKGROUND OF THE INVENTION

Description of Related Art

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

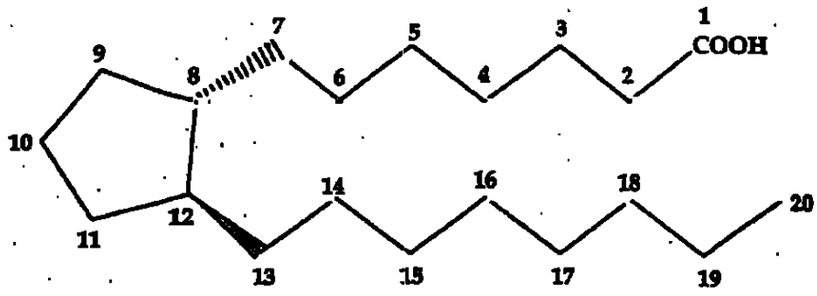
The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupilary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical β-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

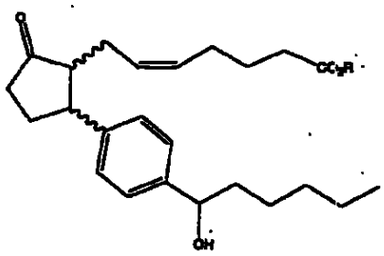
Certain eicosanoids and their derivatives have been reported to possess ocular hypotensive activity, and have been recommended for use in glaucoma management. Eicosanoids and derivatives include numerous biologically

important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:



Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin $F_{2\alpha}$ ($PGF_{2\beta}$)].

The prostaglandin E analog shown below is disclosed in the following documents, expressly incorporated herein by reference: U.S. Patent No. 5,462,968; U.S. Patent 5,698,598; and U.S. Patent No. 6,090,847.



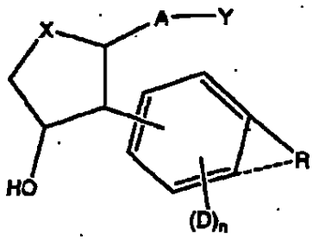
Prostaglandin EP_2 selective agonists are believed to have several medical uses. For example, U.S. Patent No. 6,437,146 teaches the use of prostaglandin EP_2 selective agonists "for treating or preventing inflammation and pain in joint and muscle (e.g., rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.), inflammatory skin condition (e.g., sunburn, burns, eczema, dermatitis, etc.), inflammatory eye condition (e.g., conjunctivitis, etc.), lung disorder in which inflammation is involved (e.g., asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.), condition of the gastrointestinal tract associated with inflammation (e.g., aphthous ulcer, Chrohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.), gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, allergic disease, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjgren's syndrome, Behcet disease, thyroiditis, type I diabetes, diabetic complication (diabetic microangiopathy, diabetic retinopathy, diabetic

neohropathy, etc.), nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, kidney dysfunction (nephritis, nephritic syndrome, etc.), liver dysfunction (hepatitis, cirrhosis, etc.), gastrointestinal dysfunction (diarrhea, inflammatory bowel disease, etc.) shock, bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis), hypercalcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculosis, lithiasis (especially, urolithiasis), solid carcinoma, mesangial proliferative glomerulonephritis, edema (e.g. cardiac edema, cerebral edema, etc.), hypertension such as malignant hypertension or the like, premenstrual tension, urinary calculus, oliguria such as the one caused by acute or chronic failure, hyperphosphaturia, or the like."

United State Patent No 6,710,072 teaches the use of EP2 agonists for the treatment or prevention of "osteoporosis, constipation, renal disorders, sexual dysfunction, baldness, diabetes, cancer and in disorder of immune regulation…various pathophysiological diseases including acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heart failure, and angina pectoris."

BRIEF DESCRIPTION OF THE INVENTION

Disclosed herein are compounds comprising



or a pharmaceutically acceptable salt or a prodrug thereof,

wherein a dashed line represents the presence or absence of a covalent bond;

Y is a carboxylic acid, sulfonic acid, or phosphonic acid; or an amide or ester thereof comprising from 0 to 12 carbon atoms; or Y is a hydroxymethyl, or tetrazolyl functional group;

A is $-(CH_2)_5-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is substituted or unsubstituted phenyl or monocyclic heteroaryl, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O;

X is C=O, CHF, CF_2, CHCl, or CHOH; wherein if X is CHOH, then OH is in the β-configuration;

R is a hydrocarbyl or a hydroxyhydrocarbyl moiety comprising from 1 to 12 carbon atoms;

D is independently a moiety comprising from 1 to 6 non-hydrogen atoms; and

n is an integer from 0 to 4.

A compound comprising a prostaglandin EP_2 selective agonist wherein the ω-chain comprises a substituted phenyl, wherein at least one substituent consists of hydrocarbyl or non-linear hydroxyhydrocarbyl, is also disclosed herein.

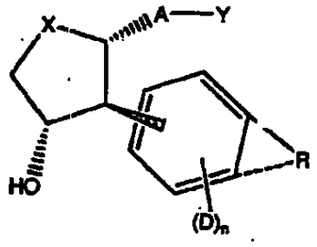
Methods, compositions, and medicaments related thereto are also disclosed.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

Figures 1-17 illustrate one way of preparing the compounds disclosed herein.

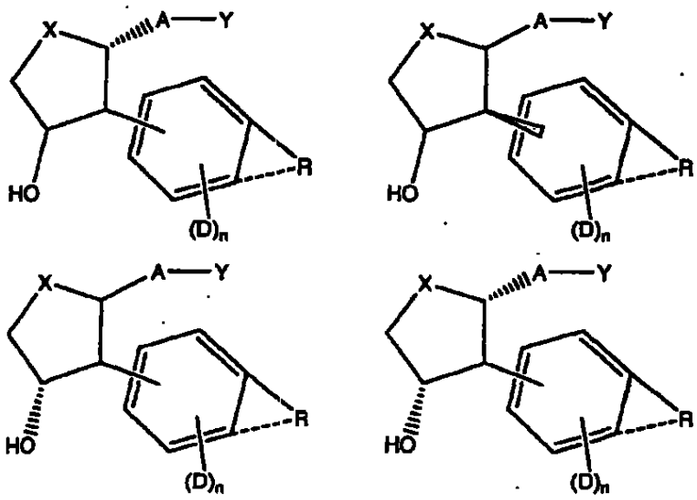
DETAILED DESCRIPTION OF THE INVENTION

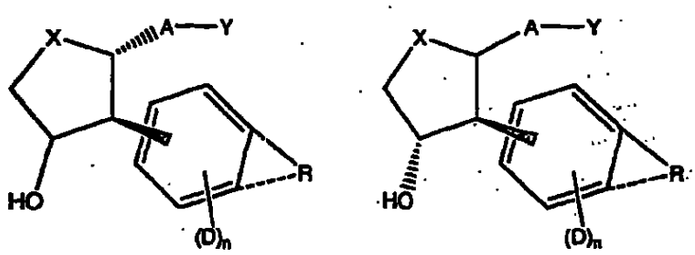
Several of the carbon atoms on these compounds are chiral centers. While not intending to limit the scope of the invention in any way, or be bound in any way by theory, it is believed that many compounds and pharmaceutically active salts or prodrugs thereof having the stereochemistry shown below are particularly useful.



A person of ordinary skill in the art understands the meaning of the stereochemistry associated with the hatched wedge/solid wedge structural features. For example, an introductory organic chemistry textbook (Francis A. Carey, Organic Chemistry, New York: McGraw-Hill Book Company 1987, p. 63) states "a wedge indicates a bond coming from the plane of the paper toward the viewer" and the hatched wedge, indicated as a "dashed line", "represents a bond receding from the viewer."

However, it is also advantageous if one or more of the bonds has the indicated stereochemistry, while the stereochemistry of other bonds to chiral centers may vary. Thus, while not intending to limit the scope of the invention in any way, compounds comprising





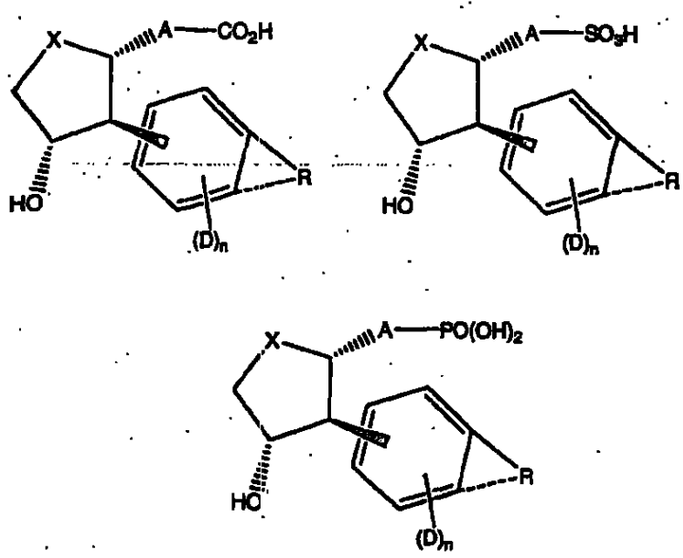
and the like, and pharmaceutically acceptable salts and prodrugs thereof, are particularly useful in the context disclosed herein.

A "pharmaceutically acceptable salt" is any salt that retains the activity of the parent compound and does not impart any additional deleterious or untoward effects on the subject to which it is administered and in the context in which it is administered compared to the parent compound. A pharmaceutically acceptable salt also refers to any salt which may form in vivo as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt.

Pharmaceutically acceptable salts of acidic functional groups may be derived from organic or inorganic bases. The salt may comprise a mono or polyvalent ion. Of particular interest are the inorganic ions, lithium, sodium, potassium, calcium, and magnesium. Organic salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Hydrochloric acid or some other pharmaceutically acceptable acid may form a salt with a compound that includes a basic group, such as an amine or a pyridine ring.

A "prodrug" is a compound which is converted to a therapeutically active compound after administration, and the term should be interpreted as broadly herein as is generally understood in the art. While not intending to limit the scope of the invention, conversion may occur by hydrolysis of an ester group or some other biologically labile group. Generally, but not necessarily, a prodrug is inactive or less active than the therapeutically active compound to which it is converted.

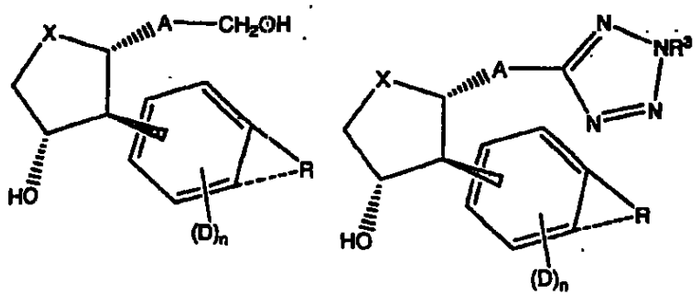
Y is a carboxylic acid, sulfonic acid, or phosphonic acid functional group; or an amide or ester thereof comprising from 0 to 12 carbon atoms; or Y is a hydroxymethyl, or tetrazolyl functional group. Thus, while not intending to limit the scope of the invention in any way, in certain compounds Y is a carboxylic acid, sulfonic acid, or phosphonic acid functional group, i.e. one of the structures shown below.



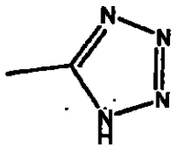
Salts of any of these acids of any pharmaceutically acceptable form may also be present.

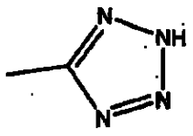
Additionally, an amide or ester of one of the organic acids shown above comprising from 0 to 12 carbon atoms is also contemplated. In an ester, a hydrocarbyl moiety replaces a hydrogen of an acid such as in a carboxylic acid ester, e.g. CO_2R^3. In an amide, an amine group replaces an OH of the acid. An amine is a moiety having a central nitrogen which has exactly three bonds to C or H. Examples of amides include $CON(R^3)_2$, $CON(OR^3)R^3$, $CON(CH_2CH_2OH)_2$, and $CONH(CH_2CH_2OH)$. Moieties such as $CONHSO_2R^3$ are also amides of the carboxylic acid notwithstanding the fact that they may also be considered to be amides of the sulfonic acid R^3-SO_2H.

Finally, while not intending to limit the scope of the invention in any way, Y may also be a hydroxymethyl, or a tetrazolyl functional group, i.e. compounds having a structure such as one of those shown below.

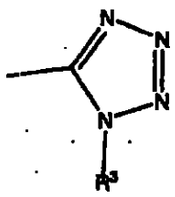


When R^3 is hydrogen, the tetrazolyl functional group has two tautomeric forms, which can rapidly interconvert in aqueous or biological media, and are thus equivalent to one another. These tautomers are shown below.





Additionally, if R^3 is C_1-C_6 alkyl, phenyl, or biphenyl, other isomeric forms of the tetrazolyl functional group such as the one shown below are also possible, all of these are considered to be within the scope of the term "tetrazolyl."

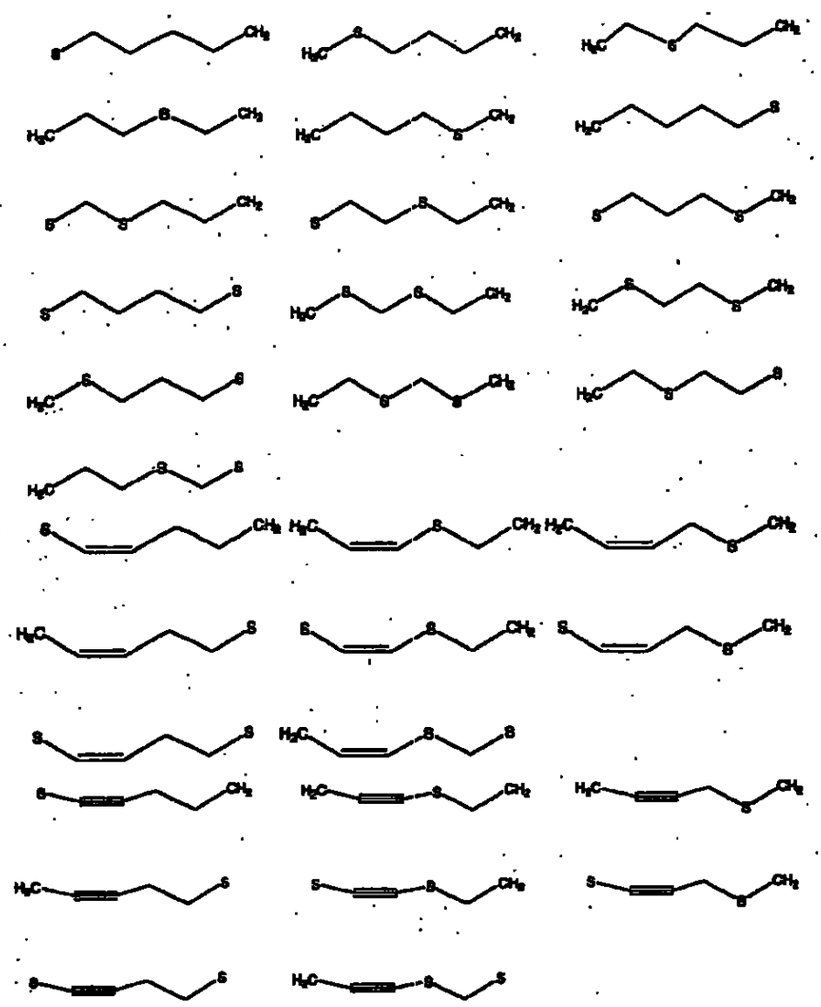


While not intending to limit the scope of the invention in any way, in one embodiment, Y is selected from the group consisting of $CO_2(R^2)$, $CON(R^2)_2$, $CON(OR^2)R^2$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH, $P(O)(OH)_2$, $CONHSO_2R^2$, $SO_2N(R^2)_2$, SO_2NHR^2, and tetrazolyl-R^2; wherein R^2 is independently H, C_1-C_6 alkyl, phenyl, or biphenyl.

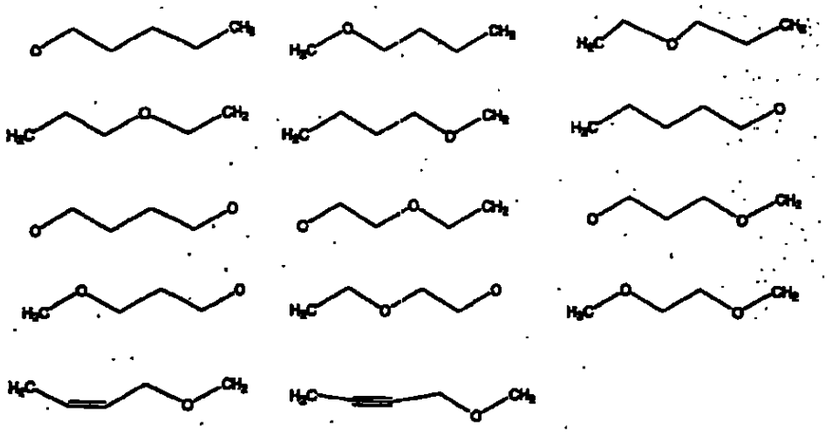
In relation to the identity of A disclosed in the chemical structures presented herein, in the broadest sense, A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is substituted or unsubstituted phenyl or monocyclic heteroaryl, the sum of m and o is from 1 to 3, and wherein one CH_2 may be substituted with S or O.

In other words, while not intending to be limiting, A may be $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$.

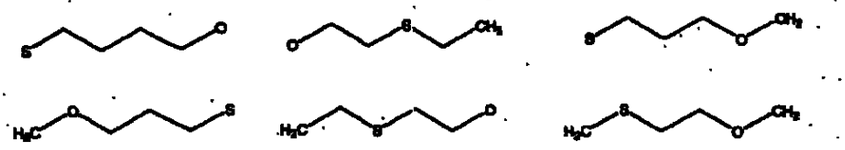
Alternatively, A may be a group which is related to one of these three moieties in that any carbon is substituted with S or O. For example, while not intending to limit the scope of the invention in any way, A may be an S substituted moiety such as one of the following or the like.



Alternatively, while not intending to limit the scope of the invention in any way, A may be an O substituted moiety such as one of the following or the like.



Alternatively, while not intending to limit the scope of the invention in any way, A may have both an O and an S substituted in the chain, such as one of the following or the like.



Alternatively, while not intending to limit the scope of the invention in any way, in certain embodiments A is $-(CH_2)_m$-Ar-$(CH_2)_o$- wherein Ar is substituted or unsubstituted phenyl or monocyclic heteroaryl, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O. In other words, while not intending to limit the scope of the invention in any way, A comprises from 1 to 4 CH_2 moieties and Ar, e.g. $-CH_2$-Ar-, $-(CH_2)_2$-Ar-, $-CH_2$-ArCH_2-, $-CH_2$Ar$(CH_2)_2$-, $-(CH_2)_2$-Ar$(CH_2)_2$-, and the like; or

A comprises O, from 0 to 3 CH_2 moieties, and Ar, as in for example, -O-Ar-, Ar-CH_2-O-, -O-Ar-$(CH_2)_2$-, -O-CH_2-Ar-, -O-CH_2-Ar-$(CH_2)_2$, and the like; or

A comprises S, from 0 to 3 CH_2 moieties, and Ar, as in for example, -S-Ar-, Ar-CH_2-S-, -S-Ar-$(CH_2)_2$-, -S-CH_2-Ar-, -S-CH_2-Ar-$(CH_2)_2$, and the like.

Ar is substituted or unsubstituted phenyl or substituted or unsubstituted monocyclic heteroaryl. In one embodiment, Ar is substituted or unsubstituted phenyl, thienyl, furyl, or pyridinyl. In another embodiment Ar is phenyl (Ph). In another embodiment A is $-(CH_2)_2$-Ph. While not intending to limit scope of the invention in any way, substituents may have 4 or less heavy atoms, or in other words, non hydrogen atoms. Any number of hydrogen atoms required for a particular substituent will also be included. Thus, the substituent may be C4 or lower hydrocarbyl, including C4 or lower alkyl, alkenyl, alkynyl, and the like; C3 or lower hydrocarbyloxy; CF_3; halo, such as F, Cl, or Br; hydroxyl; NH_2 and alkylamine functional groups up to C3; other N or S containing substituents; and the like.

In one embodiment A is $-(CH_2)_m$-Ar-$(CH_2)_o$- wherein Ar is phenyl, the sum of m and o is from 1 to 3, and wherein one CH_2 may be substituted with S or O.

In another embodiment A is $-CH_2$-Ar-OCH_2-. In another embodiment A is $-CH_2$-Ar-OCH_2- and Ar is phenyl.

In another embodiment A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_2$-Ph- wherein one CH_2 may be substituted with S or O.

In another embodiment A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_2$-Ph-.

D is a moiety comprising from 1 to 6 non-hydrogen atoms, in other words, there are from 1 to 6 atoms which are not hydrogen, and any number of hydrogen atoms required to form the complete substituent. For example, a methyl substituent has 1 carbon atom and 3 hydrogen atoms. Other example substituents include other hydrocarbyl moieties comprising from 1 to 6 carbon atoms including alkyl such as ethyl, propyl, isopropyl, butyl and isomers thereof, pentyl and isomers thereof, hexyl and isomers thereof; cyclic and unsaturated hydrocarbyls having 1 to 6 carbon atoms; CO_2H and salts thereof; alkoxy up to C_3 such as methoxy, ethoxy, propoxy, isopropoxy, a butoxy isomer, or a pentoxy isomer; carboxylic acid esters; CN; NO_2; CF_3; F; Cl; Br; I; sulfonyl esters; SO_3H and salts thereof; and the like. D may be in any reasonable position on the phenyl ring.

In certain compounds, n is 0. In other compounds n is 1, in other compounds n is 2, and in other compounds n is 3.

A hydrocarbyl moiety refers to a moiety consisting of only carbon and hydrogen. While not intending to limit the scope of the invention in any way, examples of different types of hydrocarbyl moiety are as follows.

One type of hydrocarbyl is alkyl including:

a) linear alkyl such as methyl, ethyl, propyl, n-butyl, n-pentyl, n-hexyl, and the like;

b) branched alkyl such as isopropyl, branched butyl isomers (i.e. sec-butyl, tert-butyl, etc), branched pentyl isomers (i.e. isopentyl, etc), branched hexyl isomers, and higher branched alkyl fragments;

c) cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.; and

d) alkyl fragments consisting of both cyclic and noncyclic components, whether linear or branched, which may be attached to the remainder of the molecule at any available position including terminal, internal, or ring carbon atoms.

In analogy to alkyl, there is linear, branched, cycloalkyl, and combination hydrocarbyl.

Another type of hydrocarbyl is alkenyl, which is similar to alkyl with the exception that a double bond is present.

Another type of hydrocarbyl is alk(poly)enyl, which is similar to alkenyl, except that more than one double bond is present.

Another type of hydrocarbyl is alkynyl or an alk(poly)ynyl, which is similar to alkenyl or alk(poly)ynyl except that one or more triple bonds are present.

Another type of hydrocarbyl is aryl, which includes phenyl, naphthyl and other aromatic hydrocarbyls.

Additionally, combinations of any of the above in any manner imaginable to those of ordinary skill in the art are also hydrocarbyl.

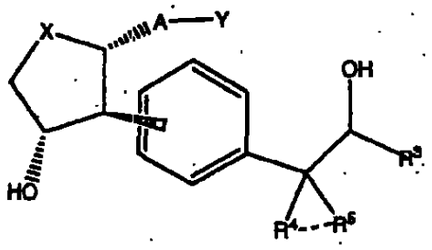
A hydrocarbyl moiety comprising a cyclic structure comprises a cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkyl(poly)enyl, cycloalkyl(poly)ynyl, aryl, and the like; and may consist of only the ring or may be a combination of the ring and one or more of the linear, branched, or cyclic hydrocarbyl fragments; or may be a fused polycyclic structure.

A hydroxyhydrocarbyl moiety consists of a combination of a hydrocarbyl moiety and a hydroxyl group. In other words, a hydrogen atom of the hydrocarbyl moiety is substituted with a hydroxyl group. The hydroxyhydrocarbyl moiety attaches to the remainder of the molecule at a carbon atom.

Thus, while not intending to limit the scope of the invention in any way, as R is a hydrocarbyl or a hydroxyhydrocarbyl moiety comprising from 1 to 12 atoms, embodiments having R as any of the hydrocarbyl or hydroxycarbyl moieties listed above are specifically contemplated herein. R may also be a different moiety which may be considered hydrocarbyl or hydroxyhydrocarbyl according to the description given herein.

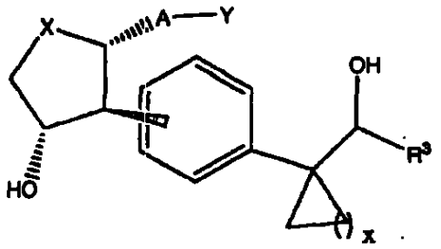
In certain compounds, R is a hydroxyhydrocarbyl having the hydroxyl group attached to the carbon atom which is also attached to the remainder of the molecule. In other words the hydroxyl group and the remainder of the molecule are on germinal positions on the hydrocarbyl moiety. This type of hydroxyhydrocarbyl moiety is referred to as a 1-hydroxyhydrocarbyl moiety herein. Non-linear hydroxyhydrocarbyl is hydroxyhydrocarbyl wherein the hydrocarbyl portion is not linear, i.e. it has branching and/or a ring.

In other compounds R is hydroxyhydrocarbyl having the hydroxyl group attached to a carbon atom which is directly attached to the remaining part of the molecule. These particular hydroxyhydrocarbyl are called 2-hydroxyhydrocarbyl herein. For example, $-C(CH_3)_2CH_2OH$ is 2-hydroxyhydrocarbyl. While not intending to limit the scope of the invention in any way, a general structure where R is 2-hydrocarbyl is shown below.



As with all other structures shown herein, pharmaceutically acceptable salts and prodrugs of compounds represent by these structures are also contemplated.

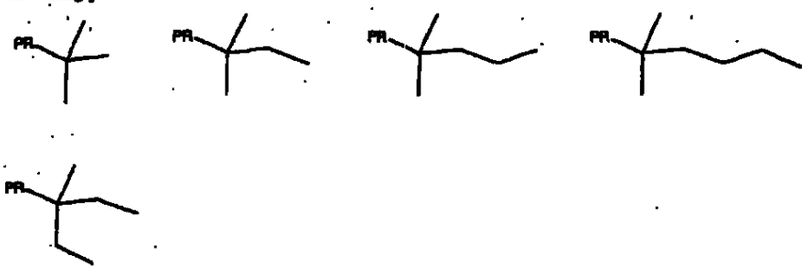
In one embodiment related to the above structure, R^3, R^4, and R^5 are independently H or C_{1-6} alkyl. As the dashed line indicates the presence or absence of a bond, R^4 and R^5 may be two separate moieties. For example, while not intending to be limiting, R^4 and R^5 may be methyl, and no bond would be present where indicated by the dashed line. Alternatively, while not intending to limit the scope of the invention in any way, R^4 and R^5 may form a ring. In other words, a compound such as the one shown below is possible, wherein x is from 1 to 6.

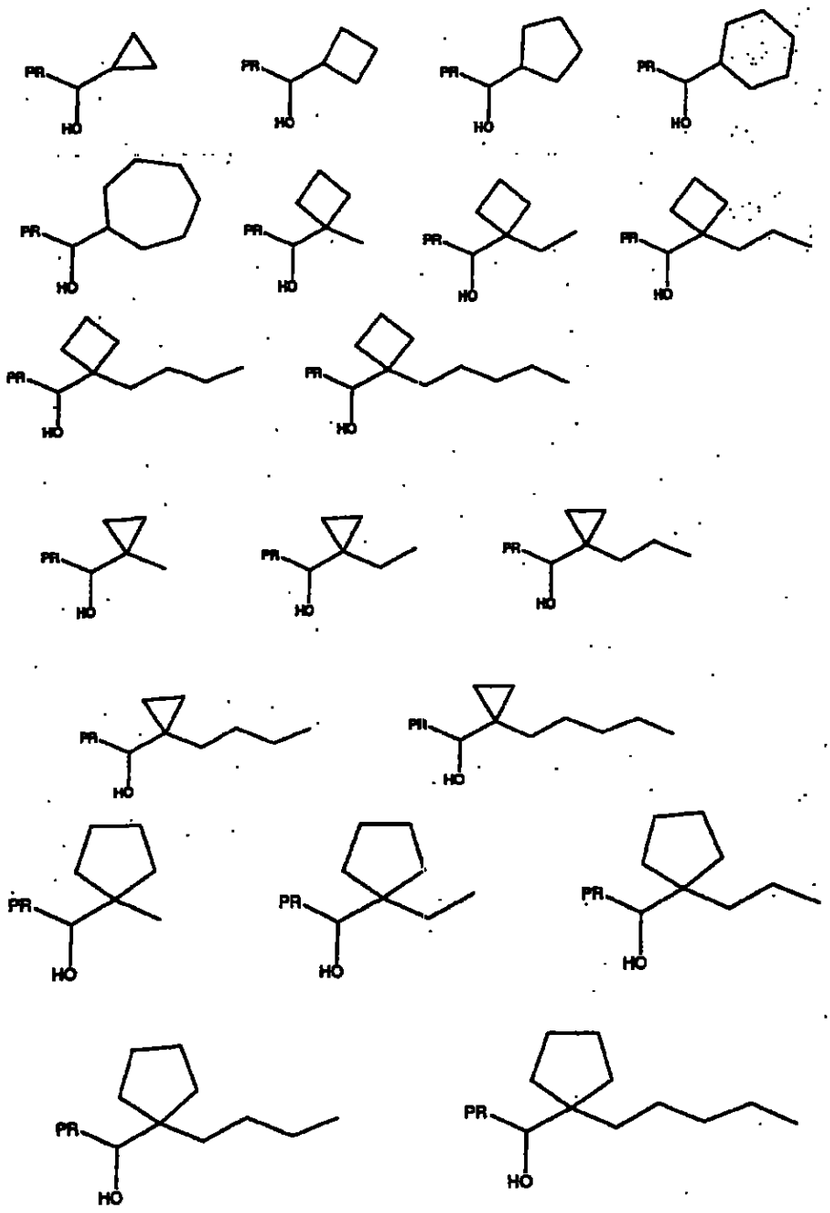


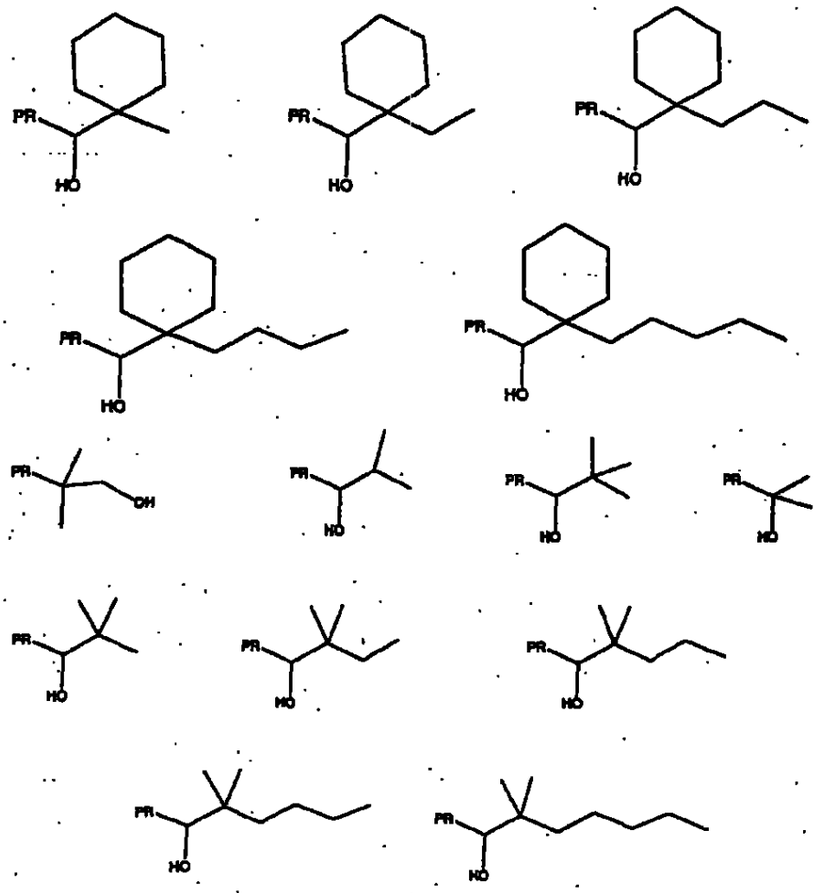
Pharmaceutically acceptable salts and prodrugs of compounds represent by these structures are also contemplated.

In certain compounds, R comprises from 6 to 9 carbon atoms and a cyclic structure. In other compounds, R comprises from 1 to 5 carbon atoms. In certain compounds R is hydroxyalkyl having from 1 to 5 carbon atoms. In other compounds R is a 1-hydroxyhydrocarbyl moiety comprising from 6 to 9 carbon atoms and a cyclic structure. In other compounds R is a 1-hydroxyhydrocarbyl moiety comprising from 6 to 9 carbon atoms and a cyclic structure comprising from 4-7 carbon atoms. In other words, the cyclic structure part of R is a cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl fragment. The cyclic structure part of R may also be a cycloalkenyl or cycloalkynyl fragment such as cyclopentene or cyclohexene. In other compounds R is a hydrocarbyl moiety comprising from 1 to 5 carbon atoms. In other words, R is methyl, ethyl, propyl, isopropyl, a butyl isomer such as t-butyl, or a pentyl isomer. In certain compounds R is t-butyl.

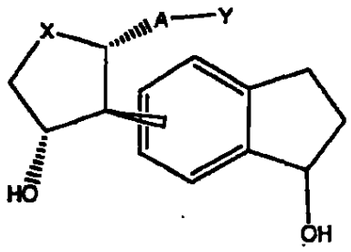
Certain R groups are specifically contemplated herein. These are shown below, where PR represents the remaining part of the molecule.




PR
HO

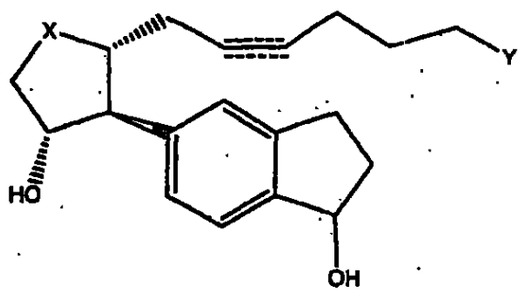


As there is a dashed line between R and the phenyl ring, cyclic structures having two carbon atoms of the phenyl ring are possible. While not intending to limit the scope of the invention in any way, compounds such as those represented by the structure below are therefore possible.



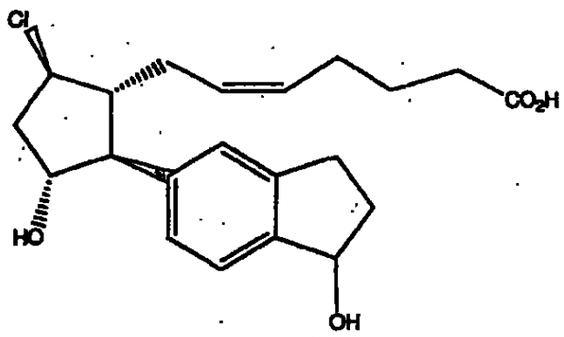
Pharmaceutically acceptable salts and prodrugs thereof are also contemplated.

Other useful compounds comprise



or a pharmaceutically acceptable salt, or a prodrug thereof.

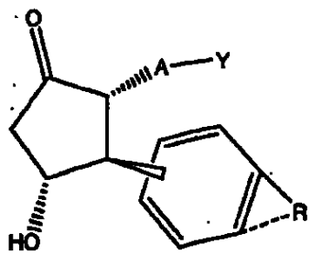
Other useful compounds comprise



or a pharmaceutically acceptable salt, or a prodrug thereof.

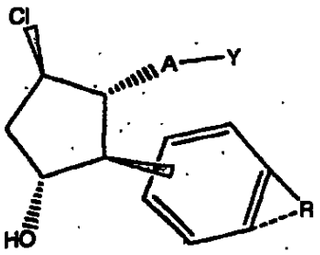
Those of ordinary skill in the art understand that any value which refers to the number of atoms, moieties, etc., on a small molecule will be an integer, i.e. 0, 1, 2, 3, etc.

Certain useful compounds comprise



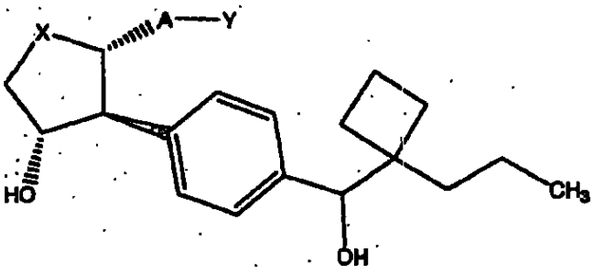
or a pharmaceutically acceptable salt, or a prodrug thereof.

Other useful compounds comprise



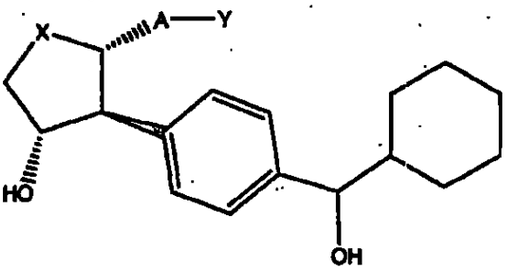
or a pharmaceutically acceptable salt, or a prodrug thereof.

Other useful examples of compounds comprise



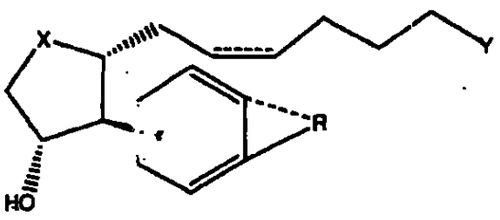
or a pharmaceutically acceptable salt, or a prodrug thereof.

Other compounds comprise



or a pharmaceutically acceptable salt, or a prodrug thereof.

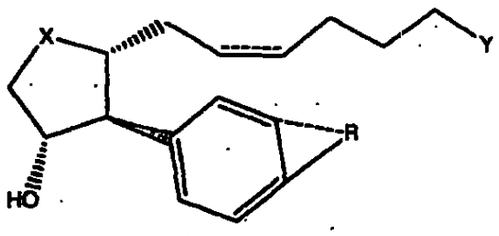
Other embodiments comprise



or a pharmaceutically acceptable salt, or a prodrug thereof,

wherein a dashed line indicates the presence or absence of a bond.

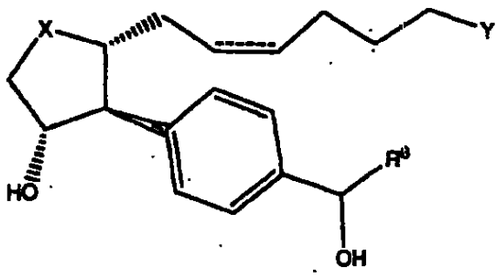
Other compounds comprise



wherein X is C=O or CHCl; and

R is alkyl having from 3 to 6 carbon atoms.

Other compounds comprise

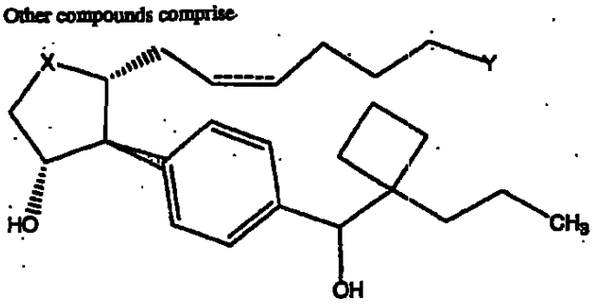


or a pharmaceutically acceptable salt, or a prodrug thereof,

wherein R^6 is cycloalkyl comprising from 3 to 10 carbon atoms; and

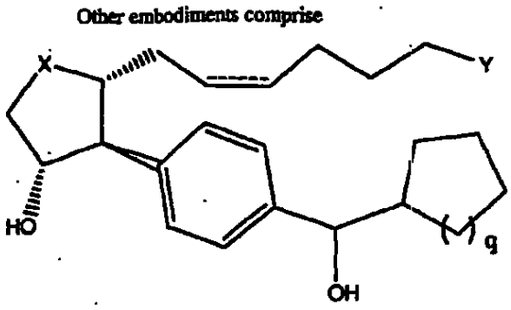
X is C=O or CHCl.

Other compounds comprise



or a pharmaceutically acceptable salt, or a prodrug thereof.

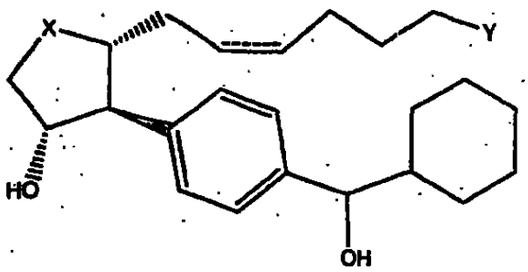
Other embodiments comprise



or a pharmaceutically acceptable salt, or a prodrug thereof

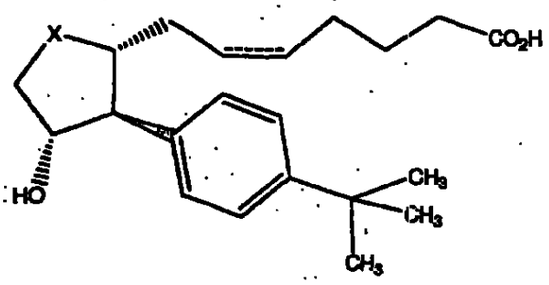
wherein q is an integer having a value of from 0 to 3.

Other compounds comprise



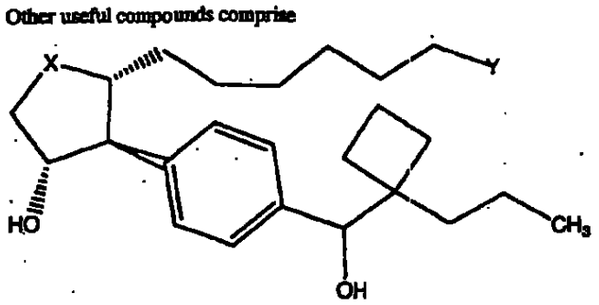
or a pharmaceutically acceptable salt, or a prodrug thereof.

Other compounds comprise



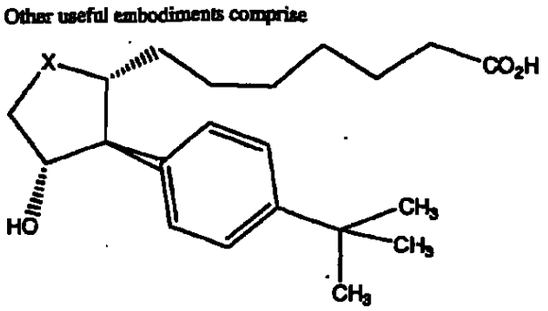
or a pharmaceutically acceptable salt, or a prodrug thereof.

Other useful compounds comprise



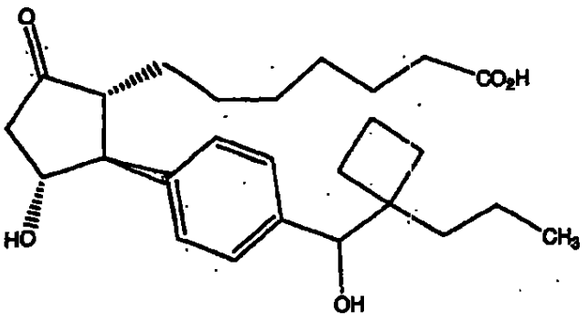
or a pharmaceutically acceptable salt, or a prodrug thereof.

Other useful embodiments comprise



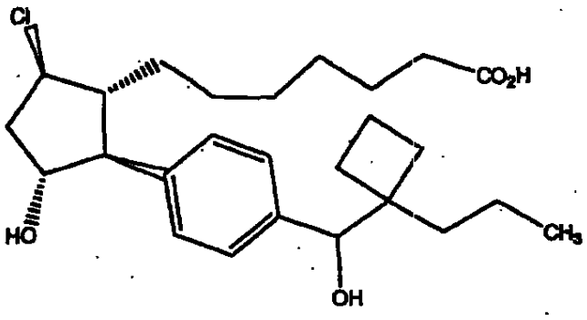
or a pharmaceutically acceptable salt, or a prodrug thereof.

Another useful compound is



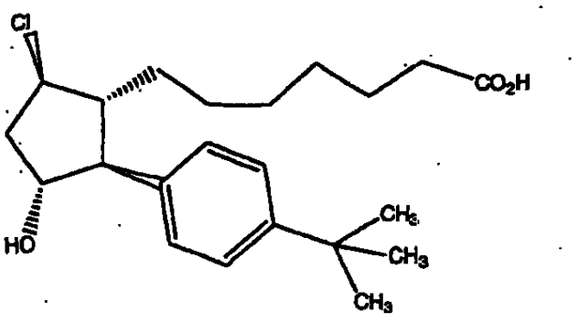
or a pharmaceutically acceptable salt, or a prodrug thereof.

Another useful compound is



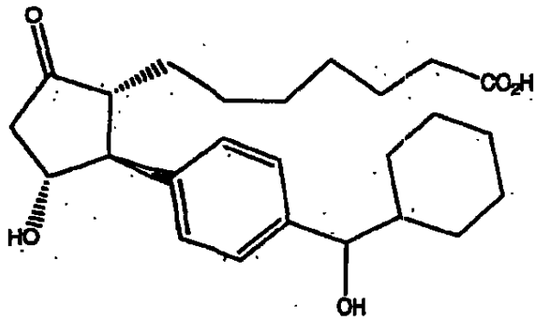
or a pharmaceutically acceptable salt, or a prodrug thereof.

Another useful compound is



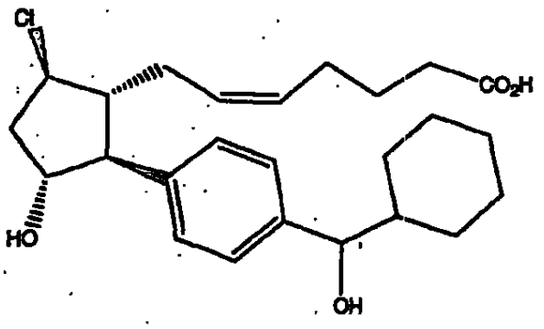
or a pharmaceutically acceptable salt, or a prodrug thereof.

Another useful compound is



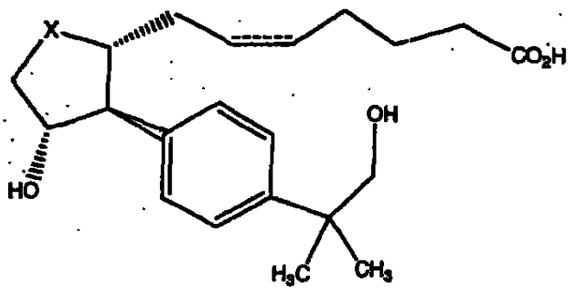
or a pharmaceutically acceptable salt, or a prodrug thereof.

Another useful compound is



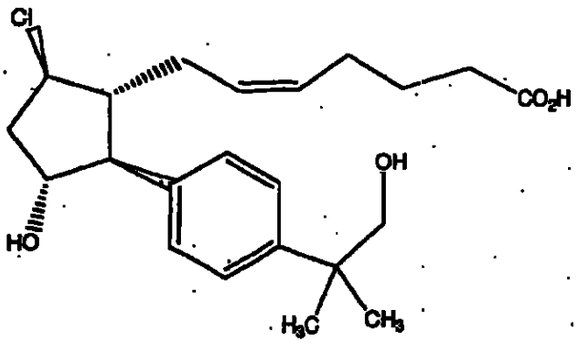
or a pharmaceutically acceptable salt, or a prodrug thereof.

Certain compounds comprise



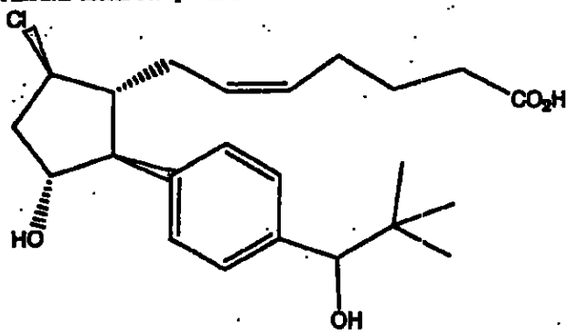
or a pharmaceutically acceptable salt or a prodrug thereof.

Other compounds comprise



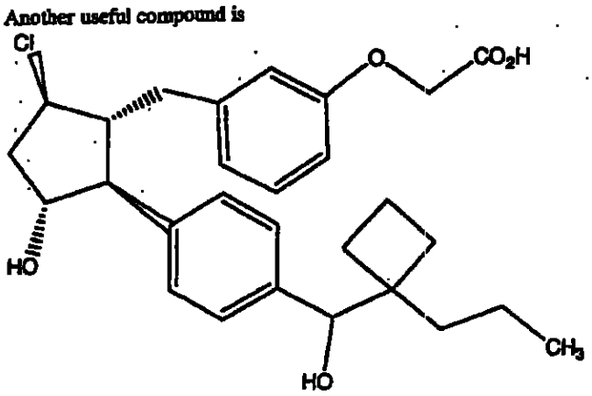
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



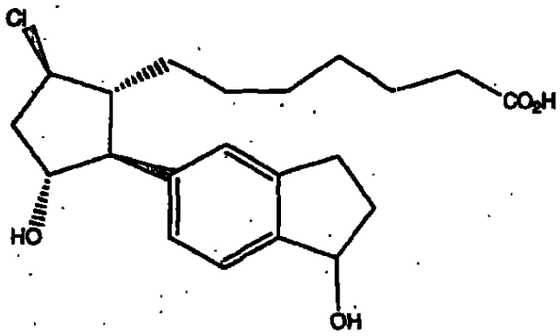
or a pharmaceutically acceptable salt, or a prodrug thereof.

Another useful compound is



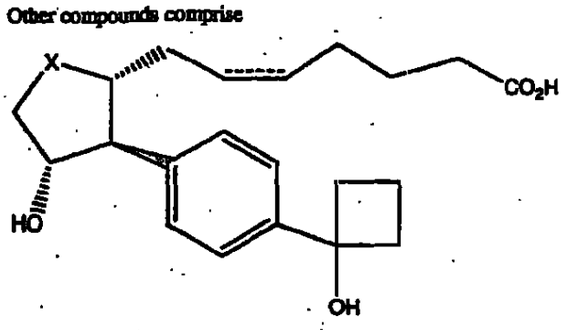
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



or a pharmaceutically acceptable salt or a prodrug thereof.

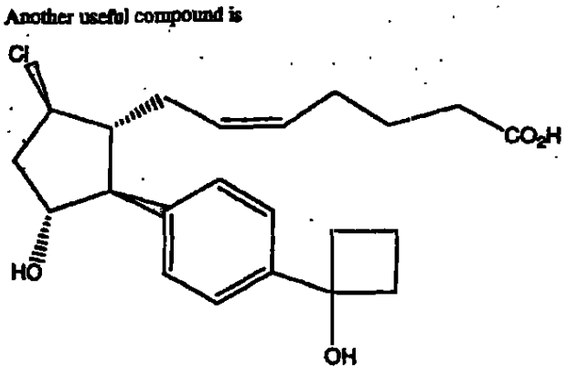
Other compounds comprise



or a pharmaceutically acceptable salt or a prodrug thereof

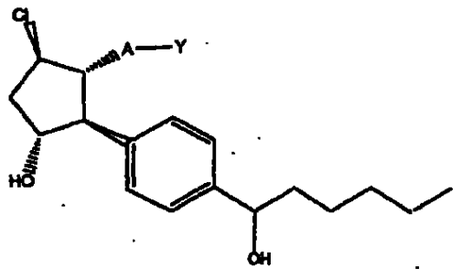
wherein X is C=O or CHCl.

Another useful compound is



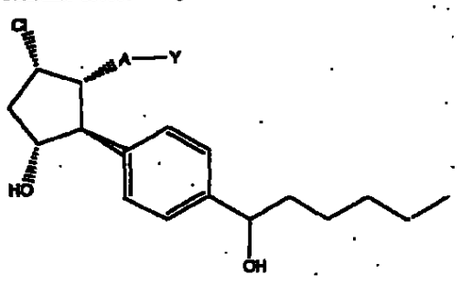
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



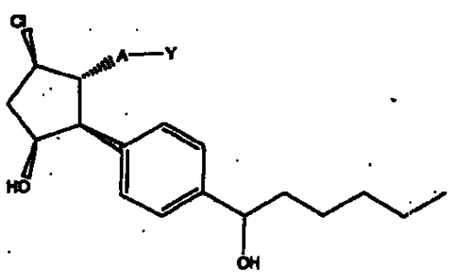
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



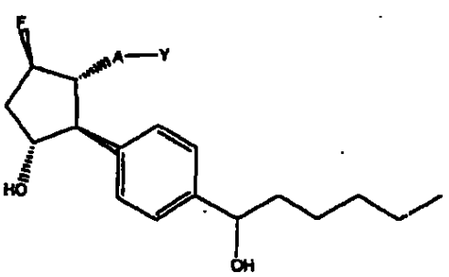
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



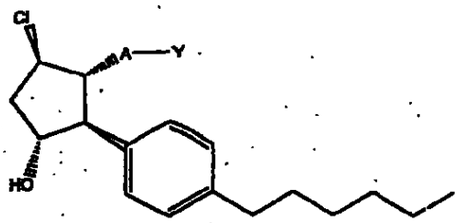
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



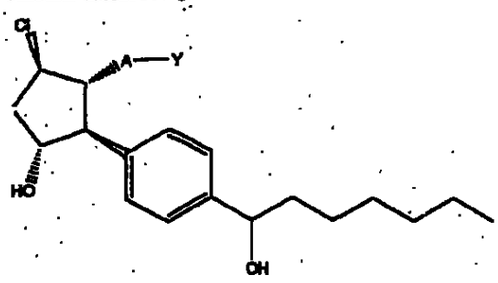
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



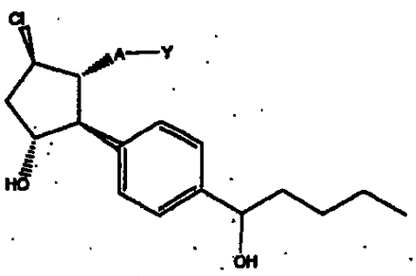
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



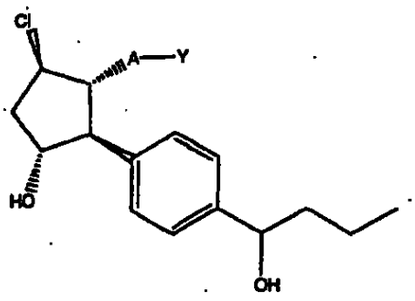
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



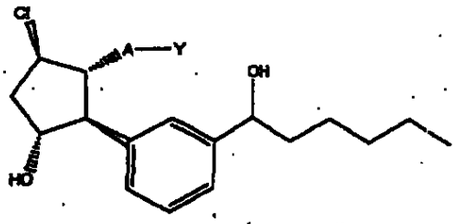
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



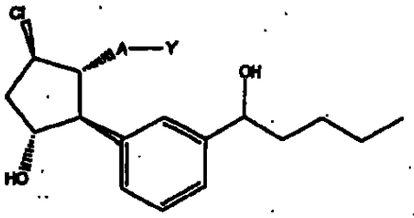
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



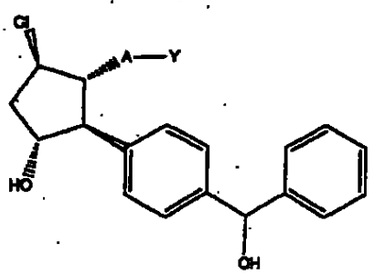
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



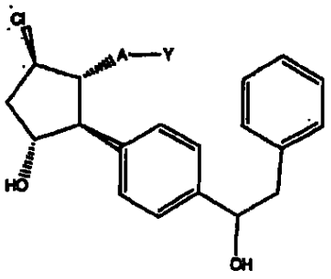
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



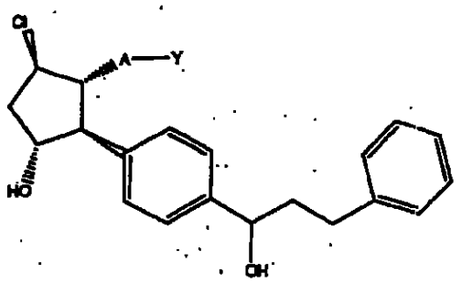
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



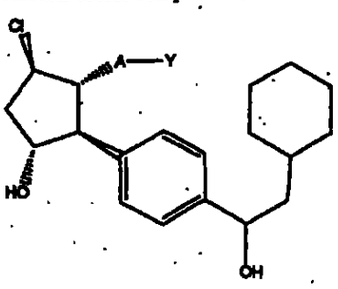
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



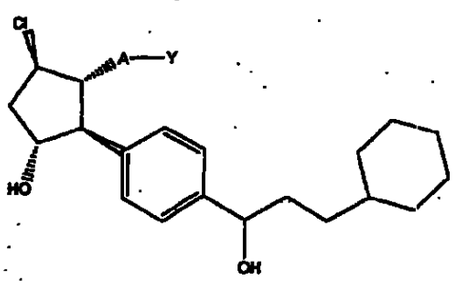
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



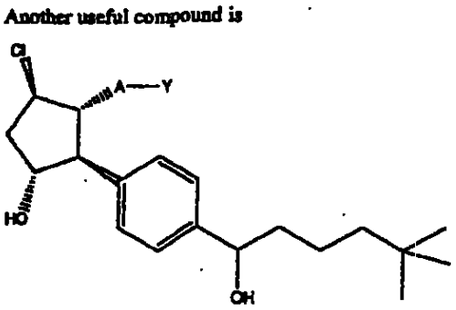
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



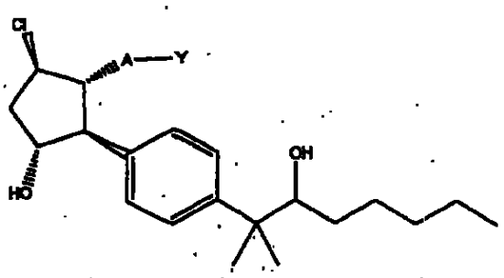
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



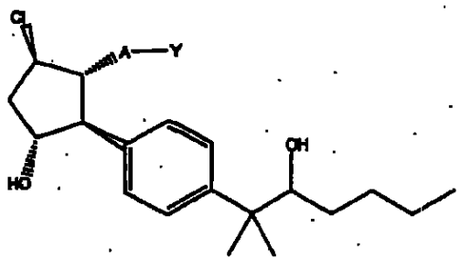
or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



or a pharmaceutically acceptable salt or a prodrug thereof.

Another useful compound is



or a pharmaceutically acceptable salt or a prodrug thereof.

These compounds can be used any compositions, methods, or medicaments contemplated for any other compound disclosed herein.

Other compounds comprise

(Z)-7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-hept-5-enoic acid methyl ester (5-4);

(Z)-7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-hept-5-enoic acid (5-5);

7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-heptanoic acid methyl ester (5-7);

7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-heptanoic acid (5-8);

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester;

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid;

7-((1R,2S,3R)-3-Hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid methyl ester;

7-((1R,2S,3R)-3-Hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid;

(Z)-7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-hept-5-enoic acid;

7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-heptanoic acid methyl ester;

7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-heptanoic acid. (Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-5-oxo-cyclopentyl}-hept-5-enoic acid methyl ester; (Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-5-oxo-cyclopentyl}-hept-5-enoic acid; 7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid methyl ester; 7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid; (Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-5-oxo-cyclopentyl}-hept-5-enoic acid methyl ester (e1-2); 7-{(1R,2S,3R)-3-Hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid methyl ester; 7-{(1R,2S,3R)-3-Hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid; (Z)-7-{(1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester; (Z)-7-{(1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid (e2-1); 7-{(1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid methyl ester; 7-{(1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid; (Z)-7-{(1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid (2-hydroxy-ethyl)-amide (e2-2, R = 2-hydroxyethyl); (Z)-7-{(1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid ethyl amide (e2-2, R = ethyl); (Z)-7-{(1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid ethyl amide (e2-2, R = H); (Z)-7-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-hept-5-enoic acid methyl ester (6-3); (Z)-7-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-hept-5-enoic acid (6-4); (Z)-7-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-hept-5-enoic acid isopropyl ester (6-5); 7-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-heptanoic acid methyl ester (6-6); 7-[(1R,2S,3R,5R)-5-Chloro-2-(4-cyclohexylmethyl-phenyl)-3-hydroxy-cyclopentyl]-heptanoic acid methyl ester (6-8); 7-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-heptanoic acid (6-7); 7-[(1R,2S,3R,5R)-5-Chloro-2-(4-cyclohexylmethyl-phenyl)-3-hydroxy-cyclopentyl]-heptanoic acid (6-9); (Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-hept-5-enoic acid methyl ester;

(Z)-7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-hept-5-enoic acid;

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-heptanoic acid methyl ester;

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-heptanoic acid;

(Z)-7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-hept-5-enoic acid methyl ester;

(Z)-7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-hept-5-enoic acid;

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-heptanoic acid methyl ester;

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-heptanoic acid;

(Z)-7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-hept-5-enoic acid;

7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-heptanoic acid methyl ester;

7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-heptanoic acid;

(Z)-7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-hept-5-enoic acid isopropyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl}-hept-5-enoic acid;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl}-heptanoic acid;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-hept-5-enoic acid;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-heptanoic acid;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-heptanoic acid isopropyl ester;

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-hept-5-enoic acid methyl ester (7-5);

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-hept-5-enoic acid (7-6);

7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-heptanoic acid methyl ester (7-7);

7-((1R,2S,3R)-3-Hydroxy-5-oxo-2-*p*-tolyl-cyclopentyl)-heptanoic acid methyl ester (7-9);

7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-heptanoic acid (7-8);

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-hept-5-enoic acid methyl ester (8-4);
(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-hept-5-enoic acid (8-5);
7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-heptanoic acid methyl ester (8-6);
7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-heptanoic acid (8-7);
(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester (9-5);
(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester (9-6);
(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (9-7);
(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (9-8);
7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester (9-9);
7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester (9-10);
7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid (9-11);
7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid (9-12);
(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-ynyloxy)-acetic acid methyl ester (10-6);
(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-ynyloxy)-acetic acid (10-7);
((Z)-4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-enyloxy)-acetic acid methyl ester (11-1);
((Z)-4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-enyloxy)-acetic acid (11-2);
(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-butoxy)-acetic acid methyl ester (11-3);
(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-butoxy)-acetic acid (11-4);
[3-((1R,2S,3R)-3-Hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentylmethyl)-phenoxy]-acetic acid methyl ester (13-3);
[3-((1R,2S,3R)-3-Hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentylmethyl)-phenoxy]-acetic acid (13-4);
[3-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentylmethyl)-phenoxy]-acetic acid methyl ester (14-3);

[3-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentylmethyl)-phenoxy]-acetic acid (14-4);

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-hept-5-enoic acid methyl ester (15-6);

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-hept-5-enoic acid (15-7);

(Z)-7-[(1R,2S,3R)-3-Hydroxy-5-oxo-2-(1-oxo-indan-5-yl)-cyclopentyl]-hept-5-enoic acid methyl ester (15-8);

(Z)-7-[(1R,2S,3R)-3-Hydroxy-5-oxo-2-(1-oxo-indan-5-yl)-cyclopentyl]-hept-5-enoic acid (15-9);

7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-heptanoic acid methyl ester (15-10);

7-((1R,2S,3R)-3-Hydroxy-2-indan-5-yl-5-oxo-cyclopentyl)-heptanoic acid methyl ester (15-12);

7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-heptanoic acid (15-11);

7-((1R,2S,3R)-3-Hydroxy-2-indan-5-yl-5-oxo-cyclopentyl)-heptanoic acid (15-13);

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid methyl ester (16-4);

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid (16-5);

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid isopropyl ester (16-6);

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid methyl ester (16-7);

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-indan-5-yl-cyclopentyl)-heptanoic acid methyl ester (16-9);

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid (16-8);

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-indan-5-yl-cyclopentyl)-heptanoic acid (16-10);

7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid methyl ester (17-3);

7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid (17-4);

(Z)-7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid methyl ester (17-5);

(Z)-7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid (17-6);

3-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-benzoic acid (18-13);

3-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-benzoic acid ethyl ester;

5-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-thiophene-2-carboxylic acid (102);

5-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-thiophene-2-carboxylic acid methyl ester;

5-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-thiophene-2-carboxylic acid isopropyl ester;

3-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentylmethyl}-phenyl)-propionic acid (20-5);

3-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentylmethyl}-phenyl)-propionic acid methyl ester;

3-{3-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentylmethyl)-phenyl]-propionic acid (104);

3-[3-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl, cyclopentylmethyl)-phenyl]-propionic acid methyl ester;

2-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-thiazole-5-carboxylic acid (21-7);

2-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-thiazole-5-carboxylic acid ethyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Fluoro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (22-3);

(Z)-7-[(1R,2S,3R,5R)-5-Fluoro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5S)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (23-5);

(Z)-7-[(1R,2S,3R,5S)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester (110);

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (24-4);

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid isopropyl ester;

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-heptanoic acid (114);

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(3-cyclohexyl-1-hydroxy-propyl)-phenyl]-3-hydroxy-cyclopentyl}-hept-5-enoic acid (115);

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(3-cyclohexyl-1-hydroxy-propyl)-phenyl]-3-hydroxy-cyclopentyl}-hept-5-enoic acid methyl ester;

7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(3-cyclohexyl-1-hydroxy-propyl)-phenyl]-3-hydroxy-cyclopentyl}-heptanoic acid (116);

7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(3-cyclohexyl-1-hydroxy-propyl)-phenyl]-3-hydroxy-cyclopentyl}-heptanoic acid methyl ester;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(2-cyclohexyl-1-hydroxy-ethyl)-phenyl]-3-hydroxy-cyclopentyl}-hept-5-enoic acid (117);

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(2-cyclohexyl-1-hydroxy-ethyl)-phenyl]-3-hydroxy-cyclopentyl}-hept-5-enoic acid methyl ester;

7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(2-cyclohexyl-1-hydroxy-ethyl)-phenyl]-3-hydroxy-cyclopentyl}-heptanoic acid (118);

7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(2-cyclohexyl-1-hydroxy-ethyl)-phenyl]-3-hydroxy-cyclopentyl}-heptanoic acid methyl ester;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-5,5-dimethyl-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-5,5-dimethyl-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (119);

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-5,5-dimethyl-hexyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-5,5-dimethyl-hexyl)-phenyl]-cyclopentyl}-heptanoic acid (120);

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-phenyl-ethyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-phenyl-ethyl)-phenyl]-cyclopentyl}-hept-5-enoic acid isopropyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-phenyl-ethyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (121);

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-phenyl-ethyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-phenyl-ethyl)-phenyl]-cyclopentyl}-heptanoic acid (122);

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-3-phenyl-propyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-3-phenyl-propyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (123);

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-3-phenyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-3-phenyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid (124);

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-heptyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-heptyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (125);

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-butyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-butyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (126);

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-butyl)-phenyl]-cyclopentyl}-hept-5-enoic acid isopropyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-pentyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-pentyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (127);

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(hydroxy-phenyl-methyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(hydroxy-phenyl-methyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (128);

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[3-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[3-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (129);

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[3-(1-hydroxy-pentyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[3-(1-hydroxy-pentyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (130);

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-heptyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-heptyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (131);

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (132);

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid (26-2);

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid isopropyl ester; and

(Z)-7-{(1R,2S,3S,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (211217).

A prostaglandin EP_2 selective agonist is a compound which is more active at a prostaglandin EP_2 receptor than at any other prostaglandin receptor.

One embodiment is a compound comprising a prostaglandin EP_2 selective agonist wherein the ω-chain comprises a substituted phenyl, wherein at least one substituent consists of hydrocarbyl or non-linear hydroxyhydrocarbyl, wherein said compound is effective in reducing IOP in a monkey by at least 20%.

Reducing IOP in a monkey as used herein is intended to mean reducing IOP using the method disclosed herein.

In one embodiment, the compound has an IC_{50} value less than 1 μM. In another embodiment, the compound is more than 100 times more active at the EP_2 receptor than at any other receptor. In another embodiment, the compound is more than 1000 times more active at the EP_2 receptor than at any other receptor.

The ω-chain has the meaning normally understood in the art. In prostaglandin E_2, the ω-chain is in the third position of the cyclopentanone ring, where the position 1 is the carbonyl and the α-chain is at position 2. However, the meaning of the term α-chain should be adapted according to synthetic variations that are made to prostaglandin E_2. A person of ordinary skill in the art can readily discern the ω-chain in synthetic analogs and derivatives of prostaglandin E_2. For example, while not intending to limit the scope of the invention in any way, the ω-chain could be at the third position in a 1-chlorocyclopentane having the α-chain in the 2 position.

A substituted phenyl, wherein at least one substituent consists of hydrocarbyl or non-linear hydroxyhydrocarbyl may have additional substituents which are not hydrocarbyl or non-linear hydroxyhydrocarbyl, i.e. at least one substituent is hydrocarbyl or non-linear hydroxyhydrocarbyl and at least one substituent is not.

The compounds of disclosed herein are useful for the prevention or treatment of glaucoma or ocular hypertension in mammals, or for the manufacture of a medicament for the treatment of glaucoma or ocular hypertension. They are also useful for the treatment of those diseases disclosed in the art as being amenable to treatment by prostaglandin EP_2 agonist, such as the ones listed previously.

Those skilled in the art will readily understand that for administration or the manufacture of medicaments the compounds disclosed herein can be admixed with pharmaceutically acceptable excipients which per se are well known in the art. Specifically, a drug to be administered systemically, it may be confected as a powder, pill, tablet or the like, or as a solution, emulsion, suspension, aerosol, syrup or elixir suitable for oral or parenteral administration or inhalation.

For solid dosage forms or medicaments, non-toxic solid carriers include, but are not limited to, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, the polyalkylene glycols, talcum, cellulose, glucose, sucrose and magnesium carbonate. The solid dosage forms may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the presently useful compounds and optional pharmaceutical adjutants in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Typical examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 16th Edition, 1980. The composition of the formulation to be administered, in any event, contains a quantity of one or more of the presently useful compounds in an amount effective to provide the desired therapeutic effect.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol and the like. In addition, if desired, the injectable pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like.

The amount of the presently useful compound or compounds administered is, of course, dependent on the therapeutic effect or effects desired, on the specific mammal being treated, on the severity and nature of the mammal's condition, on the manner of administration, on the potency and pharmacodynamics of the particular compound or compounds employed, and on the judgment of the prescribing physician. The therapeutically effective dosage of the presently useful compound or compounds is preferably in the range of about 0.5 or about 1 to about 100 mg/kg/day.

A liquid which is ophthalmically acceptable is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable: Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	1-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

Example 1

1-Propyl-cyclobutanecarboxylic acid methyl ester (1-2). Ester 1-1 (2.043 g, 15.9 mmol) was added to a -78 °C solution of LDA (8 mL, 16 mmol, 2 M in heptane/THF/ethyl benzene) in THF (16 mL), rinsing with 1 mL THF. The reaction was stirred for 30 min. at -78 °C and then was allowed to warm to room temperature. The enolate solution was then added, by cannula, to a solution of *n*-propyl iodide (4.087 g, 24 mmol) in 8 mL DMSO. The internal temperature was maintained between 16-20 °C by cooling with an ice-bath. After 1 h, The solvent was removed and the residue diluted with H_2O (150 mL). The resulting mixture was extracted with hexanes (2 x 120 mL) and the combined organic solution was washed with 2% HCl (100 mL) and brine (100 mL). The organic solution was then dried (Na_2SO_4), filtered and evaporated. The crude product was combined with the crude product from another reaction run (starting with 14.858 g, 116 mmol of 1-1) and the combined product was purified by simple distillation under reduced pressure to give 1-2 (9.744 g, 49%).

(1-Propyl-cyclobutyl)-methanol (1-3). $LiBH_4$ (524 mg, 24 mmol) and methanol (1 mL) were added to a 0 °C solution of 1-2 (1.935 g, 11.4 mmol) in ether (22 mL). After 1 h at 0 °C and 1.5 h at room temperature, 41 mL 2 M NaOH was slowly added and the resulting mixture was stirred for 1 h. The mixture was then extracted with dichloromethane (3 x 40 mL) and the combined dichloromethane solution was washed with saturated NH_4Cl solution and brine (150 mL each). The organic solution was then dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (dichloromethane) gave 1-3 (1.229 g, 87%).

1-Propyl-cyclobutanecarbaldehyde (1-4). An ice-cold mixture of 4-methylmorpholine N-oxide (NMO) (1.683 g, 14.4 mmol), 1-3 (1.229 g, 9.59 mmol) and 4Å molecular sieves (5.5 g) in dichloromethane (20 mL) was treated with tetrapropylammonium perruthenate (TPAP) (179 mg, 0.51 mmol). The mixture was stirred at 0 °C for 5 min. and then was allowed to warm to room temperature. After 1 h, the mixture was filtered through a pad of silica gel (dichloromethane) and the dichloromethane was evaporated. The crude product was combined with the crude product from another batch (starting with 4.986 g, 38.9 mmol of 1-3) and the combined product was purified by distillation under reduced pressure followed by flash chromatography on silica gel (15% ether/pentane) to give 1-4 (2.649 g, 43%).

2-(4-Bromo-phenyl)-2-methyl-propan-1-ol (2-2). $LiBH_4$ (387 mg, 17.8 mmol) and methanol (0.75 mL) were added to a 0 °C solution of 2-1 (2.07 g, 8.05 mmol) in ether (75 mL). After 30 min. at 0 °C and 1.5 h at room temperature, the reaction was quenched by slow addition of 40 mL 2 M NaOH. The layers were separated and the aqueous layer was further extracted with dichloromethane (3 x 40 mL). The combined organic solution was washed with brine and then was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (20% ethyl acetate/hexanes) gave 2-2 (1.780 g, 97%).

[2-(4-Bromo-phenyl)-2-methyl-propoxy]-*tert*-butyl-dimethyl-silane (2-3). TBSOTf (2.9 mL, 12.6 mmol) was added to a 0 °C solution of 2-2 (1.893 g, 8.26 mmol) and 2,6-lutidine (2.9 mL, 24.9 mmol) in dichloromethane (24 mL). The reaction was allowed to warm to room temperature and after 1h, 50 mL saturated $NaHCO_3$ solution was added. The resulting mixture was extracted with ethyl acetate (3 x 60 mL) and the combined ethyl acetate solution was washed with brine. The solution was then dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (hexanes) gave 2-3 (2.767 g, 98%).

1-(4-Bromo-phenyl)-cyclobutanol (3-1). *n*-Butyllithium (1.2 mL 1.92 mmol, 1.6 M/hexanes) was added to a -78 °C solution of 1,4-dibromobenzene (489 mg, 2.07 mmol) in THF (4.2 mL). After 30 min., a solution of cyclobutanone

(141 mg, 2.01 mmol) in 1 mL THF was added by cannula, rinsing with 0.5 mL THF. The reaction was allowed to warm to room temperature and after 2 h, saturated NH_4Cl solution was added. The resulting mixture was extracted with ethyl acetate (3 x 30 mL) and the combined ethyl acetate solution was washed with brine. The solution was then dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (5% → 10% ethyl acetate/hexanes) gave 3-1 (235 mg, 54%).

[1-(4-Bromo-phenyl)-cyclobutoxy]-*tert*-butyl-dimethyl-silane (3-2). TBSOTf (360 µL, 1.57 mmol) was added to a 0 °C solution of 3-1 (235 mg, 1.04 mmol) and triethylamine (450 µL, 3.23 mmol) in dichloromethane (3 mL). The reaction was allowed to warm to room temperature and after 1h, saturated $NaHCO_3$ solution was added. The resulting mixture was extracted with ethyl acetate (3 x 30 mL) and the combined ethyl acetate solution was washed with brine. The solution was then dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (hexanes) gave 3-2 (329 mg, 93%).

Representative procedure for reaction of dibromobenzene with aldehydes: (4-Bromo-phenyl)-cyclohexyl-methanol (4-2, R = cyclohexyl, para substitution). *n*-BuLi (14.4 mL, 23 mmol) was added to a -78 °C solution of 1,4-dibromobenzene (5.442 g, 23.1 mmol) in THF (48 mL). The resulting mixture was stirred for 30 min. and then a solution of cyclohexanecarboxaldehyde (2.9 mL, 24.1 mmol) in THF (10 mL) was added by cannula. The resulting cloudy solution was allowed to warm to room temperature and was stirred further for 2 h. Saturated NH_4Cl solution (200 mL) was then added and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined ethyl acetate solution was washed with brine (150 mL) and then was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (10% ethyl acetate/hexanes → 15% → 20%) gave the title alcohol (5.095 g, 18.9 mmol, 82%).

Representative procedure for TBS protection of bottom chain alcohols: [(4-Bromo-phenyl)-cyclohexyl-methoxy]-*tert*-butyl-dimethyl-silane (4-3, R = cyclohexyl, para substitution). An ice-cold solution of 4-2 (5.095 g, 18.9 mmol) was treated with 2,6-lutidine (2.9 mL, 24.9 mmol) and TBSOTf (5.2 mL, 22.6 mmol). After 2 h, 100 mL saturated $NaHCO_3$ solution was added and the resulting mixture was extracted with 50 mL dichloromethane. The dichloromethane solution was washed with 1 M HCl (100 mL) and 100 mL brine and then was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel gave the title TBS ether (6.772 g, 17.7 mmol, 94%).

[(4-Bromo-phenyl)-(1-propyl-cyclobutyl)-methoxy]-*tert*-butyl-dimethyl-silane (4-3, R = 1-propylcyclobutyl, para substitution). This compound was prepared using the representative sequence (figure 4), starting with 1,4-dibromobenzene and aldehyde 1-4.

[(3-Bromo-phenyl)-(1-propyl-cyclobutyl)-methoxy]-*tert*-butyl-dimethyl-silane (4-3, R = 1-propylcyclobutyl, meta substitution). This compound was prepared using the representative sequence (figure 4), starting with 1,3-dibromobenzene and aldehyde 1-4.

Representative procedure for 2-component coupling: (Z)-7-((1R,2S,3R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-{4-[(*tert*-butyl-dimethyl-silanyloxy)-cyclohexyl-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester (5-3). *n*- BuLi (1.1 mL, 1.76 mmol, 1.6 M/hexanes) was added to a -78 °C solution of thiophene (195 mg, 2.32 mmol) in ether (2 mL). The reaction was allowed to stir at 0 °C for 1 h and then was recooled to -78 °C. The resulting solution of the lithio thiophene was cannula transferred to a mixture of CuCN (226 mg) in ether (2 mL). The resulting suspension was allowed to stir at room temperature for 30 min. and at -78 °C for 30 min.

In another flask, *t*-BuLi (2.3 mL, 3.91 mmol) was added to a -78 °C solution of 5-1 (747 mg, 1.95 mmol) in ether (2 mL). The suspension was stirred for 1 h and then cannula transferred to the lithium 2-thienylcyanocuprate mixture, rinsing with 1 mL ether. The resulting mixture was stirred for 15 min. at 0 °C and then was recooled to -78 °C. A solution of enone 5-2 (578 mg, 1.64 mmol, obtained from Nissan Chemical Industries, LTD, Chemicals Division 3-7-1 Kanda-Nishiki-cho, Chiyoda-ku, Tokyo 101-0054, Japan) in ether (2 mL) was then added by cannula, rinsing with 1 mL ether. The reaction was stirred for 1 h at -78 °C, 1 h at 0 °C and for 15 min. at room temperature.

The reaction was then quenched by addition of a 10% solution of concentrated NH_4OH in saturated NH_4Cl. The resulting mixture was extracted with ethyl acetate (3x) and the combined ethyl acetate solution was washed with brine. The organic solution was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (4% ethyl acetate/hexanes → 5%) gave the title ketone (760 mg, 71%).

Representative prodecure for TBS deprotection with HF-pyridine: (Z)-7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-hept-5-enoic acid methyl ester (5-4). HF-pyridine (1.8 mL) was added to an ice-cold CH_3CN (9 mL) solution of 5-3 (196 mg, 0.30 mmol). The reaction was stirred for 1 h and then was quenched by addition of saturated $NaHCO_3$ solution. The resulting mixture was extracted with dichloromethane and the combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (50% ethyl acetate/hexanes) gave the title diol 5-4 (117 mg, 91%).

Representative procedure for hydrolysis of methyl esters with rabbit liver esterase: (Z)-7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-hept-5-enoic acid (5-5). A mixture of 5-4 (46 mg, 0.11 mmol) and rabbit liver esterase (8 mg) in CH_3CN (0.45 mL)/pH 7.2 phosphate buffer (9 mL) was stirred overnight. The mixture was co-evaporated with CH_3CN and the residue purified by flash chromatography on silica gel (5% methanol/dichloromethane) to give the title acid 5-5 (36 mg, 80%). 300 MHz ^1H NMR ($CDCl_3$, ppm). δ 7.3-7.1 (4 H, m) 5.3-5.2 (2 H, m) 5.5-4.5 (3 H, broad s) 4.4-4.3 (2 H, m) 3.0-2.7 (2 H, m) 2.6-0.8 (21 H, overlapping m).

Representative procedure for hydrogenation of the top chain: 7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-heptanoic acid methyl ester (5-7). A mixture of ester 5-4 (67 mg, 0.16 mmol) and 5% Pd/C (49 mg) in methanol (1.2 mL) was stirred under 1 atm H_2 for 4 h. The mixture was filtered through celite and the solvent evaporated. Purification by flash chromatography on silica gel (50% ethyl acetate/hexanes) gave the title ester (15 mg, 22%).

7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-heptanoic acid (5-8). The representative procedure using rabbit liver esterase was followed.

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-[4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl)-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester. A sequence analogous to the one used to prepare 5-4 (figure 4,5) was followed, starting from [(4-Bromo-phenyl)-(1-propyl-cyclobutyl)-methoxy]-*tert*-butyl-dimethyl-silane (4-3).

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-[4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid. The representative procedure using rabbit liver esterase was followed, starting from the corresponding methyl ester.

7-((1R,2S,3R)-3-Hydroxy-2-[4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid methyl ester. A sequence analogous to the one used to prepare 5-7 (figure 5) was followed.

7-((1R,2S,3R)-3-Hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid. The representative procedure using rabbit liver esterase was followed, starting from the corresponding methyl ester.

(Z)-7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-hept-5-enoic acid methyl ester. A sequence analogous to the one used to prepare 5-4 (figure 5) was followed, starting from 1-bromo-4-*tert*-butylbenzene in the place of 5-1.

(Z)-7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-hept-5-enoic acid. The representative procedure using rabbit liver esterase was followed, starting from the corresponding methyl ester.

7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-heptanoic acid methyl ester. The representative hydrogenation procedure was followed.

7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-heptanoic acid. The representative procedure using rabbit liver esterase was followed, starting from the corresponding methyl ester.

(Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-5-oxo-cyclopentyl}-hept-5-enoic acid methyl ester. A sequence analogous to the one used to prepare 5-4 (figure 2, 5) was followed, starting with 2-3 instead of 5-1.

(Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-5-oxo-cyclopentyl}-hept-5-enoic acid. The representative procedure using rabbit liver esterase was followed, starting from the corresponding methyl ester.

7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid methyl ester. The representative hydrogenation procedure was followed, using ethyl acetate as solvent and stirring overnight.

7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid. The representative procedure using rabbit liver esterase was followed, starting from the corresponding methyl ester.

(Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-5-oxo-cyclopentyl}-hept-5-enoic acid methyl ester (e1-2). A sequence analogous to the one used to prepare 5-4 was followed [starting from 3-2 instead of 5-1 (figure 3, 5)] with the exception of the TBS deprotection step, which was done using the following procedure (see equation 1): A mixture of e1-1 (46 mg,0.075 mmol) in AcOH/H_2O/THF 3:1:1 (0.6 mL) was allowed to stir at room temperature. After 2 days, saturated $NaHCO_3$ solution was added and the resulting mixture was extracted with dichloromethane (3 x 25 mL). The combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (50% ethyl acetate/hexanes) gave the title diol e1-2 (6 mg, 21%).

(Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-5-oxo-cyclopentyl}-hept-5-enoic acid. The representative procedure using rabbit liver esterase was followed, starting with e1-2.

7-{(1R,2S,3R)-3-Hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid methyl ester. The representative hydrogenation procedure was followed, using ethyl acetate as solvent and stirring overnight.

7-{(1R,2S,3R)-3-Hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid. The representative procedure using rabbit liver esterase was followed, starting from the corresponding methyl ester.

(Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester. A sequence analogous to the one used to prepare 5-4 (figure 4,5) was followed, starting from [(3-Bromo-phenyl)-(1-propyl-cyclobutyl)-methoxy]-*tert*-butyl-dimethyl-silane (4-3).

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid (e2-1). The representative procedure using rabbit liver esterase was followed, starting from the corresponding methyl ester.

7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid methyl ester. The representative hydrogenation procedure was used.

7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid. The representative procedure using rabbit liver esterase was followed, starting from the corresponding methyl ester.

Representative procedure for secondary amide formation: (Z)-7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid (2-hydroxy-ethyl)-amide (e2-2, R = 2-hydroxyethyl, equation 2). DMF (0.5 mL) and N-hydroxysuccinimide (12 mg, 0.10 mmol) were added to acid e2-1 (8 mg, 0.02 mmol). The mixture was stirred for 5 min. and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (39 mg, 0.20 mmol) was added. This mixture was stirred for 4 h at room temperature and 2-aminoethanol (6 μL, 0.10 mmol) was added. After stirring overnight, the reaction was diluted with ethyl acetate and the resulting mixture was washed with H_2O (3 x 15 mL) and brine. The organic solution was then dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash chromatography on silica gel (5% → 7% methanol/dichloromethane) gave the title amide (5.4 mg, 63%).

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid ethyl amide (e2-2, R = ethyl). A procedure analogous to the one used above was followed.

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid ethyl amide (e2-2, R = H). Dichloromethane (0.2 mL) and triethylamine (15 μL, 0.11 mmol) were added to e2-1 (8 mg, 0.02 mmol). The reaction was stirred for 10 min., cooled in an ice bath and ethyl chloroformate (7 μL, 0.073 mmol) was added. After 1 h at 0 °C, concentrated NH_4OH_{aq} (10 μL, 0.26 mmol) was added. The reaction was stirred overnight at room temperature and then 0.5 M HCl (5 mL) was added. The resulting mixture was extracted with ethyl acetate (3 x 25 mL) and the combined ethyl acetate solution was washed with saturated $NaHCO_3$ solution and brine. The solution was then dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash chromatography on silica gel (5% methanol/dichloromethane) gave the title amide (2.2 mg, 28%).

Representative procedure for reduction of the C9 ketone: (Z)-7-((1R,2S,3R,5S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-[4-[(*tert*-butyl-dimethyl-silanyloxy)-cyclohexyl-methyl]-phenyl}-5-hydroxy-cyclopentyl)-hept-5-enoic acid methyl ester (6-1). L-selectride (300 μL, 0.3 mmol, 1 M/THF) was added to a -78 °C solution of ketone 5-3 (159 mg, 0.24 mmol) in 12 mL THF. The reaction was stirred for 30 min. at -78 °C and then 3% H_2O_2 (7 mL) was added. The reaction was stirred for 2 h at room temperature and then was poured into saturated NH_4Cl solution. The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined ethyl acetate solution was washed with brine and then was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (8% ethyl acetate/hexanes) gave the title alcohol (149 mg, 93%).

Representative procedure for conversion of the C9 alcohol to the C9 chloride: (Z)-7-((1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-[4-[(*tert*-butyl-dimethyl-silanyloxy)-cyclohexyl-methyl]-phenyl]-5-chloro-cyclopentyl)-hept-5-enoic acid methyl ester (6-2). MsCl (125 μL, 1.62 mmol) was added to a solution of 6-1 (117 mg, 0.18 mmol) and triethylamine (250 μL, 1.79 mmol) in 1,2-dichloroethane (0.5 mL). The reaction was stirred for

3 h and then was quenched by addition of saturated $NaHCO_3$. The mixture was extracted with dichloromethane (3 x 40 mL) and the combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated to give the crude mesylate (196 mg).

A mixture of the crude mesylate and $(n\text{-}Bu)_4NCl$ (214 mg, 0.077 mmol) in toluene (1.8 mL) was stirred at 40 °C overnight. The mixture was then filtered through silica gel, washing with ethyl acetate and the ethyl acetate evaporated. The residue was purified by flash chromatography on silica gel to give the title chloride 6-2 (24 mg, 20%) along with a mono TBS containing compound (36 mg, 36%).

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl]-hept-5-enoic acid methyl ester (6-3). HF-pyridine (0.60 mL) was added to a 0 °C CH_3CN solution of chloride 6-2 (24 mg, 20%) and the mono TBS derivative (36 mg, 36%). The reaction was stirred for 1 h, and then was quenched by addition of saturated $NaHCO_3$ solution. The mixture was extracted with dichloromethane (3 x 30 mL) and the combined dichloromethane solution dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (20% ethyl acetate/hexanes) gave the title diol 6-3 (37 mg, 93%).

Representative procedure for hydrolysis of the C1 methyl ester with LiOH: (Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl]-hept-5-enoic acid (6-4). Aqueous LiOH (0.75 mL, 0.75 mmol, 1 M) was added to a solution of ester 6-3 (32 mg, 0.07 mmol) in THF (4 mL). The reaction was stirred overnight and then 1 M HCl was added. The resulting mixture was extracted with dichloromethane and the combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (3% methanol/dichloromethane) followed by preparative thin layer chromatography (5% methanol/dichloromethane) gave the title acid (26 mg, 83%). 300 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.3-7.2 (4 H, m) 5.41-5.35 (2 H, m) 4.42-4.36 (1 H, m) 4.34 (1 H, d, J = 7.3 Hz) 4.2-4.1 (1 H, m) 2.7-0.8 (23 H, overlapping m's).

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl]-hept-5-enoic acid isopropyl ester (6-5). A procedure analogous to the one used to prepare 16-6 was followed.

7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl]-heptanoic acid methyl ester (6-6) and 7-[(1R,2S,3R,5R)-5-Chloro-2-(4-cyclohexylmethyl-phenyl)-3-hydroxy-cyclopentyl]-heptanoic acid methyl ester (6-8). The representative hydrogenation procedure was used, starting with 6-3 (52 mg, 0.12 mmol), 5% Pd/C (32 mg) in 6 mL methanol. Purification by flash chromatography on silica gel (50% ethyl acetate/hexanes) gave 6-6 (18 mg, 35%) and deoxygenated product 6-8 (27 mg, 52%).

7-[(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl]-heptanoic acid (6-7). The representative LiOH procedure was used.

7-[(1R,2S,3R,5R)-5-Chloro-2-(4-cyclohexylmethyl-phenyl)-3-hydroxy-cyclopentyl]-heptanoic acid (6-9). The representative LiOH procedure was used.

(Z)-7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-hept-5-enoic acid methyl ester. A sequence analogous to the one used to prepare 6-3 (figure 6) was followed.

(Z)-7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-hept-5-enoic acid. The representative LiOH procedure was used, starting with the corresponding methyl ester.

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-heptanoic acid methyl ester. A sequence analogous to the one used to prepare 6-6 (figure 6) was followed.

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-heptanoic acid. The representative LiOH procedure was used, starting with the corresponding methyl ester.

(Z)-7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-hept-5-enoic acid methyl ester. A sequence analogous to the one used to prepare 6-3 (figure 6) was followed.

(Z)-7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl]-cyclopentyl)-hept-5-enoic acid. The representative LiOH procedure was used, starting with the corresponding methyl ester.

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-heptanoic acid methyl ester. A sequence analogous to the one used to prepare 6-6 (figure 6) was followed.

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl]-cyclopentyl)-heptanoic acid. The representative LiOH procedure was used, starting with the corresponding methyl ester.

(Z)-7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-hept-5-enoic acid methyl ester. A sequence analogous to the one used to prepare 6-3 (figure 6) was followed.

(Z)-7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-hept-5-enoic acid. The representative LiOH procedure was used, starting with the corresponding methyl ester.

7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-heptanoic acid methyl ester. The representative hydrogenation procedure was followed, stirring the reaction overnight.

7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-heptanoic acid. The representative LiOH procedure was used, starting with the corresponding methyl ester.

(Z)-7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-hept-5-enoic acid isopropyl ester. A procedure analogous to the one used to prepare 16-6 was followed.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester. A sequence analogous to the one used to prepare 6-3 was followed with the exception of the TBS deprotection step, which was done using a procedure analogous to the one used to prepare e1-2.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl]-hept-5-enoic acid. The representative LiOH procedure was used, starting with the corresponding methyl ester.

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester. The representative hydrogenation procedure was followed, using ethyl acetate as solvent and stirring overnight.

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl}-heptanoic acid. The representative LiOH procedure was used, starting with the corresponding methyl ester.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl]-hept-5-enoic acid methyl ester. A sequence analogous to the one used to prepare 6-3 (figure 2,5,6) was followed, starting from 2-3 instead of 5-1.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-hept-5-enoic acid. The representative LiOH procedure was used, starting with the corresponding methyl ester.

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl]-heptanoic acid methyl ester. The representative hydrogenation procedure was followed, using ethyl acetate as solvent and stirring overnight.

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-heptanoic acid. The representative LiOH procedure was used, starting with the corresponding methyl ester.

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl]-heptanoic acid isopropyl ester. A procedure analogous to the one used to prepare 16-6 was followed, starting from the corresponding acid.

4-Bromobenzyl (4-methoxybenzyl) ether (7-2). A solution of 4-bromobenzyl alcohol (2.011g, 10.7 mmol) in THF (42 mL) was added to a mixture of NaH (663 mg, 16.6 mmol, 60% in oil) in DMF (13 mL). The mixture was stirred for 1.5 h and 4-methoxybenzyl chloride (MPMCl, 2 mL, 14.8 mmol) was added. After 24 h, 100 mL saturated NH_4Cl solution was added. The resulting mixture was extracted with ethyl acetate (3 x 60 mL) and the combined ethyl acetate solution was washed with water and brine. The solution was then dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash chromatography on silica gel (5% ethyl acetate/hexanes) gave 7-2 (2.43 g, 98%).

(Z)-7-[(1R,2S,3R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-[4-(4-methoxy-benzyloxymethyl)-phenyl]-5-oxo-cyclopentyl]-hept-5-enoic acid methyl ester (7-3). The representative 2-component coupling procedure, as described for 5-3, was followed and resulted in 7-3 (1.548 g, 73%).

Representative procedure for DDQ deprotection of MPM ethers: (Z)-7-[(1R,2S,3R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-hept-5-enoic acid methyl ester (7-4): DDQ (24 mg, 0.10 mmol) was added to a mixture of 7-3 (47 mg, 0.08 mmol) in dichloromethane (1.6 mL)/H_2O (80 μL). After 1.5 h, 10 mL saturated $NaHCO_3$ solution was added. The resulting mixture was extracted with ethyl acetate (3 x 30 mL) and the combined ethyl acetate solution was washed with brine. The solution was then dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (25% ethyl acetate/hexanes) gave 7-4 (25 mg, 67%).

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-hept-5-enoic acid methyl ester (7-5). The representative HF-pyridine deprotection procedure was used to give 7-5 (165 mg, 65%).

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-hept-5-enoic acid (7-6). The representative rabbit liver esterase procedure was used.

7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-heptanoic acid methyl ester (7-7). A mixture of 7-5 (17 mg, 0.05 mmol) and Wilkinson's catalyst (12 mg, 0.01 mmol) in 1 mL THF was stirred for 5 h under 1 atm H_2 (balloon). The mixture was then filtered through Celite and the volatiles evaporated. Purification of the residue by flash chromatography on silica gel (65% ethyl acetate/hexanes) gave 7-7 (11 mg, 62%).

7-((1R,2S,3R)-3-Hydroxy-5-oxo-2-*p*-tolyl-cyclopentyl)-heptanoic acid methyl ester (7-9). The representative H_2, Pd/C procedure was used, replacing methanol with ethyl acetate as solvent and stirring overnight. This afforded 7-9 (43 mg, 79%).

7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-heptanoic acid (7-8). The representative rabbit liver esterase procedure was used.

7-((1R,2S,3R)-3-Hydroxy-5-oxo-2-*p*-tolyl-cyclopentyl)-heptanoic acid (7-10). The representative rabbit liver esterase procedure was used.

(Z)-7-[(1R,2S,3R,5S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-hydroxy-2-[4-(4-methoxy-benzyloxymethyl)-phenyl]-cyclopentyl]-hept-5-enoic acid methyl ester (8-1). The representative L-selectride procedure was used.

(Z)-7-[(1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-chloro-2-[4-(4-methoxy-benzyloxymethyl)-phenyl]-cyclopentyl]-hept-5-enoic acid methyl ester (8-2) and (Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(4-methoxy-benzyloxymethyl)-phenyl]-cyclopentyl]-hept-5-enoic acid methyl ester (8-3). The representative procedure was used which gave 8-2 (365 mg, 39%) and 8-3 (290 mg, 38%).

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-hept-5-enoic acid methyl ester (8-4). The representative DDQ procedure was used resulting in 8-4 (184 mg, 84%).

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-hept-5-enoic acid (8-5). The representative LiOH hydrolysis procedure was used.

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-heptanoic acid methyl ester (8-6). The representative H_2, Pd/C procedure was followed using ethyl acetate as solvent.

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-heptanoic acid (8-7). The representative LiOH hydrolysis procedure was used.

(Z)-7-[(1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-chloro-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-hept-5-enoic acid methyl ester (9-1). The representative DDQ procedure was used.

(Z)-7-[(1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-chloro-2-(4-formyl-phenyl)-cyclopentyl]-hept-5-enoic acid methyl ester (9-2). An ice cold mixture of 9-1 (43 mg, 0.089 mmol), 4Å molecular sieves (56 mg) and NMO (16 mg, 0.14 mmol) in dichloromethane (0.5 mL) was treated with TPAP (3 mg, 0.009 mmol). The mixture was stirred for 5 min. at 0 °C and then for 1 h at room temperature. The mixture was then filtered through a pad of silica gel, washing with ethyl acetate. The solvents were evaporated and the residue was purified by flash chromatography on silica gel (10% ethyl acetate/hexanes) to give 9-2 (34 mg, 79%).

(Z)-7-[(1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-chloro-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl]-hept-5-enoic acid methyl ester (9-3). *i*-Propylmagnesium chloride (335 µL, 0.67 mmol, 2 M/THF) was added to an ice cold solution of 9-2 (161 mg 0.34 mmol) in THF (1.4 mL). The reaction was stirred for 3 h at 0 °C and then was quenched by addition of 20 mL saturated NH_4Cl solution. The mixture was extracted with ethyl acetate (3 x 30 mL) and the combined ethyl acetate solution was washed with brine. The solution was then dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash chromatography on silica gel (5% → 7% → 9% ethyl acetate/hexanes) gave 9-3 (76 mg, 43%).

(Z)-7-[(1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-chloro-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl]-hept-5-enoic acid methyl ester (9-4). The above procedure was followed using *t*-BuMgCl in place of *i*-Propylmagnesium chloride to give 9-4 (60 mg, 62%).

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl]-hept-5-enoic acid methyl ester (9-5). The representative HF-pyridine deprotection procedure was followed to give 9-5 (45 mg, 81%).

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl]-hept-5-enoic acid methyl ester (9-6). The representative HF-pyridine deprotection procedure was followed to give 9-6 (84 mg, 96%).

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl]-hept-5-enoic acid (9-7). The representative LiOH mediated hydrolysis procedure was followed.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl]-hept-5-enoic acid (9-8). The representative LiOH mediated hydrolysis procedure was followed.

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl]-heptanoic acid methyl ester (9-9). The representative hydrogenation procedure was followed using ethyl acetate as the solvent.

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester (9-10). The representative hydrogenation procedure was followed using ethyl acetate as the solvent.

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid (9-11). The representative LiOH procedure was used.

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid (9-12). The representative LiOH procedure was used.

Representative three component coupling procedure: [4-((1R,2S,3R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-[4-[(*tert*-butyl-dimethyl-silanyloxy)-cyclohexyl-methyl]-phenyl]-5-oxo-cyclopentyl)-but-2-ynyloxy]-acetic acid methyl ester (10-3). *s*-BuLi (3.3 mL, 5.6 mmol, 1.7 M/pentane) was added to a -78 °C THF (4.0 mL) solution of 5-1 (990 mg, 2.58 mmol). After 30 min., Me_2Zn (1.5 mL, 3.0 mmol, 2 M/toluene) was added and the flask was placed in an ice bath for 15 min. The reaction was recooled to -78 °C and a solution of enone 10-1 (387 mg, 1.83 mmol, obtained from Evotec OAI, 151 Milton Park, Abington, Oxon, OX 14 4SD, UK) in THF (2.0 mL) was added by syringe pump over 1.75 h., rinsing with 0.5 mL THF. The reaction was allowed to stir for 30 min. and then HMPA (2.8 mL, 16.1 mmol) was added followed by iodide 10-2 (2.487 g, 9.3 mmol, prepared according to U.S. Patent Application Serial Number 861,957, filed June 3, 2004). The reaction was stirred at -40 °C for 19 h and then was quenched by addition of saturated NH_4Cl solution (40 mL). A little H_2O was added to dissolve solids and the mixture was extracted with dichloromethane (3 x 30 mL). The combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel gave the title ketone (563 mg, 0.86 mmol, 47%).

[4-((1R,2S,3R,5S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-[4-[(*tert*-butyl-dimethyl-silanyloxy)-cyclohexyl-methyl]-phenyl]-5-hydroxy-cyclopentyl)-but-2-ynyloxy]-acetic acid methyl ester (10-4). L-selectride (0.76 mL, 0.76 mmol, 1 M/THF) was added to a -78 °C THF (20 mL) solution of 10-3 (415 mg, 0.63 mmol). The reaction was stirred for 1 h and then 3% H_2O_2 (14 mL) was added. The resulting mixture was stirred at room temperature for 45 min. and then saturated NH_4Cl solution (60 mL) was added. The resulting mixture was extracted with ethyl acetate (3 x 40 mL) and the combined ethyl acetate solution was washed with brine. The solution was then dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (25% ethyl acetate/hexanes) gave the title alcohol (255 mg, 0.39 mmol, 61%).

[4-((1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-[4-[(*tert*-butyl-dimethyl-silanyloxy)-cyclohexyl-methyl]-phenyl]-5-chloro-cyclopentyl)-but-2-ynyloxy]-acetic acid methyl ester (10-5). MsCl (0.13 mL, 1.7 mmol) was added to a dichloromethane (2 mL) solution of the alcohol (255 mg, 0.39 mmol) and triethylamine (0.27 mL, 1.9 mmol). After 2.5 h, 20 mL saturated $NaHCO_3$ solution was added and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined dichloromethane solution was then dried (Na_2SO_4), filtered and evaporated.

A mixture of the crude mesylate and $(n\text{-}Bu)_4NCl$ (1.032 g, 3.7 mmol) in toluene (3.5 mL) was stirred at 40 °C for 22 h. The mixture was allowed to cool to room temperature and then was filtered through silica gel eluting with ethyl acetate. The solvent was evaporated and the residue taken on to the next step.

(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-ynyloxy)-acetic acid methyl ester (10-6). HF-pyridine (1.7 mL) was added to a 0 °C CH_3CN (10 mL) solution of the crude chloride from above (0.39 mmol). The reaction was stirred at 0 °C for 21 h and then saturated $NaHCO_3$

solution (255 mL) was added. The resulting mixture was extracted with dichloromethane (3 x 100 mL) and the combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (40% ethyl acetate/hexanes → 45% → 50%) gave the title diol (152 mg, 0.34 mmol, 87% from **10-4**).

(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-ynyloxy)-acetic acid (10-7). A mixture of the ester (11 mg, 0.024 mmol) and rabbit liver esterase (5 mg) in CH_3CN (0.2 mL)/pH 7.2 phosphate buffer (2 mL) was stirred for 24 h. The mixture was then coevaporated with CH_3CN (2 x 50 mL) and the residue was taken into 10% methanol/dichloromethane and filtered through glass wool. Purification by preparative thin layer chromatography (20% methanol/dichloromethane) gave the title acid (6 mg, 0.014 mmol, 57%).

((Z)-4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-enyloxy)-acetic acid methyl ester (11-1). Ethanol (95%, 2 mL) was added to $NiCl_2$ (47 mg, 0.36 mmol) and $NaBH_4$ (5 mg, 0.13 mmol). The resulting black mixture was stirred for 5 min. and then ethylenediamine (35 µL, 0.52 mmol) was added. After 15 min., a solution of alkyne **10-6** (29 mg, 0.065 mmol) in 0.5 mL 95% ethanol was added, rinsing with 0.5 mL ethanol. The flask was purged with H_2 and allowed to stir under 1 atm H_2 for 24 h. The mixture was then filtered through celite, evaporated and the residue was purified by flash chromatography on silica gel (45 → 50% ethyl acetate/hexanes) to give 17 mg (0.038 mmol, 58%) of **11-1**.

((Z)-4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-enyloxy)-acetic acid (11-2). The representative rabbit liver esterase procedure was followed, starting with the corresponding methyl ester.

(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-butoxy)-acetic acid methyl ester (11-3). A mixture of **10-6** (11 mg, 0.024 mmol) and 5% Pd/C (6 mg, 0.003 mmol) in ethyl acetate (1 mL) was stirred under 1 atm H_2 (balloon) for 18 h. The mixture was filtered and evaporated. The residue was purified by preparative TLC on silica gel (45% ethyl acetate/hexanes) to give **11-3** (8 mg, 0.018 mmol, 75%).

(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-butoxy)-acetic acid (11-4). The representative rabbit liver esterase procedure was followed, starting with the corresponding methyl ester.

(3-Hydroxymethyl-phenoxy)-acetic acid methyl ester (12-2). A mixture of **12-1** (5.031 g, 40.5 mmol) and K_2CO_3 (5.750 g, 41.6 mmol) in 10 mL methanol was treated with methyl bromoacetate (3.9 mL, 42.4 mmol). The reaction was stirred in a 50 °C oil bath for 23 h and then was allowed to cool to room temperature. HCl (100 mL, 1 M) was then added and the mixture was extracted with dichloromethane (3 x 75 mL). The combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated and the residue was purified by flash chromatography on silica gel (10% → 15% → 20% → 25% ethyl acetate/hexanes) to give **12-2** (5.795 g, 29.5 mmol, 73%).

(3-Iodomethyl-phenoxy)-acetic acid methyl ester (12-3). Dichloromethane (85 mL) was added to Ph_3P (4.942 g, 18.8 mmol), imidazole (1.311 g, 19.3 mmol) and I_2 (4.735 g, 18.7 mmol). The mixture was stirred for 5 min. and then a solution of **12-2** (2.937 g, 15.0 mmol) in 15 mL dichloromethane was added by cannula. The reaction was stirred for 3 h, silica gel was added and the mixture evaporated. The residue was purified by flash chromatography on silica gel (10% → 20% → 30% ethyl acetate/hexanes) to give **12-3** (4.246 g, 13.9 mmol, 93%).

[3-((1R,2S,3R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-{3-[(*tert*-butyl-dimethyl-silanyloxy)-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentylmethyl)-phenoxy]-acetic acid methyl ester (13-2). The representative three component coupling method, as described for 10-3, was used giving 13-2 (278 mg, 43%).

[3-((1R,2S,3R)-3-Hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentylmethyl)-phenoxy]-acetic acid methyl ester (13-3). The representative HF-pyridine deprotection procedure was used.

[3-((1R,2S,3R)-3-Hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentylmethyl)-phenoxy]-acetic acid (13-4). The representative rabbit liver esterase procedure was followed, starting with 13-3.

[3-((1R,2S,3R,5S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-{3-[(S)-(*tert*-butyl-dimethyl-silanyloxy)-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-hydroxy-cyclopentylmethyl)-phenoxy]-acetic acid methyl ester (14-1). The representative L-selectride procedure was used.

[3-((1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-{3-[(S)-(*tert*-butyl-dimethyl-silanyloxy)-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-chloro-cyclopentylmethyl)-phenoxy]-acetic acid methyl ester (14-2). The representative method for conversion of the C9 alcohol to the C9 chloride, as described for 6-2, was used.

[3-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentylmethyl)-phenoxy]-acetic acid methyl ester (14-3). The representative HF-pyridine deprotection procedure was used.

[3-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentylmethyl)-phenoxy]-acetic acid (14-4). The representative rabbit liver esterase procedure was followed.

5-Bromo-indan-1-ol (15-2). $NaBH_4$ (350 mg, 9.25 mmol) was added to an ice cold solution of ketone 15-1 (1.632 g, 7.73 mmol) in methanol (15 mL). The reaction was allowed to warm to room temperature and after 45 min., 50 mL 1 M HCl was added. The resulting mixture was extracted with ethyl acetate (3 x 60 mL) and the combined ethyl acetate solution was washed with brine. The solution was then dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (25% ethyl acetate/hexanes) to give 15-2 (1.607 g, 98%).

5-Bromo-1-(4-methoxy-benzyloxy)-indan (15-3). A similar procedure as for 7-2 was used.

(Z)-7-{(1R,2S,3R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-[1-(4-methoxy-benzyloxy)-indan-5-yl]-5-oxo-cyclopentyl}-hept-5-enoic acid methyl ester (15-4). A -78 °C solution of thiophene (240 µL, 3.0 mmol) in ether (2.5 mL) was treated with *n*-BuLi (2.1 mL, 3.36 mmol, 1.6 M/hexanes). The reaction was stirred at 0 °C for 1 h and then was recooled to -78 °C. The resulting mixture was then cannula transferred to a -78 °C mixture of CuCN (306 mg, 3.4 mmol) in 2.5 mL ether. The reaction was stirred at room temperature for 30 min. and then was recooled to -78 °C.

In another flask, a -78 °C solution of aryl bromide 15-3 (833 mg, 2.5 mmol) in 5 mL ether was treated with *t*-BuLi (3.2 mL, 5.4 mmol, 1.7 M/pentane). The resulting mixture was stirred for 1 h at -78 °C and then was added to the 2-thienylCuCNLi mixture from above, rinsing with 1 mL ether. The reaction was stirred for 15 min. at 0 °C and then recooled to -78 °C at which time a solution of the enone 5-2 (893 mg, 2.5 mmol, obtained from Nissan Chemical Industries, LTD, Chemicals Division 3-7-1 Kanda-Nishiki-cho, Chiyoda-ku, Tokyo 101-0054, Japan) in 3 mL ether was added by cannula. The reaction was stirred for 15 min. at -78 °C and then allowed to warm to room temperature.

After 1 h, the reaction was quenched by addition of 65 mL 10% NH_4OH (conc.)/ saturated NH_4Cl solution. The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined ethyl acetate solution was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (15% ethyl acetate/hexanes) gave the title compound (792 mg, 1.3 mmol, 52%).

(Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[1-(4-methoxy-benzyloxy)-indan-5-yl]-5-oxo-cyclopentyl}-hept-5-enoic acid methyl ester (15-5). A mixture of 15-4 (20 mg, 0.032 mmol) in acetic acid (0.3 mL)/water (0.1 mL)/THF (0.1 mL) was stirred at room temperature. After two days, saturated $NaHCO_3$ solution was added and the resulting mixture was extracted with dichloromethane (3 x 20 mL). The combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (20% ethyl acetate/hexanes → 30% → 40%) which gave the title compound (11 mg, 67%).

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-hept-5-enoic acid methyl ester (15-6). DDQ (41 mg, 0.18 mmol) was added to a mixture of 15-5 (11 mg, 0.021 mmol) in dichloromethane (3.5 mL)/water (175 μL). After 55 min., saturated $NaHCO_3$ solution was added and the resulting mixture was extracted with dichloromethane (3 x 50 mL). The combined dichloromethane solution was washed with brine and then was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (50% → 60% ethyl acetate/hexanes) gave 15-6 (34 mg, 60%).

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-hept-5-enoic acid (15-7). The representative rabbit liver esterase procedure was followed.

(Z)-7-[(1R,2S,3R)-3-Hydroxy-5-oxo-2-(1-oxo-indan-5-yl)-cyclopentyl]-hept-5-enoic acid methyl ester (15-8). DDQ (10 mg, 0.041 mmol) was added to a mixture of 15-5 (11 mg, 0.021 mmol) in dichloromethane (0.5 mL)/water (25 μL). After 1 h, dichloroethane (0.5 mL) was added and the reaction was stirred overnight. Saturated $NaHCO_3$ solution was added and the resulting mixture was extracted with dichloromethane (3 x 20 mL). The combined dichloromethane solution was washed with brine and then was dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash chromatography on silica gel (60% ethyl acetate/hexanes) gave 15-8 (5 mg, 59%).

Z)-7-[(1R,2S,3R)-3-Hydroxy-5-oxo-2-(1-oxo-indan-5-yl)-cyclopentyl]-hept-5-enoic acid (15-9). The representative rabbit liver esterase procedure was followed.

7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-heptanoic acid methyl ester (15-10) and 7-((1R,2S,3R)-3-Hydroxy-2-indan-5-yl-5-oxo-cyclopentyl)-heptanoic acid methyl ester (15-12). The representative hydrogenation procedure was followed, using ethyl acetate as solvent, and afforded 15-10 (13 mg, 0.034 mmol, 63%) and 15-12 (3.9 mg, 0.011 mmol, 20%).

7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-heptanoic acid (15-11). The representative rabbit liver esterase procedure was followed.

7-((1R,2S,3R)-3-Hydroxy-2-indan-5-yl-5-oxo-cyclopentyl)-heptanoic acid (15-13). The representative rabbit liver esterase procedure was followed.

(Z)-7-{(1R,2S,3R,5S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-hydroxy-2-[1-(4-methoxy-benzyloxy)-indan-5-yl]-cyclopentyl}-hept-5-enoic acid methyl ester (16-1). The representative L-selectride procedure was used.

(Z)-7-{(1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-chloro-2-[1-(4-methoxy-benzyloxy)-indan-5-yl]-cyclopentyl}-hept-5-enoic acid methyl ester (16-2). The representative procedure was used.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[1-(4-methoxy-benzyloxy)-indan-5-yl]-cyclopentyl]-hept-5-enoic acid methyl ester (16-3). A procedure analogous to the one used to prepare 15-5 was used.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid methyl ester (16-4). A procedure analogous to the one used to prepare 15-6 was used.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid (16-5). The representative rabbit liver esterase hydrolysis was used.

Representative procedure for preparation of isopropyl esters: (Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid isopropyl ester (16-6). Isopropyl iodide (32 μL, 0.32 mmol) was added to a solution of 16-5 (12 mg, 0.032 mmol) in acetone (0.5 mL). After 3 days, HCl (10 mL, 1 M) was added and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (50% ethyl acetate/hexanes → 53%) to give 16-6 (9 mg, 0.021 mmol, 67%).

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid methyl ester (16-7) and 7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-indan-5-yl-cyclopentyl)-heptanoic acid methyl ester (16-9). A mixture of 16-4 (22 mg, 0.056 mmol) and 5% Pd/C (13 mg, 0.006 mmol) in ethyl acetate (2.5 mL) was stirred under 1 atm H_2 (balloon). After 19 h, the mixture was filtered through celite and evaporated. Purification by flash chromatography on silica gel (40% → 45% ethyl acetate/hexanes) gave 12 mg (0.030 mmol, 53%) of 16-7 and 10 mg (0.025 mmol, 45%) of 16-9.

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid (16-8). The representative rabbit liver esterase procedure was used.

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-indan-5-yl-cyclopentyl)-heptanoic acid (16-10). The representative rabbit liver esterase procedure was used.

(Z)-7-[(1R,2S,3R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-fluoro-2-[1-(4-methoxy-benzyloxy)-indan-5-yl]-cyclopentyl}-hept-5-enoic acid methyl ester (17-1) and (Z)-7-{(4R,5R)-4-(*tert*-Butyl-dimethyl-silanyloxy)-5-[1-(4-methoxy-benzyloxy)-indan-5-yl]-cyclopent-1-enyl}-hept-5-enoic acid methyl ester (17-2). A solution of 16-1 (212 mg, 0.35 mmol) in 1 mL THF was added to a -78 °C solution of (diethylamino)sulfur trifluoride (DAST, 50 μL, 0.38 mmol) in 1 mL THF, rinsing with 0.5 mL THF. The reaction was stirred at room temperature for 1.5 h and the volatiles were evaporated. The residue was purified by flash chromatography on silica gel (5% → 8% ethyl acetate/hexanes) to give 17-1 (54 mg, 25%) and 17-2 (54 mg, 26%).

7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid methyl ester (17-3). This compound was prepared by an analogous sequence to the 9-chloro derivative (16-7, figure 16).

7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid (17-4). The representative LiOH procedure was used.

(Z)-7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid methyl ester (17-5). This compound was prepared by an analogous sequence to the 9-chloro derivative (16-4, figure 16).

(Z)-7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid (17-6). The representative LiOH procedure was used.

EXPERIMENTAL

(R)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-iodo-cyclopent-2-enone (18-2). A procedure similar to the one described in A.G. Myers and P. S. Dragovich *J. Am. Chem. Soc.* 1993,*115*,7021 was followed. A 0 °C solution of enone 10-1 (3.163 g, 14.9 mmol,Evotec OAI, 151 Milton Park, Abington, Oxon, OX 14 4SD, UK) and pyridine (5 mL) in dichloromethane (5 mL) was treated with a solution of I_2 (6.511 g, 25.7 mmol) in pyridine (12 mL)/dichloromethane (12 mL). The reaction was allowed to warm to room temperature and after 2 h, 1 M HCl (60 mL) was added. The resulting mixture was poured into 100 mL 1 M HCl and then was extracted with dichloromethane (3 x 60 mL). The combined dichloromethane solution was washed with saturated $NaHSO_3$ solution and with brine and then was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (5% ethyl acetate/hexanes) gave the title compound (4.600 g, 91%).

1-(4-Bromo-phenyl)-hexan-1-ol (18-4). *n*-PentylMgBr (29 mL, 58 mmol, 2 M/ether) was added to a 0 °C solution of 4-bromobenzaldehyde (9.953 g, 54 mmol) in THF (100 mL). After 1 h, the reaction was quenched by addition of 200 mL saturated ammonium chloride solution. The resulting mixture was extracted with ethyl acetate (3 x 100 mL) and the combined ethyl acetate solution was dried (Na2SO4), filtered and evaporated. Purification of the residue by flash chromatography on silica gel gave 18-4 (10.501 g, 76%).

[1-(4-Bromo-phenyl)-hexyloxy]-*tert*-butyl-dimethyl-silane (18-5). TBSOTf (2.9 mL, 12.6 mmol) was added to an ice-cold solution of 18-4 (3.017 g, 11.7 mmol) and 2,6-lutidine (1.6 mL, 13.7 mmol) in dichloromethane (30 mL). The reaction was stirred for 2 h at room temperature and then 100 mL saturated sodium bicarbonate solution was added. The resulting mixture was extracted with dichloromethane (30 mL) and the dichloromethane layer was washed with 1 M HCl (2 x 50 mL) and brine (50 mL). The dichloromethane solution was then dried ($MgSO_4$), filtered and evaporated. Purification of the residue by flash chromatography on silica gel (hexanes) gave 18-5 (3.843 g, 88%).

3-Allyl-benzoic acid ethyl ester (18-7). A -45 °C solution of ethyl 3-iodobenzoate (2.434 g, 8.8 mmol) in 40 mL THF was treated with *i*-PrMgCl (4.8 mL, 9.6 mmol, 2 M/ether). After 1 h, allyl bromide (1.6 mL, 18.9 mmol) was added followed by CuCN (79 mg, 0.88 mmol). The reaction was stirred for 1 h and then was quenched by addition of 50 mL saturated NH_4Cl solution. Water (30 mL) was added and the resulting mixture was extracted with ethyl acetate (3 x 50 mL). The combined ethyl acetate solution was dried ($MgSO_4$), filtered and evaporated. Purification by flash chromatography on silica gel (5% ethyl acetate/hexanes → 10%) gave the title compound (1.145 g, 68%).

3-{3-[(R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-oxo-cyclopent-1-enyl]-propyl}-benzoic acid ethyl ester (1-8). A solution of 18-7 (303 mg, 1.6 mmol) in 0.5 mL THF was added to a solution of 9-BBN dimer (393 mg, 1.6 mmol) in 6 mL THF. After 4 h, 0.1 mL H_2O was added. The solution was stirred for 20 min. and then was cannula transferred to a mixture of $PdCl_2$(dppf) (78 mg, 0.11 mmol) and 18-2 (387 mg, 2.0 mmol) in DMF (3.2 mL). K_3PO_4 (0.7 mL, 2.1 mmol, 3 M) was added and the dark solution was stirred for 1.25 h. The solution was then poured into 50 mL brine and the resulting mixture was extracted with ethyl acetate (2 x 30 mL). The combined ethyl acetate solution was dried ($MgSO_4$), filtered and evaporated. Purification by flash chromatography on silica gel gave 292 mg (46%) of enone 1-8.

1-8 →→ 3-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-benzoic acid (18-13). The sequence leading to 18-13 was completed as shown in scheme 18 and as described in fig. 5,6.

5-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-thiophene-2-carboxylic acid methyl ester. The title compound was prepared using an analogous procedure to that described for

18-12, starting with 5-Bromo-thiophene-2-carboxylic acid methyl ester, which was prepared from 5-Bromo-thiophene-2-carboxylic acid as follows: Acetyl chloride (6.87 mL, 96.6 mmol) was added to a solution of 5-Bromo-thiophene-2-carboxylic acid (4.0 g, 19.3 mmol) in methanol (30 mL). The reaction was allowed to stir overnight and then was heated to reflux for 1.5 h. The reaction was allowed to cool to room temperature and then was evaporated. The residue was treated with 120 mL saturated sodium bicarbonate solution and the resulting mixture was extracted with dichloromethane (3 x 100 mL). The combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated to give 3.57 g (84%) of 5-Bromo-thiophene-2-carboxylic acid methyl ester.

5-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-thiophene-2-carboxylic acid (102). The title compound was prepared by hydrolysis of the methyl ester using the rabbit liver esterase procedure described.

5-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-thiophene-2-carboxylic acid isopropyl ester. The title compound was prepared from the corresponding acid using the standard procedure described.

(E)-3-(3-Hydroxymethyl-phenyl)-acrylic acid methyl ester (19-3). The procedure described in Reich, S.H. *et.al. J.Med.Chem.* 2000, *43*, 1670 was followed. $Pd(OAc)_2$ (8.2 mg, 0.037 mmol) and triethylamine (0.360 mL, 2.58 mmol) were added to a solution of 3-iodobenzyl alcohol 19-1 (0.27 mL, 2.13 mmol) and methyl acrylate 19-2 (0.220 mL, 2.44 mmol) in CH_3CN (4.5 mL). The reaction vessel was sealed with a Teflon screw-cap and was heated at 100 °C for 5 h. At this time, the reaction was allowed to cool to room temperature and the tube was charged with 0.22 mL more of methyl acrylate, 11.7 mg $Pd(OAc)_2$ and 0.360 mL triethylamine. The reaction was heated at 100 °C overnight and then 10 mL saturated ammonium chloride solution was added. The resulting mixture was extracted with dichloromethane (3 x 40 mL) and the combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (30 % ethyl acetate/hexanes) gave 395 mg (97%) of 19-3.

3-(3-Hydroxymethyl-phenyl)-propionic acid methyl ester (19-4). $(Ph_3P)_3RhCl$ (11.5 mg, 0.012 mmol) was added to a solution of 19-3 (25 mg, 0.13 mmol) in 0.400 mL ethanol. The reaction was stirred under 1 atm H_2 balloon for 20 h and then was filtered through Celite. Evaporation to dryness and purification by flash chromatography on silica gel (30% ethyl acetate/hexanes) gave 192-4 (21 mg, 82%).

3-(3-Iodomethyl-phenyl)-propionic acid methyl ester (19-5). A mixture of Ph_3P (36 mg, 0.14 mmol), I_2 (41 mg, 0.16 mmol) and imidazole (10.5 mg, 0.15 mmol) in 0.40 mL 1,2-dichloroethane was stirred for 15 min. and then a solution of 2-4 (20.5 mg, 0.11 mmol) in 0.1 mL 1,2-dichloroethane was added by cannula. The resulting mixture was stirred for 1 h and then was filtered through basic alumina, washing with ethyl acetate. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel to give 19-5 (26 mg, 81%).

3-[3-((1R,2S,3R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-{4-[1-(*tert*-butyl-dimethyl-silanyloxy)-hexyl]-phenyl}-5-oxo-cyclopentylmethyl)-phenyl]-propionic acid methyl ester (20-1). A -78 °C solution of aryl bromide 18-5 (759 mg, 2.0 mmol) in THF (3 mL) was treated with *tert*-butyllithium (2.6 mL, 4.4 mmol, 1.7 M/pentane). After 30 min., Me_2Zn (1.1 mL, 2.2 mmol, 2 M/toluene) was added and the resulting solution was stirred for 15 min. at 0 °C and then was recooled to -78 °C. A solution of enone 10-1 (319 mg, 1.5 mmol, Evotec OAI, 151 Milton Park, Abington, Oxon, OX 14 4SD, UK) in 1.7 mL THF was added by syringe pump over 1 h. The resulting mixture was stirred at -78 °C for 2 h, and then HMPA (2.2 mL, 12.6 mmol) was added followed by a solution of 19-5 (2.641 g, 8.7 mmol) in THF (1.6 mL). The reaction was stirred overnight at -40 °C and then was quenched by addition of 40 mL

saturated ammonium chloride solution. A little water was added to dissolve the solids and the resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined ethyl acetate solution was dried ($MgSO_4$), filtered and evaporated. Purification by flash chromatography on silica gel (10 % ethyl acetate/hexanes) gave the title ketone contaminated with ca. 35% of benzyl iodide 19-5 (438 mg).

3-[3-((1R,2S,3R,5S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-[4-[1-(*tert*-butyl-dimethyl-silanyloxy)-hexyl]-phenyl]-5-hydroxy-cyclopentylmethyl)-phenyl]-propionic acid methyl ester (20-2). The standard L-selectride procedure described previously was used, which gave 224 mg (22% from enone 1-1) of pure 20-2.

3-2 → → 3-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentylmethyl}-phenyl)-propionic acid (20-5). The sequence was completed as shown in scheme 3 using the standard procedures in fig.6.

3-[3-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl]-cyclopentylmethyl)-phenyl]-propionic acid methyl ester and 3-[3-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl]-cyclopentylmethyl)-phenyl]-propionic acid (104). The title compounds were prepared similarly to 20-4/20-5 starting with aryl bromide 20-6 (prepared as described in fig. 1,4).

(2R,3S,4R)-2-Allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-3-[4-[1-(*tert*-butyl-dimethyl-silanyloxy)-hexyl]-phenyl]-cyclopentanone (21-1). Compound 21-1 was prepared using an analogous procedure to that described for 16-1.

4-1 → (1S,2R,3S,4R)-2-Allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-3-[4-[1-(*tert*-butyl-dimethyl-silanyloxy)-hexyl]-phenyl]-cyclopentanol (21-2) → 1-[(1S,2R,3R,5R)-2-Allyl-5-(*tert*-butyl-dimethyl-silanyloxy)-3-chloro-cyclopentyl]-4-[1-(*tert*-butyl-dimethyl-silanyloxy)-hexyl]-benzene (21-3). This sequence was performed as described in fig.6.

2-[3-((1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-[4-[1-(*tert*-butyl-dimethyl-silanyloxy)-hexyl]-phenyl]-5-chloro-cyclopentyl)-propyl]-thiazole-5-carboxylic acid ethyl ester (21-5). A solution of 21-3 (39 mg, 0.069 mmol) in 0.2 mL THF was cannula transferred to a mixture of 9-BBN dimer (17 mg, 0.07 mmol) in 0.2 mL THF, rinsing with 0.2 mL THF. The reaction was placed in a 50 °C oil bath for 2.5 h, was allowed to cool to room temperature and H_2O (10 µL) was added. After 30 min., the solution was cannula transferred to a solution of ethyl 2-bromothiazole-5-carboxylate 21-4 (15 mg, 0.063 mmol) and $PdCl_2$(dppf) (5 mg, 0.007 mmol) in DMF (0.2 mL). K_3PO_4 (31 µL, 0.09 mmol, 3 M) was added and the solution was placed in a 50 °C oil bath. The reaction was stirred overnight and then partitioned between 15 mL ethyl acetate/15 mL water (a little brine was added). The aqueous layer was further extracted with 15 mL ethyl acetate and the combined ethyl acetate solution was dried ($MgSO_4$), filtered and evaporated. Purification by preparative TLC on silica gel (10% ethyl acetate/hexanes) gave the title compound (4 mg, 0.0057 mmol, 8%).

4-5 → 2-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-thiazole-5-carboxylic acid ethyl ester (21-6) → 2-(3-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-propyl)-thiazole-5-carboxylic acid (21-7). This sequence was performed as described in application 17693,fig.6.

(Z)-7-((1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-{4-[1-(*tert*-butyl-dimethyl-silanyloxy)-hexyl]-phenyl}-5-fluoro-cyclopentyl)-hept-5-enoic acid methyl ester (22-1). A solution of 22-0 (109 mg, 0.17 mmol) in 0.5 mL dichloromethane was cannula transferred to a -78 °C solution of deoxofluor [bis(2-

methoxyethyl)aminosulfur trifluoride, 34 μL, 0.18 mmol) in 0.75 mL dichloromethane, rinsing with 0.25 mL dichloromethane. The reaction was stirred for 2 h at -78 °C and then was quenched by addition of 10 mL saturated $NaHCO_3$. The mixture was extracted with dichloromethane (3 x 15 mL) and the combined dichloromethane solution was dried ($MgSO_4$), filtered and evaporated. Purification by flash chromatography on silica gel (1% ethyl acetate/hexanes → 2%) gave 53 mg of impure 22-1.

(Z)-7-{(1R,2S,3R,5R)-5-Fluoro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester (22-2). The HF-pyridine procedure described in application 17693 was followed, which gave 30 mg of impure 22-2 after flash chromatography on silica gel (40% ethyl acetate/hexanes). Further purification by preparative TLC (35% ethyl acetate/hexanes) gave 7 mg of pure 22-2.

(Z)-7-{(1R,2S,3R,5R)-5-Fluoro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (22-3). The previously described LiOH procedure was used.

(Z)-7-((1R,2S,3R,5S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-{4-[1-(*tert*-butyl-dimethyl-silanyloxy)-hexyl]-phenyl}-5-hydroxy-cyclopentyl)-hept-5-enoic acid methyl ester (18-0) and (Z)-7-((1R,2S,3R,5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-{4-[1-(*tert*-butyl-dimethyl-silanyloxy)-hexyl]-phenyl}-5-hydroxy-cyclopentyl)-hept-5-enoic acid methyl ester (23-2). $NaBH_4$ (9 mg, 0.24 mmol) was added to a solution of (Z)-7-((1R,2S,3R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-{4-[1-(*tert*-butyl-dimethyl-silanyloxy)-hexyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester (23-1) (55 mg, 0.087 mmol, prepared as described in fig.5) in methanol (0.5 mL). After 20 min., 1 M HCl (10 mL) was added and the resulting mixture was extracted with dichloromethane (3 x 10 mL). The combined dichloromethane solution was dried ($MgSO_4$), filtered and evaporated. Purification by flash chromatography on silica gel (10% ethyl acetate/hexanes → 15%) gave 27 mg (49%) of 23-2 and 16 mg (29%) of 22-0 along with an 8 mg mixed fraction.

(Z)-7-((1R,2S,3R,5S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-{4-[1-(*tert*-butyl-dimethyl-silanyloxy)-hexyl]-phenyl}-5-chloro-cyclopentyl)-hept-5-enoic acid methyl ester (23-3). Methanesulfonyl chloride (15 μL, 0.19 mmol) and triethylamine (30 μL, 0.21 mmol) were added to a solution of 23-2 (50 mg, 0.08 mmol) in dichloromethane (0.3 mL). After 1.5 h, saturated sodium bicarbonate solution (15 mL) was added and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined dichloromethane solution was evaporated to give the crude mesylate.

The crude mesylate was taken into 0.7 mL toluene and $(n\text{-Bu})_4NCl$ (246 mg, 0.90 mmol) was added. The mixture was stirred at 80 °C for 1 h and then was filtered through silica gel (20% ethyl acetate/hexanes) to give 22-3 (40 mg, 77%).

7-3 → (Z)-7-{(1R,2S,3R,5S)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester (23-4) → (Z)-7-{(1R,2S,3R,5S)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (23-5). This sequence was completed as shown in figure 23, following procedures described previously.

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (24-4). The title compound was prepared as shown in figure 24, in a similar manner to that described in fig.9.

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid isopropyl ester (24-5). The title compound was prepared using the standard procedure described previously.

Preparation of the individual diastereomers of 20-4. The individual diastereomers were separated by preparative HPLC at the stage of 24-2: ca. 5 mg sample/run; Chiralcel OD semiprep column (1 x 25 cm), 2.4 mL/min. flow rate, 10% isopropyl alcohol/hexanes; retention times = 17.6 min. and 23.8 min. The individual diastereomers were then taken on separately as shown in scheme 8 and as describedpreviously.

Compounds 115-130. These compounds were prepared in an analogous fashion to24-4 (Fig. 24).

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-heptyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (131) and (Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (132). The title compounds were prepared as shown in Fig. 25, using analogous procedures to those described in fig. 7-9.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid methyl ester (26-1). Et_3SiH (30 µL, 0.19 mmol) followed by TFA (90 µL, 1.17 mmol) were added to a solution of 24-3 (23 mg, 0.046 mmol) in dichloroethane (0.10 mL). After 15 min., the reaction was quenched by addition of 4 mL saturated sodium bicarbonate solution. The resulting mixture was extracted with dichloromethane (3 x 30 mL) and the combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (10% ethyl acetate/hexanes → 15% → 20%) gave 21 mg (110%) of 26-1.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid (26-2). The title compound was prepared using the standard LiOH procedure described previously.

(Z)-7-[(1R,2S,3R,5R)-2-[4-(1-Acetoxy-hexyl)-phenyl]-3-(*tert*-butyl-dimethyl-silanyloxy)-5-chloro-cyclopentyl]-hept-5-enoic acid methyl ester (27-1). *n*-PentylMgBr (130 µL, 0.26 mmol) was added to a 0 °C solution of 24-1 (114 mg, 0.24 mmol) in THF (0.9 mL). After 2.5 h, 1 mL ethyl acetate was added and the reaction was allowed to warm to room temperature. After 30 min. at room temperature, 10 mL saturated ammonium chloride solution was added and the resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined ethyl acetate solution was dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (10% ethyl acetate/hexanes) gave 113 mg (80%) of 27-1.

(Z)-7-{(1R,2S,3R,5R)-2-[4-(1-Acetoxy-hexyl)-phenyl]-5-chloro-3-hydroxy-cyclopentyl}-hept-5-enoic acid methyl ester (27-2). The standard HF-pyridine deprotection described in previously was used.

4-Nitro-benzoic acid (1S,2S,3R,4R)-2-[4-(1-acetoxy-hexyl)-phenyl]-4-chloro-3-((Z)-6-methoxycarbonyl-hex-2-enyl)-cyclopentyl ester (27-3). Diisopropyl azodicarboxylate (11 µL, 0.057 mmol) was added to a mixture of Ph_3P (15.6 mg, 0.059 mmol), 4-nitrobenzoic acid (8.3 mg, 0.050 mmol), and 27-2 (17 mg, 0.036 mmol) in THF (0.600 mL). The reaction was stirred overnight and then the volatiles were evaporated in vacuo. Purification of the residue by flash chromatography on silica gel (30% ethyl acetate/hexanes) gave 10 mg (45%) of 27-3.

(Z)-7-{(1R,2S,3S,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid (27-4). The standard LiOH hydrolysis procedure described previously was used.

Example 2

Binding Data

Ki

Competition binding experiments were performed in a medium containing Hank's balanced salt solution, Hepes 20 mM, pH 7.3, membranes (~60 µg protein) or $2x10^5$ cells from HEK 293 cells stably expressing human EP2 receptors, [^{3}H]PGE2 (10 nM) and various concentrations of test compounds in a total volume of 300 µl. Reaction mixtures were incubated at 23 °C for 60 min, and were filtered over Whatman GF/B filters under vacuum. Filters were washed three times with 5 ml ice-cold buffer containing 50 mM Tris/HCl (pH 7.3). Non-specific binding was estimated in the presence of excess unlabeled PGE2 (10 µM). Binding data fitted to the binding model for a single class of binding sites, using nonlinear regression analysis. IC_{50} values thus obtained were converted to Ki using the equation of $Ki=(IC_{50}/(1+[L]/K_D)$ where [L] represents PGE2 concentration (10 nM) and K_D the dissociation constant for [^{3}H]PGE2 at human EP2 receptors (40 nM).

Radioligand Binding

Cells Stably Expressing EP_1, EP_2, EP_4 and FP Receptors

HEK-293 cells stably expressing the human or feline FP receptor, or EP_1, EP_2, or EP_4 receptors were washed with TME buffer, scraped from the bottom of the flasks, and homogenized for 30 sec using a Brinkman PT 10/35 polytron. TME buffer was added to achieve a final 40 ml volume in the centrifuge tubes (the composition of TME is 100 mM TRIS base, 20 mM $MgCl_2$, 2M EDTA; 10N HCl is added to achieve a pH of 7.4).

The cell homogenate was centrifuged at 19000 r.p.m. for 20 min at 4° C using a Beckman Ti-60 rotor. The resultant pellet was resuspended in TME buffer to give a final 1 mg/ml protein concentration, as determined by Biorad assay. Radioligand binding competition assays vs. [^{3}H-]17 –phenyl $PGF_{2\alpha}$ (5 nM) were performed in a 100µl volume for 60 min. Binding reactions were started by adding plasma membrane fraction. The reaction was terminated by the addition of 4 ml ice-cold TRIS-HCl buffer and rapid filtration through glass fiber GF/B filters using a Brandel cell harvester. The filters were washed 3 times with ice-cold buffer and oven dried for one hour.

[^{3}H-] PGE_2 (specific activity 180 Ci mmol) was used as the radioligand for EP receptors. [^{3}H] 17-phenyl $PGF_{2\alpha}$ was employed for FP receptor binding studies. Binding studies employing EP_1, EP_2, EP_4 and FP receptors were performed in duplicate in at least three separate experiments. A 200µl assay volume was used. Incubations were for 60 min at 25°C and were terminated by the addition of 4 ml of ice-cold 50 mM TRIS-HCl, followed by rapid filtration through Whatman GF/B filters and three additional 4 ml washes in a cell harvester (Brandel). Competition studies were performed using a final concentration of 5 nM [^{3}H]-PGE_2, or 5 nM [^{3}H] 17-phenyl $PGF_{2\alpha}$ and non-specific binding determined with 10^{-5}M of unlabeled PGE_2, or 17-phenyl $PGF_{2\alpha}$, according to receptor subtype studied.

METHODS FOR FLIPR™ STUDIES

(a) CELL CULTURE

HEK-293(EBNA) cells, stably expressing one type or subtype of recombinant human prostaglandin receptors (prostaglandin receptors expressed: hDP/Gqs5; hEP_1; hEP_2/Gqs5; hEP_{3A}/Gqi5; hEP_4/Gqs5; hFP; hIP; hTP), were cultured in 100 mm culture dishes in high-glucose DMEM medium containing 10% fetal bovine serum, 2 mM l-glutamine, 250 µg/ml geneticin (G418) and 200 µg/ml hygromycin B as selection markers, and 100 units/ml penicillin G, 100 µg/ml streptomycin and 0.25 µg/ml amphotericin B.

(b) CALCIUM SIGNAL STUDIES ON THE FLIPR™

Cells were seeded at a density of $5x10^4$ cells per well in Biocoat® Poly-D-lysine-coated black-wall, clear-bottom 96-well plates (Becton-Dickinson) and allowed to attach overnight in an incubator at 37 °C. Cells were then

washed two times with HBSS-HEPES buffer (Hanks Balanced Salt Solution without bicarbonate and phenol red, 20 mM HEPES, pH 7.4) using a Denley Cellwash plate washer (Labsystems). After 45 minutes of dye-loading in the dark, using the calcium-sensitive dye Fluo-4 AM at a final concentration of 2 μM, plates were washed four times with HBSS-HEPES buffer to remove excess dye leaving 100 μl in each well. Plates were re-equilibrated to 37 °C for a few minutes.

Cells were excited with an Argon laser at 488 nm, and emission was measured through a 510-570 nm bandwidth emission filter (FLIPR™, Molecular Devices, Sunnyvale, CA). Drug solution was added in a 50 μl volume to each well to give the desired final concentration. The peak increase in fluorescence intensity was recorded for each well. On each plate, four wells each served as negative (HBSS-HEPES buffer) and positive controls (standard agonists: BW245C (hDP); PGE_2 (hEP_1; hEP_2/Gqs5; hEP_{3A}/Gqi5; hEP_4/Gqs5); $PGF_{2\alpha}$ (hFP); carbacyclin (hIP); U-46619 (hTP), depending on receptor). The peak fluorescence change in each drug-containing well was then expressed relative to the controls.

Compounds were tested in a high-throughput (HTS) or concentration-response (CoRe) format. In the HTS format, forty-four compounds per plate were examined in duplicates at a concentration of 10^{-5} M. To generate concentration-response curves, four compounds per plate were tested in duplicates in a concentration range between 10^{-5} and 10^{-11} M. The duplicate values were averaged. In either, HTS or CoRe format each compound was tested on at least 3 separate plates using cells from different passages to give an $n \geq 3$.

The results of the binding and activity studies, presented in Table 1 below, demonstrate that the compounds disclosed herein are selective prostaglandin EP_2 agonists, and are thus useful for the treatment of glaucoma, ocular hypertension, the other diseases or conditions disclosed herein.

Table 1

NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
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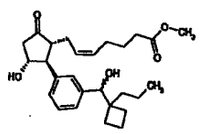
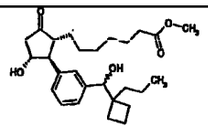
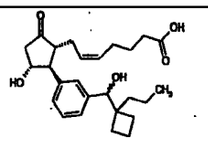
					NA	NA	>10K	>10K	>10K	NA	NA	NA
					NA	NA	>10K	>10K	>10K	NA	>10K	>10K
					NA	NA	5294	1698	NA	NA	NA	NA

Table 1

NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
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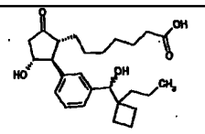
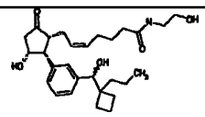
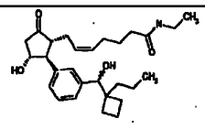
					NA	NA	5259		NA	NA	NA	NA
e2-2					NA	NA	NA	NA	NA	NA	NA	NA
e2-2					NA	NA	>10K	NA	>10K	NA	NA	NA

Table 1

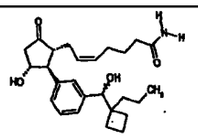
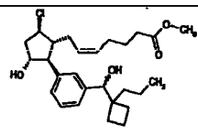
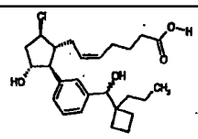
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
e2-2					NA	NA	NA	NA	NA	NA	NA	NA
					NA	NA	>10K	>10K	NA	>10K	NA	NA
					NA	NA	322	455	NA	>10K	NA	>10K

Table 1

		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
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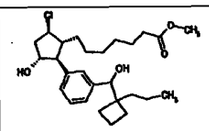
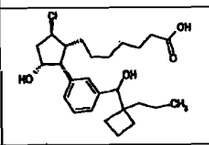
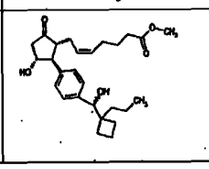
					NA	NA	NA	NA	NA	NA	NA	NA
					NA	NA	1479	3118	NA	NA	NA	NA
					NA	NA	NA	NA	NA	>10K	NA	NA

Table 1

NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
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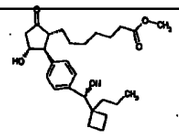
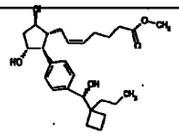
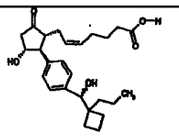
					NA	NA	>10K	NA	NA	NA	NA	NA
					NA	NA	>10K	NA	NA	NA	NA	NA
					NA	NA	3723	NA	NA	NA	NA	NA

Table 1

		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
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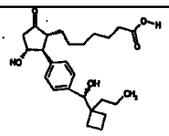
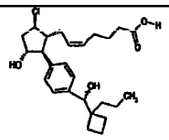
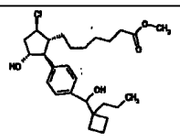
					NA	NA	635	NA	NA	NA	NA	NA
					NA	NA	2270	NA	NA	NA	NA	NA
					NA	NA	NA	NA	NA	NA	NA	NA

Table 1

NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
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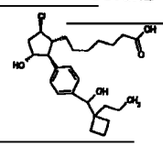
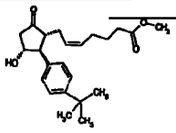
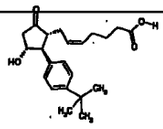
					NA	NA	546	NA	NA	NA	NA	NA
					NA	NA	>10K	NA	NA	>10K	NA	NA
					NA	>10K	1709	NA	NA	NA	NA	NA

Table 1

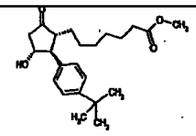
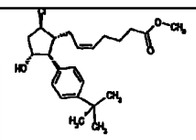
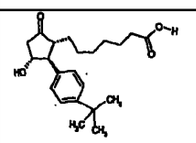
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
					NA	NA	936	>10K	>10K	>10K	NA	NA
					NA	NA	>10K	>10K	NA	NA	NA	NA
					NA	>10K	102	3390	NA	4273	>10K	NA

Table 1

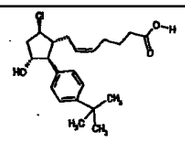
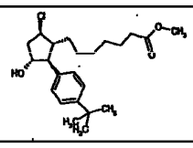
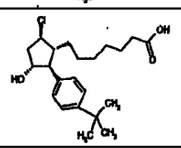
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
					NA	>10K	118	2053	>10K	1269	NA	>10K
					NA	NA	>10K	NA	NA	NA	NA	NA
					NA	>10K	284	>10K	NA	>10K	NA	>10K

Table 1

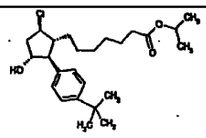
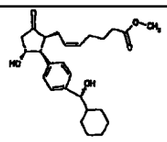
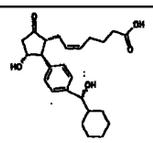
		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
NUMBER	STRUCTURE	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
					NA	NA	NA	NA		NA	NA	NA
5-4					NA	NA	>10K	NA	>10K	NA	NA	NA
5-5					NA	NA	>10K	NA	NA	NA	NA	NA

Table 1

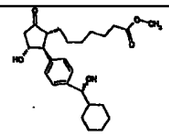
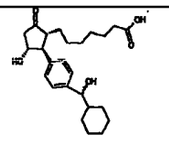
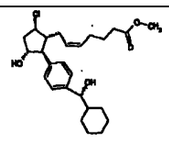
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
5-7					NA	NA	>10K	NA	NA	NA	NA	NA
5-8					NA	NA	450	NA	NA	NA	NA	NA
6-3					NA	NA	>10K	NA	NA	NA	NA	NA

Table 1

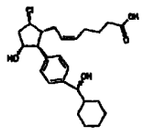
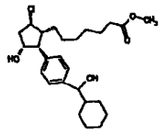
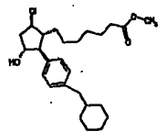
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
6-4					NA	NA	392	NA	NA	NA	NA	NA
6-6					NA	NA	NA	NA	NA	NA	NA	NA
6-8					NA	NA	NA	NA	NA	NA	NA	NA

Table 1

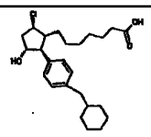
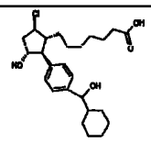
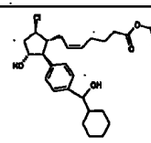
		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
NUMBER	STRUCTURE	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
6-9					NA	NA	3445	NA	NA	NA	NA	>10K
6-7					NA	NA	2813	NA	NA	NA	NA	NA
6-5					NA	NA	NA	NA	NA	NA	NA	NA

Table 1

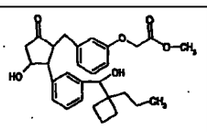
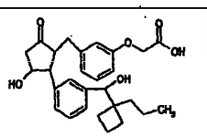
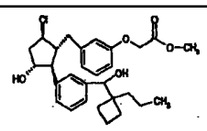
		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
NUMBER	STRUCTURE	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
13-3					NA	NA	NA	NA	NA	NA	NA	NA
13-4					NA	NA	NA	NA	NA	NA	NA	>10K
14-3					NA	NA	NA	NA	NA	NA	NA	NA

Table 1

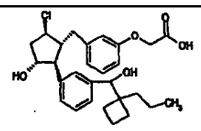
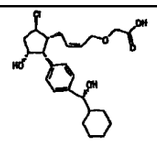
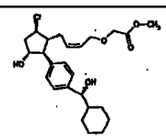
		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
NUMBER	STRUCTURE	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
14-4		5200	NA	NA	NA	NA	266	NA	NA	NA	NA	
11-2					NA	NA	3844	NA	NA	NA	NA	NA
11-1					NA	NA	NA	NA	NA	NA	NA	NA

Table 1

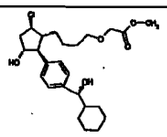
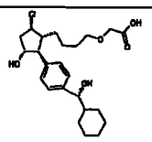
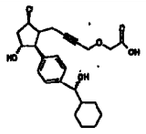
		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
NUMBER	STRUCTURE	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
11-3					NA	NA	NA	NA	NA	NA	NA	NA
11-4					NA	NA	20773	NA	NA	NA	NA	NA
10-7					NA	NA	1550	NA	NA	NA	NA	NA

Table 1

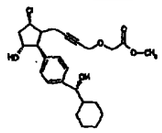
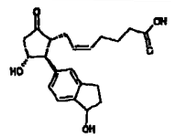
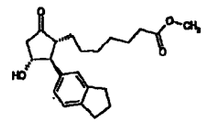
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
10-6					NA	NA	NA	NA	NA	NA	NA	NA
15-7					NA	NA		NA	NA	NA	NA	NA
15-12					NA	NA	>10K	>10K	>10K	>10K	NA	NA

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Table 1

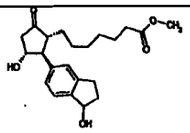
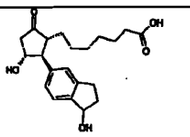
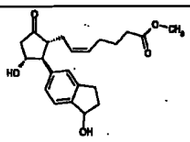
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
15-10					NA	NA	NA	NA	NA	NA	NA	NA
15-11					NA	NA		NA	NA	>10K	NA	NA
15-6					NA	NA	NA	NA	NA	NA	NA	NA

Table 1

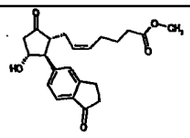
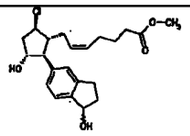
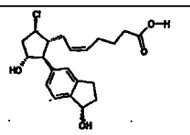
		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
NUMBER	STRUCTURE	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
15-8					NA	NA	NA	NA	NA	NA	NA	NA
16-4							NA		NA			
16-5		2281			NA	NA	405	NA	NA	NA	NA	NA

Table 1

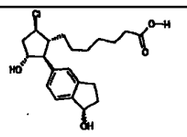
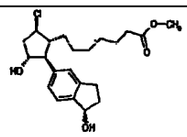
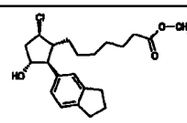
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
16-8		13139			NA	NA	529	NA	NA	2993	NA	NA
16-7					NA	NA	NA	NA	22457	17525	NA	NA
16-9				13100	NA	NA	NA	NA	NA	506	NA	NA

Table 1

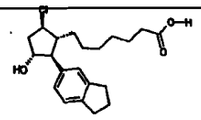
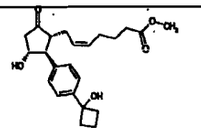
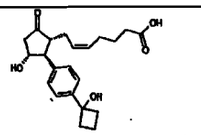
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
16-10		6251			NA	221	818	NA	NA	200	NA	
e1-2					NA	NA	NA	NA	NA	NA	NA	NA
					NA	NA	>10K	NA	NA	NA	NA	NA

Table 1

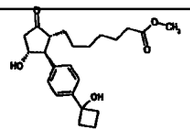
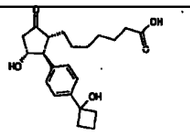
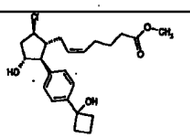
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
					NA	NA	NA	NA	NA	NA	NA	NA
					NA	NA	>10K	NA	NA	NA	>10K	NA
					NA	NA	>10K	NA	NA	NA	NA	NA

Table 1

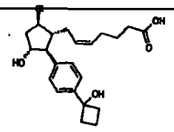
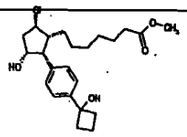
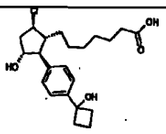
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
					NA	NA	513	NA	NA	>10K	NA	NA
					NA	NA	>10K	NA	NA	>10K	NA	NA
					NA	NA	743	NA	NA	>10K	NA	NA

Table 1

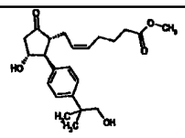
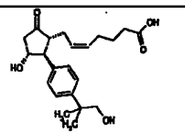
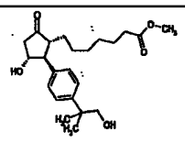
		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
NUMBER	STRUCTURE	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
							NA		>10K			
					NA	NA	>10K	NA		NA	NA	NA
					NA	NA	>10K	NA	26289	NA	NA	NA

Table 1

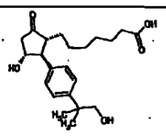
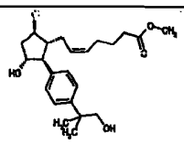
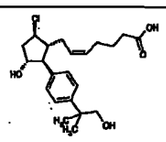
		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
NUMBER	STRUCTURE	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
		18735			NA	NA	526	NA		NA	NA	NA
		48765					>10K		>10K			
		4185			NA	NA	173	NA		NA	NA	NA

Table 1

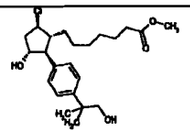
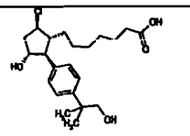
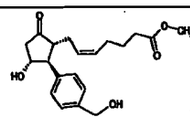
		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
NUMBER	STRUCTURE	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
							>10K		>10K			
		8950			NA	NA	708	NA	>10K	NA	NA	NA
7-5							NA		NA			

Table 1

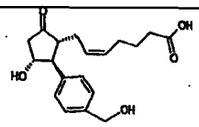
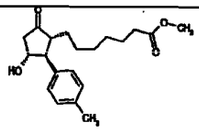
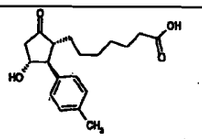
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
7-6							NA		NA			
7-9					NA	NA	>10K	NA	NA	NA	NA	NA
7-10					NA	1873	3128	NA	NA	94	NA	NA

Table 1

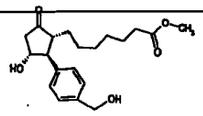
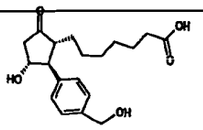
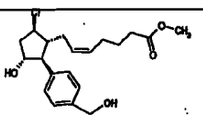
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
7-7							NA		NA			
7-8							NA		NA			
8-4							>10K		NA			

Table 1

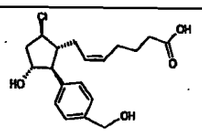
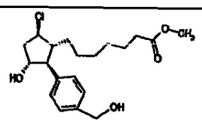
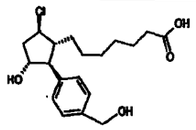
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
8-5		13150			NA	NA		NA	NA	NA	NA	NA
8-6							NA		>10K			
8-7							>10K		NA			

Table 1

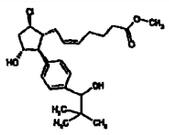
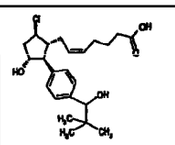
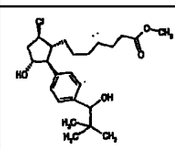
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
9-6					NA	NA	4995	NA	>10K	NA	NA	NA
9-8		1537			NA	NA	779	NA	>10K	NA	NA	NA
					NA	NA	6575	NA	>10K	NA	NA	NA

Table 1

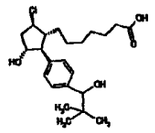
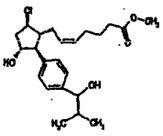
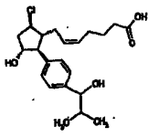
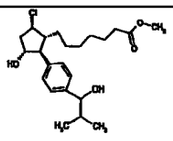
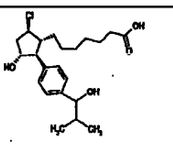
NUMBER	STRUCTURE	BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
		3630			NA	NA	1265	NA	>10K	NA	NA	NA
9-5							>10K		>10K			
9-7			KI 1340		NA	NA	497	NA	NA	NA	NA	NA

Table 1

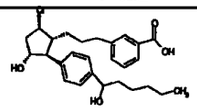
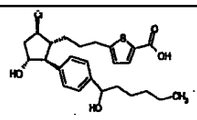
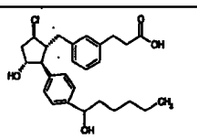
		BINDING IC50 (nm)			FUNCTIONAL EC50 (nm)							
NUMBER	STRUCTURE	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
							>10K		>10K			
			Ki 3022				>10K		NA			

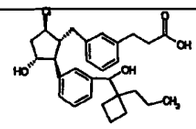
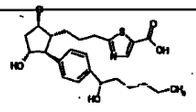
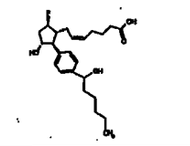
NA means "not active"

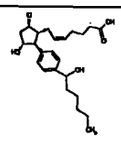
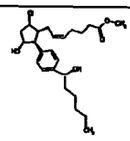
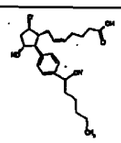
cAMP assay.

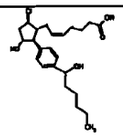
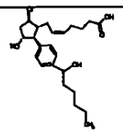
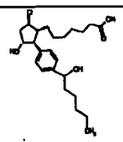
A 384-well drug plate was prepared to contain 6 test compounds, PGE2 and cAMP in 16 serial dilutions in triplicate, using a Biomek station. HEK-EBNA cells expressing a target PG receptor subtype (EP2 or EP4) were suspended in a stimulation buffer (HBSS, 0.1 % BSA, 0.5 mM IBMX and 5 mM HEPES, pH 7.4) in a density of 10^4 cells/5µl. The reaction was initiated by mixing 5 µL drug dilutions with 5 µl of HEK-EBNA cells in a well, carried out for 30 min at room temperature, and followed by the addition of 5 µl anti-cAMP acceptor beads in the control buffer with Tween-20 (25 mM NaCl, 0.03 % Tween-20, 5 mM HEPES, pH7.4). After 30 min in the dark at room temperature, the mixtures were incubated with 15 µl biotinylated-cAMP/strepavidin donor beads in Lysis/Detection buffer (0.1 % BSA, 0.3 % Tween-20 and 5 mM HEPES, pH7.4) for 45 min at the room temperature. Fluorescence changes were read using a Fusion-alpha HT microplate reader.

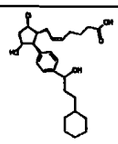
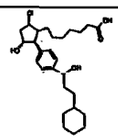
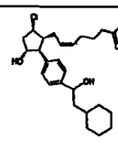
Table 2 provides data for additional compound which were tested with the cAMP assay, as well as those described above.

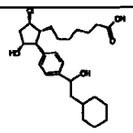
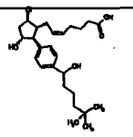
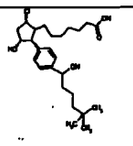
Cmpd	STRUCTURE[a]	BINDING-Ki (nM)		Ca^{2+} Signal-EC50 (nM)[b]							
		EP2	EP4	FP	EP1	EP2	EP3	EP4	TP	IP	DP
18-13				not active	917	2446	4152	not active	not active	not active	not active
102		24	3018	not active	664	4 (2)	348	not active	not active	not active	not active
20-5		2779	3950	not active	not active	158 (56)	4674		not active	not active	not active

104		>10K	>10K	not active	not active	4111 (69)	not active	>10K	not active	not active	not active
21-7		6175		not active	not active	619 (1065)	not active	>10K	not active	not active	not active
22-3		804	>10K	not active	not active	53 (8)	1451	not active	not active	10061	not active

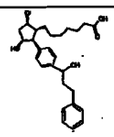
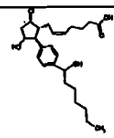
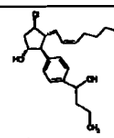
23-5		3951	4586	not active	not active	242 (324)	7235	947	not active	6882	not active
110				not active	not active	3956	not active	not active	not active	not active	not active
24-4		209	>10K	not active	not active	7 (3)	456	>10K	not active	not active	not active

24-4[c]		209	>10K	not active	not active	36 (38)	not active	>10K	not active	not active	not active
24-4[d]		73	>10K	not active	not active	11 (3)	2999	>10K	not active	not active	not active
114		287	8612	not active	not active	28 (76)	477	>10K	not active	not active	not active

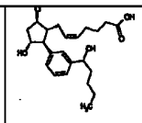
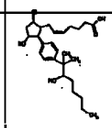
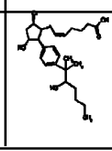
115		260	3812	not active	not active	495 (176)	2224	not active	not active	not active	not active
116		1289	5581	not active	not active	2334 (5259)	1708	not active	not active	not active	not active
117		483	15922	not active	not active	953 (495)	not active	not active	not active	not active	not active

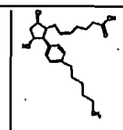
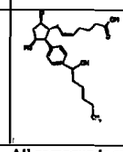
118		2287	4940	not active	not active	2254 (2660)	not active	>10K	not active	not active	not active
119		1053	6287			>10K (815)		>10K			
120		3849	3805	not active	not active	5394 (>10K)	4449	10725	not active	not active	not active

121		77	>10K	not active	not active	9 (14)	not active	>10K	not active	not active	not active
122		148	>10K	not active	not active	51 (59)	not active	15806	not active	not active	not active
123		1128	>10K	not active	not active	548 (125)	13712	>10K	not active	not active	not active

124		2162	>10K	not active	4523	735 (628)	8826	>10K	not active	not active	not active
125		278	2263	not active	not active	58 (12)	5932	not active	not active	not active	not active
126		1657	>10K	not active	not active	154 (7)	not active	not active	not active	not active	not active

127		589		not active	not active	(10)	not active	not active	not active	not active	not active
128		564	not active	not active	not active	142 (9)	not active	not active	not active	1647	
129		1388	>10K	not active	not active	119 (38)	37	not active	not active	8489	not active

130		1255	>10K	not active	not active	68 (10)	23	not active	3747	2059	not active
131		182	5406	not active	not active	544 (19)	1301	not active	not active	not active	not active
132		225	9636	not active	not active	164 (9)	2811	not active	not active	not active	not active

26-2		83	>10K	not active	not active	26 (27)	not active	>10K	not active	not active	not active
27-4		12		not active	not active	16 (5)	25	not active	6931	3283	not active

a) All compounds are mixtures of diastereomers except where indicated
b) Data in parentheses refer to measurement of cAMP (see experimental for details)
c) Faster eluting diastereomer (HPLC); stereochemistry not determined
d) Slower eluting diastereomer (HPLC); stereochemistry not determined

In Vivo Testing

Intraocular Pressure (IOP)

Intraocular pressure studies in dogs involved pneumatonometry performed in conscious, Beagle dogs of both sexes (10-15 kg). The animals remained conscious throughout the study and were gently restrained by hand. Drugs were administered topically to one eye as a 25 µL volume drop, the other eye received 25 µL vehicle (0.1% polysorbate 80:10 mM TRIS) as a control. Proparacaine (0.1%) was used for corneal anesthesia during tonometry. Intraocular pressure was determined just before drug administration and at 2, 4 and 6 hr thereafter on each day of the 5 day study. Drug was administered immediately after the first IOP reading.

Ocular Surface Hyperemia

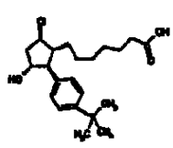
Ocular surface hyperemia was visually assessed and scored according to a system typically used clinically.

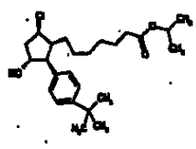
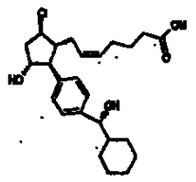
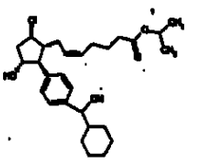
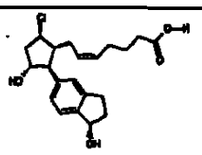
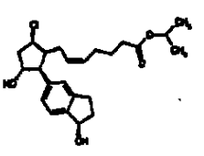
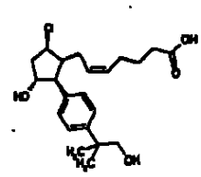
Hyperemia Score	Assigned Value
<1 trace	0.5
1 mild	1
moderate	2
severe	3

Ocular surface hyperemia was evaluated at the same time points as intraocular pressure measurement. It should be noted that untreated dog eyes frequently have a pink/red tone. Thus, values of trace or even mild are not necessarily out of the normal range. Similar tests were used to determine ocular surface hyperemia on monkeys and rabbits.

Tables 3 and 4 below present the results of the *in vivo testing*.

Table 3

NUMBER	STRUCTURE		DOG		MONKEY	RABBIT
		Conc. (g/100 mL)	Max. ΔIOP (mm Hg)	Max. hyperemia	Max. ΔIOP (mm Hg)	Max. hyperemia
		0.10%	-4	0.9		0

NUMBER	STRUCTURE		DOG		MONKEY	RABBIT
		Conc. (g/100 mL)	Max. ΔIOP (mm Hg)	Max. hyperemia	Max. ΔIOP (mm Hg)	Max. hyperemia
		0.01%			8	0.1
6-4		0.10%	-4	1		0
6-5		0.01%	-4	0.6	5	
16-5		0.30%	-7	1	7	
16-6		0.10%	-12			0.25
		0.30%	-8	0.9		

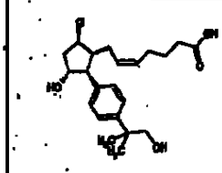
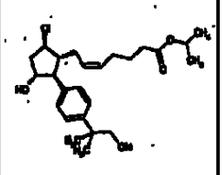
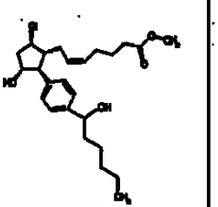
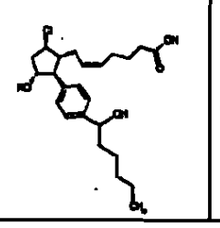
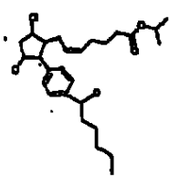
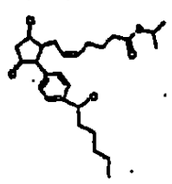
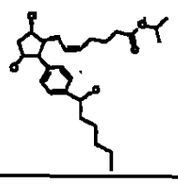
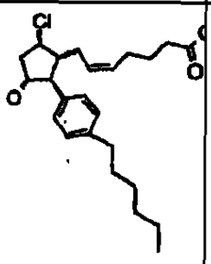
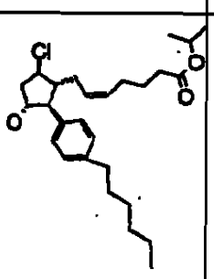
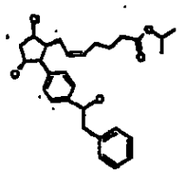
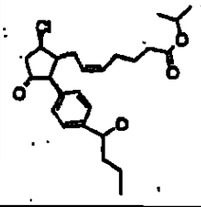
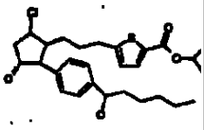
NUMBER	STRUCTURE		DOG		MONKEY	RABBIT
		Conc. (g/100 mL)	Max. ΔIOP (mm Hg)	Max. hyperemia	Max. ΔIOP (mm Hg)	Max. hyperemia
						
		0.10%	-5	0.7	6	0.1

Table 4

ENTRY	STRUCTURE		DOG		MONKEY	RABBIT
		Conc. (g/100 mL)	Max. ΔIOP (%)	Max. hyperemia	Max. ΔIOP (%)	Max. hyperemia
24-3[a]		0.1%	-50	1.5		
24-4[a]		0.03%	-21	1	21	0

ENTRY	STRUCTURE		DOG		MONKEY	RABBIT
		Conc. (g/100 mL)	Max. ΔIOP (%)	Max. hyperemia	Max. ΔIOP (%)	Max. hyperemia
24-5[a]		0.03%	-33	1	16	0.2
24-5[b]		0.1%	-13	0.5	24	
24-5[c]		0.1%	-47	1.5	28	1.5
26-2		0.1%	-43	0.6	32	0.25
207		0.1	20	0.5	21	

10

ENTRY	STRUCTURE	Conc. (g/100 mL)	DOG		MONKEY	RABBIT
			Max. ΔIOP (%)	Max. hyperemia	Max. ΔIOP (%)	Max. hyperemia
208		0.1%	-40	0.8	39	0
209		0.1%	-36	0.5	35	
210		0.1	-50	1.8		1

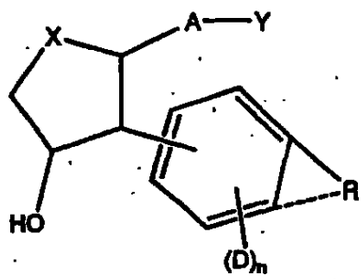
(a) mixture of diastereomers
(b) faster eluting (HPLC) diastereomer
(c) slower eluting (HPLC) diastereomer

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

CLAIMS

What is claimed is:

1. A compound comprising



or a pharmaceutically acceptable salt or a prodrug thereof,

wherein a dashed line represents the presence or absence of a covalent bond;

Y is a carboxylic acid, sulfonic acid, or phosphonic acid; or an amide or ester thereof comprising from 0 to 12 carbon atoms; or Y is a hydroxymethyl, or tetrazolyl functional group;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is substituted or unsubstituted phenyl or monocyclic heteroaryl, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O;

X is C=O, CHF, CF_2, CHCl, or CHOH; wherein if X is CHOH, then OH is in the β-configuration;

R is a hydrocarbyl or a hydroxyhydrocarbyl moiety comprising from 1 to 12 carbon atoms;

D is independently a moiety comprising from 1 to 6 non-hydrogen atoms; and

n is an integer from 0 to 4.

2. The compound of claim 1 wherein n is 0.

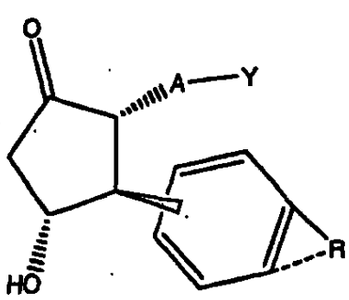
3. The compound of claim 1 wherein R comprises from 6 to 9 carbon atoms and a cyclic structure.

4. The compound of claim 3 wherein R is a 1-hydroxyhydrocarbyl moiety.

5. The compound of claim 1 wherein R comprises from 1 to 5 carbon atoms.

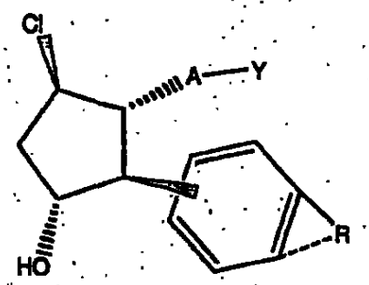
6. The compound of claim 5 wherein R consists of t-butyl.

7. The compound of claim 1 comprising



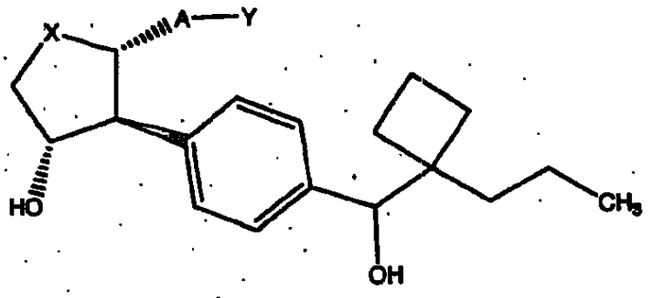
or a pharmaceutically acceptable salt, or a prodrug thereof.

8. The compound of claim 1 comprising



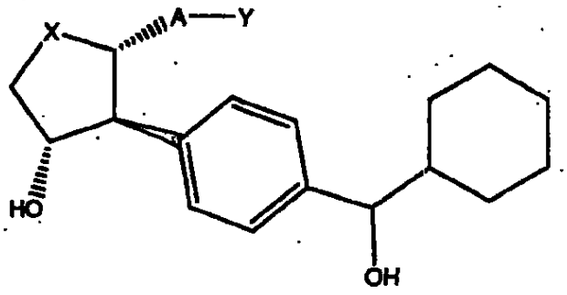
or a pharmaceutically acceptable salt, or a prodrug thereof.

9. The compound of claim 4 comprising



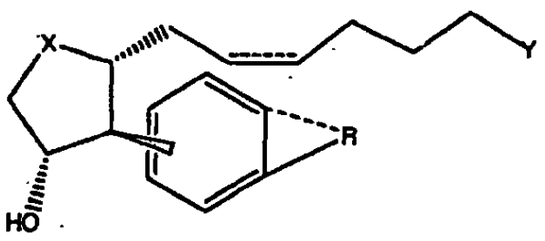
or a pharmaceutically acceptable salt, or a prodrug thereof.

10. The compound of claim 4 comprising



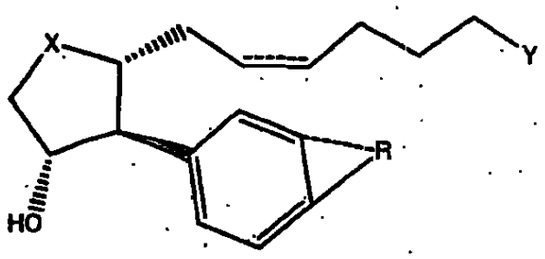
or a pharmaceutically acceptable salt, or a prodrug thereof.

11. The compound of claim 1 comprising



or a pharmaceutically acceptable salt, or a prodrug thereof.

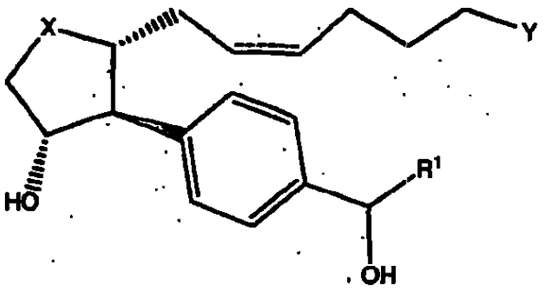
12. The compound of claim 11 comprising



wherein X is C=O or CHCl; and

R is alkyl having from 3 to 6 carbon atoms.

13. The compound of claim 11 comprising

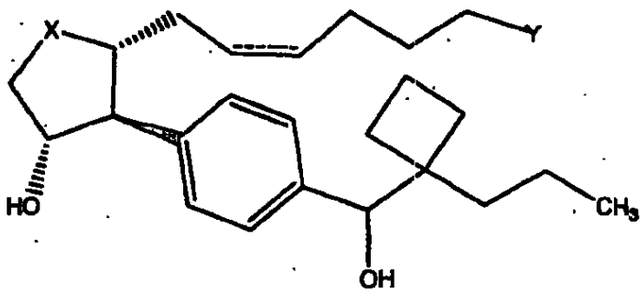


or a pharmaceutically acceptable salt, or a prodrug thereof,

wherein R^1 is cycloalkyl comprising from 3 to 10 carbon atoms; and

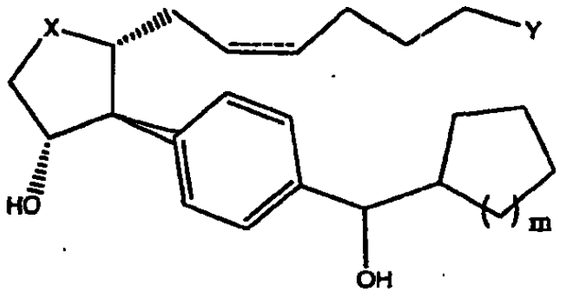
X is C=O or CHCl.

14. The compound of claim 13 comprising



or a pharmaceutically acceptable salt, or a prodrug thereof.

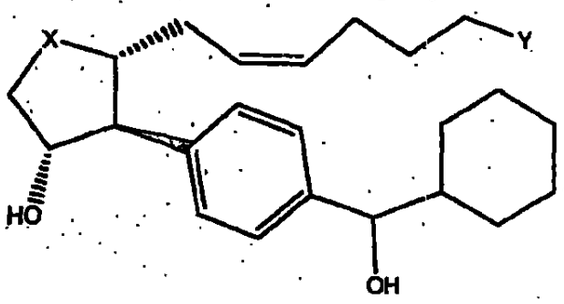
15. The compound of claim 13 comprising



or a pharmaceutically acceptable salt, or a prodrug thereof

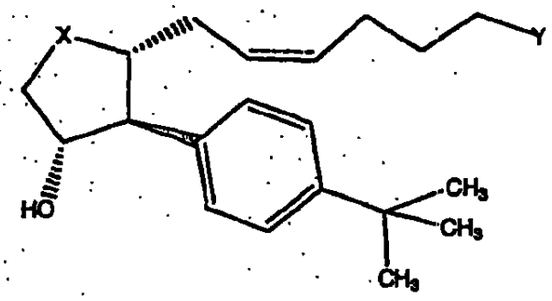
wherein m is an integer having a value of from 0 to 3.

16. The compound of claim 15 comprising .



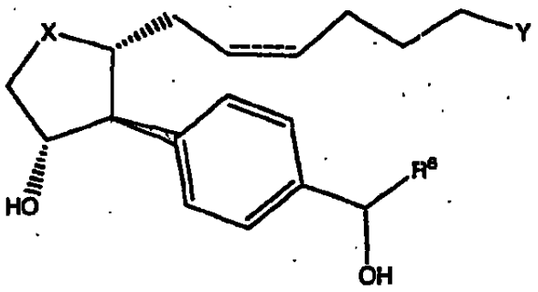
or a pharmaceutically acceptable salt, or a prodrug thereof.

17. The compound of claim 12 comprising .



or a pharmaceutically acceptable salt, or a prodrug thereof.

18. The compound of claim 11 comprising .



or a pharmaceutically acceptable salt, or a prodrug thereof,

wherein R^6 is branched alkyl comprising from 3 to 10 carbon atoms; and

X is C=O or CHCl.

19. The compound of claim 11 comprising

(Z)-7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-hept-5-enoic acid;

7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R)-2-[4-(Cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-5-oxo-cyclopentyl}-heptanoic acid;

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester;

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid;

7-((1R,2S,3R)-3-Hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid methyl ester;

7-((1R,2S,3R)-3-Hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid;

(Z)-7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-hept-5-enoic acid;

7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-heptanoic acid methyl ester;

7-[(1R,2S,3R)-2-(4-*tert*-Butyl-phenyl)-3-hydroxy-5-oxo-cyclopentyl]-heptanoic acid. (Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-5-oxo-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl[-5-oxo-cyclopentyl}-hept-5-enoic acid;

7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R)-3-Hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid;

(Z)-7-{(1R,2S,3R)-3-Hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-5-oxo-cyclopentyl}-hept-5-enoic acid methyl ester;

7-{(1R,2S,3R)-3-Hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R)-3-Hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-5-oxo-cyclopentyl}-heptanoic acid;

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester;

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid;

7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid methyl ester;

7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-heptanoic acid;

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid (2-hydroxy-ethyl)-amide;

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid ethyl amide;

(Z)-7-((1R,2S,3R)-3-Hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentyl)-hept-5-enoic acid ethyl amide;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-hept-5-enoic acid;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-hept-5-enoic acid isopropyl ester;

7-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-heptanoic acid methyl ester;

7-[(1R,2S,3R,5R)-5-Chloro-2-(4-cyclohexylmethyl-phenyl)-3-hydroxy-cyclopentyl]-heptanoic acid methyl ester;

7-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-heptanoic acid;

7-[(1R,2S,3R,5R)-5-Chloro-2-(4-cyclohexylmethyl-phenyl)-3-hydroxy-cyclopentyl]-heptanoic acid;

(Z)-7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-hept-5-enoic acid methyl ester;

(Z)-7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-hept-5-enoic acid;

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-heptanoic acid methyl ester;

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-heptanoic acid;

(Z)-7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-hept-5-enoic acid methyl ester;

(Z)-7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-hept-5-enoic acid;

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-heptanoic acid methyl ester;

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{4-[hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentyl)-heptanoic acid;

(Z)-7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-hept-5-enoic acid;

7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-heptanoic acid methyl ester;

7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-heptanoic acid;

(Z)-7-[(1R,2S,3R,5R)-2-(4-*tert*-Butyl-phenyl)-5-chloro-3-hydroxy-cyclopentyl]-hept-5-enoic acid isopropyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl}-hept-5-enoic acid;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-cyclobutyl)-phenyl]-cyclopentyl}-heptanoic acid;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-hept-5-enoic acid;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-heptanoic acid;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(2-hydroxy-1,1-dimethyl-ethyl)-phenyl]-cyclopentyl}-heptanoic acid isopropyl ester;

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-hept-5-enoic acid;

7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-heptanoic acid methyl ester;

7-((1R,2S,3R)-3-Hydroxy-5-oxo-2-*p*-tolyl-cyclopentyl)-heptanoic acid methyl ester;

7-[(1R,2S,3R)-3-Hydroxy-2-(4-hydroxymethyl-phenyl)-5-oxo-cyclopentyl]-heptanoic acid;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-hept-5-enoic acid;

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-heptanoic acid methyl ester;

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(4-hydroxymethyl-phenyl)-cyclopentyl]-heptanoic acid;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl}-hept-5-enoic acid;

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl}-hept-5-enoic acid;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid methyl ester;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2-methyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid;

7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-2,2-dimethyl-propyl)-phenyl]-cyclopentyl}-heptanoic acid;

(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-ynyloxy)-acetic acid methyl ester;

(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-ynyloxy)-acetic acid;

((Z)-4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-enyloxy)-acetic acid methyl ester;

((Z)-4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-but-2-enyloxy)-acetic acid;

(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-butoxy)-acetic acid methyl ester;

(4-{(1R,2S,3R,5R)-5-Chloro-2-[4-(cyclohexyl-hydroxy-methyl)-phenyl]-3-hydroxy-cyclopentyl}-butoxy)-acetic acid;

[3-((1R,2S,3R)-3-Hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentylmethyl)-phenoxy]-acetic acid methyl ester;

[3-((1R,2S,3R)-3-Hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-5-oxo-cyclopentylmethyl)-phenoxy]-acetic acid;

[3-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentylmethyl)-phenoxy]-acetic acid methyl ester;

[3-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-{3-[(S)-hydroxy-(1-propyl-cyclobutyl)-methyl]-phenyl}-cyclopentylmethyl)-phenoxy]-acetic acid;

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-hept-5-enoic acid;

(Z)-7-[(1R,2S,3R)-3-Hydroxy-5-oxo-2-(1-oxo-indan-5-yl)-cyclopentyl]-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R)-3-Hydroxy-5-oxo-2-(1-oxo-indan-5-yl)-cyclopentyl]-hept-5-enoic acid;

7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-heptanoic acid methyl ester;

7-((1R,2S,3R)-3-Hydroxy-2-indan-5-yl-5-oxo-cyclopentyl)-heptanoic acid methyl ester;

7-[(1R,2S,3R)-3-Hydroxy-2-(1-hydroxy-indan-5-yl)-5-oxo-cyclopentyl]-heptanoic acid;

7-((1R,2S,3R)-3-Hydroxy-2-indan-5-yl-5-oxo-cyclopentyl)-heptanoic acid;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid isopropyl ester;

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid methyl ester;

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-indan-5-yl-cyclopentyl)-heptanoic acid methyl ester;

7-[(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid;

7-((1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-indan-5-yl-cyclopentyl)-heptanoic acid;

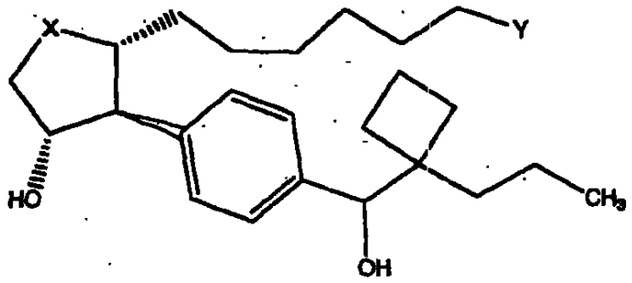
7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid methyl ester;

7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-heptanoic acid;

(Z)-7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid methyl ester; or

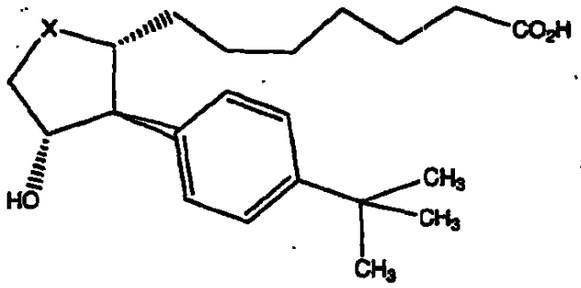
(Z)-7-[(1R,2S,3R)-5-Fluoro-3-hydroxy-2-(1-hydroxy-indan-5-yl)-cyclopentyl]-hept-5-enoic acid.

20. The compound of claim 14 comprising



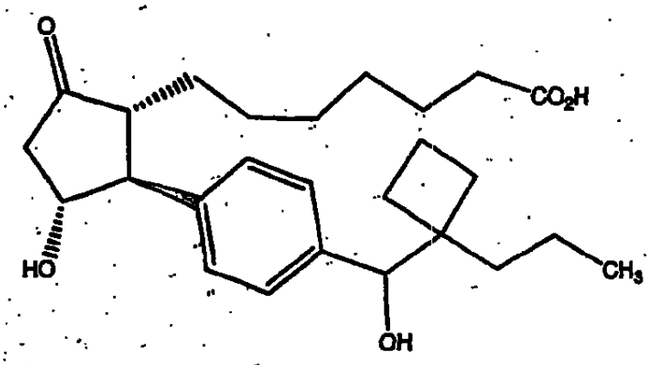
or a pharmaceutically acceptable salt, or a prodrug thereof.

21. The compound of claim 12 comprising;



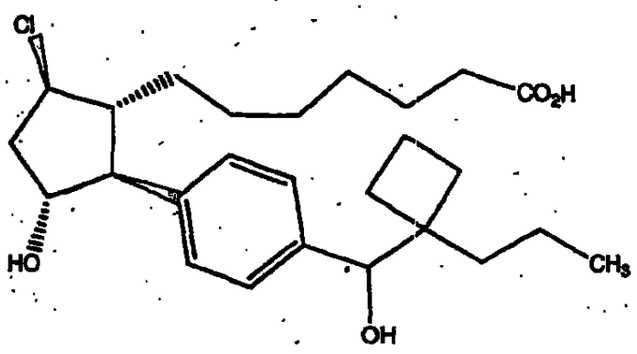
or a pharmaceutically acceptable salt, or a prodrug thereof.

22. The compound of claim 20 comprising



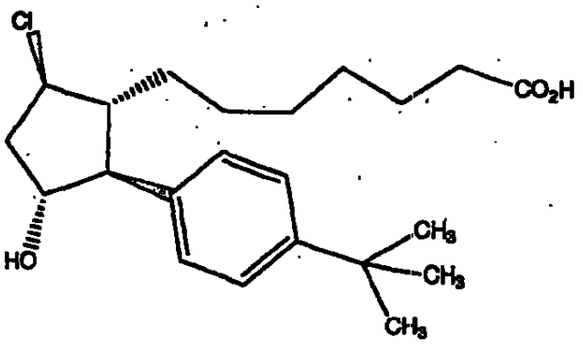
or a pharmaceutically acceptable salt, or a prodrug thereof.

23. The compound of claim 20 comprising



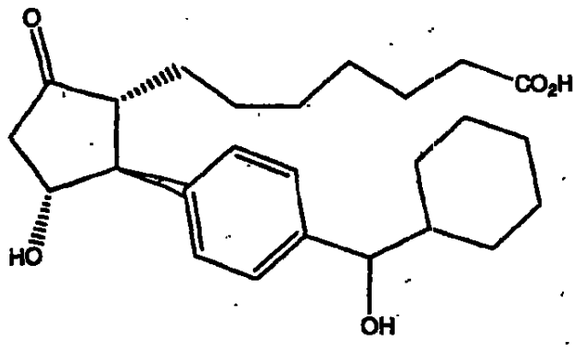
or a pharmaceutically acceptable salt, or a prodrug thereof.

24. The compound of claim 21 comprising



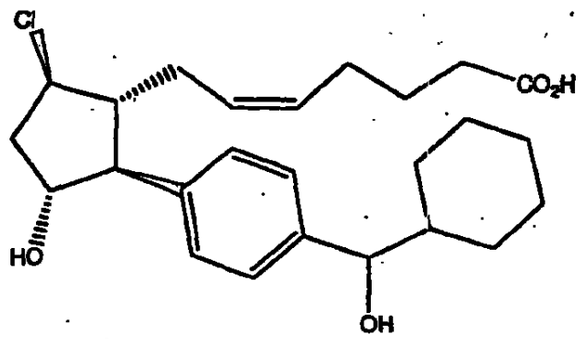
or a pharmaceutically acceptable salt, or a prodrug thereof.

25. The compound of claim 16 comprising



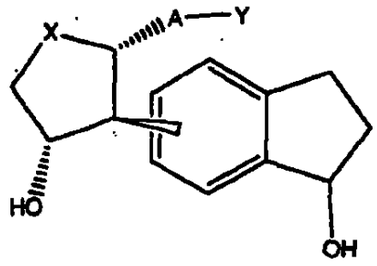
or a pharmaceutically acceptable salt, or a prodrug thereof.

26. The compound of claim 16 comprising



or a pharmaceutically acceptable salt, or a prodrug thereof.

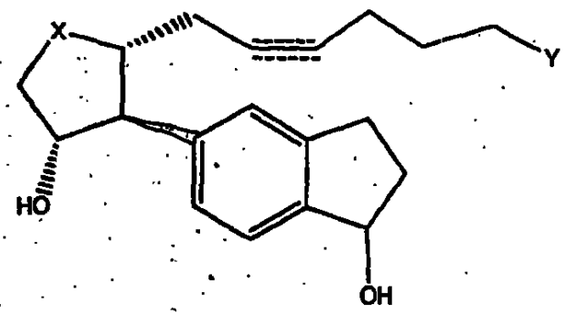
27. The compound of claim 1 comprising.



or a pharmaceutically acceptable salt or a prodrug thereof.

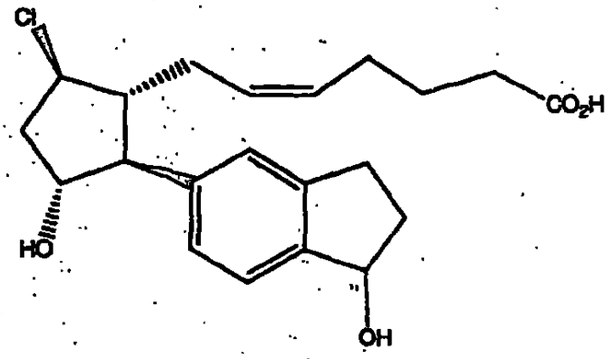
28. The compound of claim 27 wherein *A* is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$.

29. The compound of claim 28 comprising



or a pharmaceutically acceptable salt or a prodrug thereof.

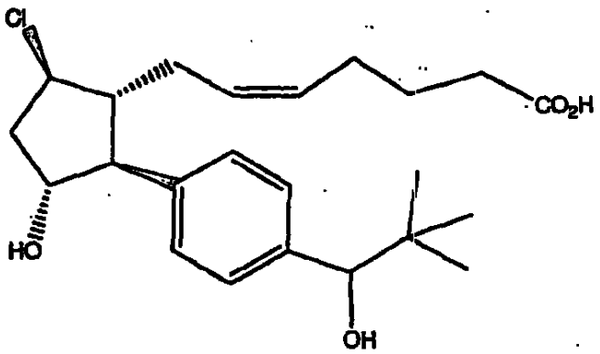
30. The compound of claim 29 comprising



or a pharmaceutically acceptable salt or a prodrug thereof.

31. The compound of claim 5 wherein R is 1-hydroxyalkyl having from 1 to 5 carbon atoms.

32. The compound of claim 31 comprising

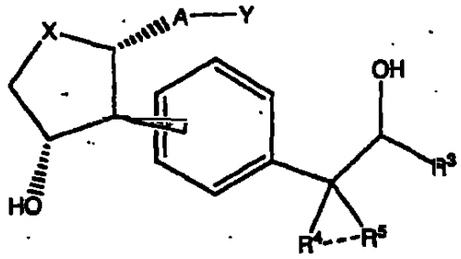


or a pharmaceutically acceptable salt or a prodrug thereof.

33. The compound of claim 1 wherein Y is selected from the group consisting of $CO_2(R^3)$, $CON(R^3)_2$, $CON(OR^3)R^3$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH, $P(O)(OH)_2$, $CONHSO_2R^3$, $SO_2N(R^3)_2$, SO_2NHR^3, and tetrazolyl-R^3; wherein R^3 is independently H, C_1-C_6 alkyl, phenyl, or biphenyl.

34. The compound of claim 1 wherein R is 2-hydroxyhydrocarbyl.

35. The compound of claim 34 comprising

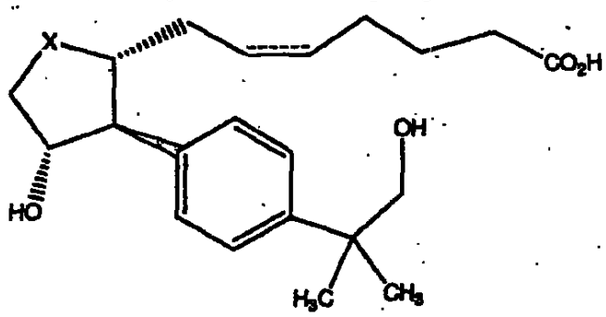


or a pharmaceutically acceptable salt or a prodrug thereof;

wherein R^3, R^4, and R^5 are independently H or C_{1-6} alkyl.

36. The compound of claim 35 wherein R^4 and R^5 are methyl.

37. The compound of claim 36 comprising



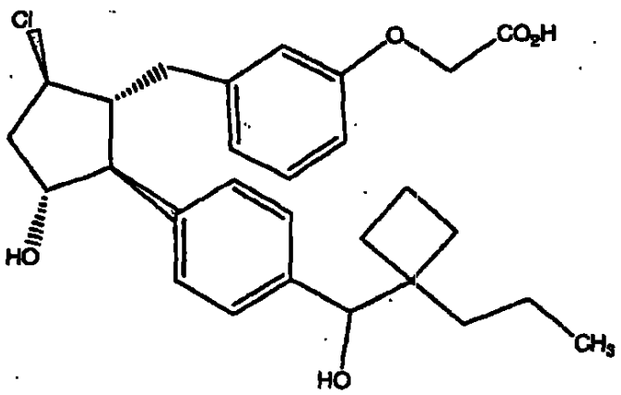
or a pharmaceutically acceptable salt or a prodrug thereof,

wherein X is C=O or CHCl.

38. The compound of claim 1 wherein A is $-(CH_2)_m$-Ar-$(CH_2)_o$- wherein Ar is phenyl, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O.

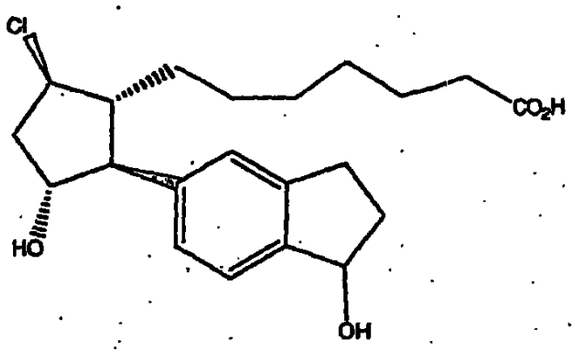
39. The compound of claim 38 wherein A is $-CH_2$-Ar-O-CH_2-.

40. The compound of claim 39 comprising



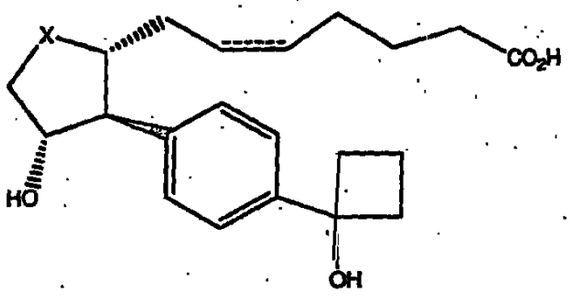
or a pharmaceutically acceptable salt or a prodrug thereof.

41. The compound of claim 29 comprising



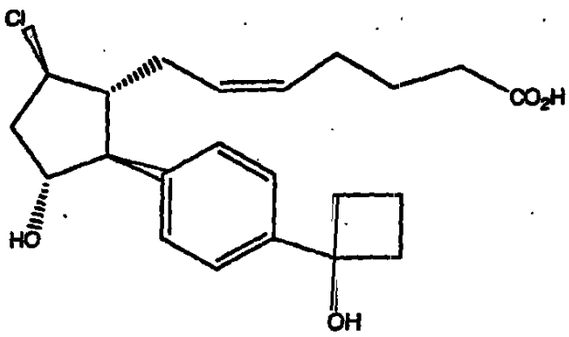
or a pharmaceutically acceptable salt or a prodrug thereof.

42. The compound of claim 31 comprising



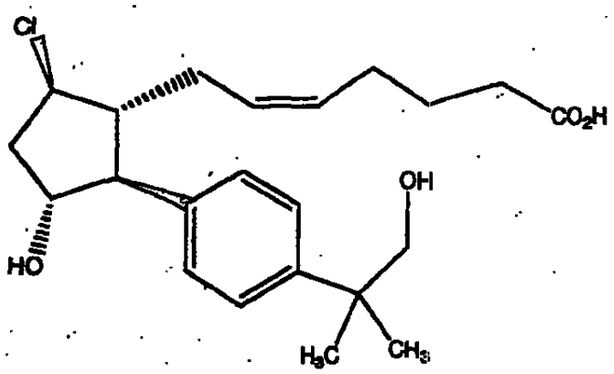
or a pharmaceutically acceptable salt or a prodrug thereof wherein X is C=O or CHCl.

43. The compound of claim 42 comprising:



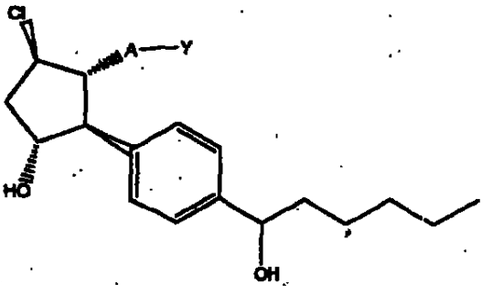
or a pharmaceutically acceptable salt or a prodrug thereof.

44. The compound of claim 37 comprising



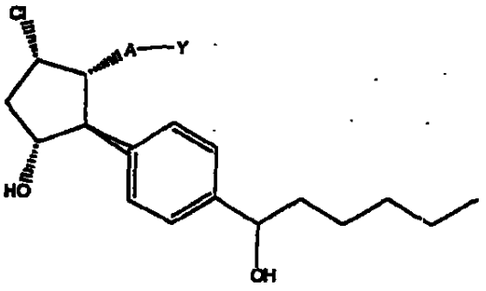
or a pharmaceutically acceptable salt or a prodrug thereof.

45. The compound of claim 2 comprising



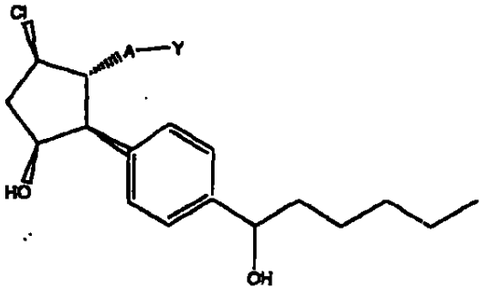
or a pharmaceutically acceptable salt or a prodrug thereof.

46. The compound of claim 2 comprising



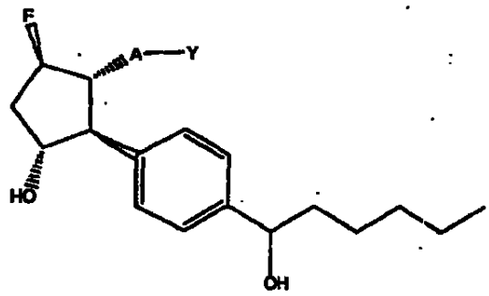
or a pharmaceutically acceptable salt or a prodrug thereof.

47. The compound of claim 2 comprising



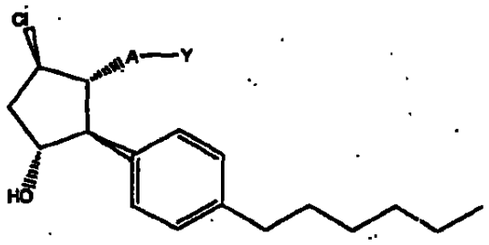
or a pharmaceutically acceptable salt or a prodrug thereof.

48. The compound of claim 2 comprising



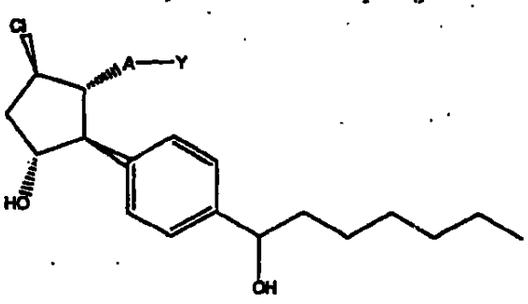
or a pharmaceutically acceptable salt or a prodrug thereof.

49. The compound of claim 2 comprising



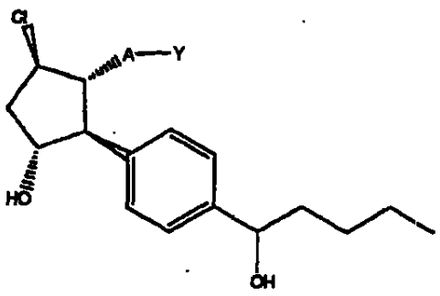
or a pharmaceutically acceptable salt or a prodrug thereof.

50. The compound of claim 2 comprising



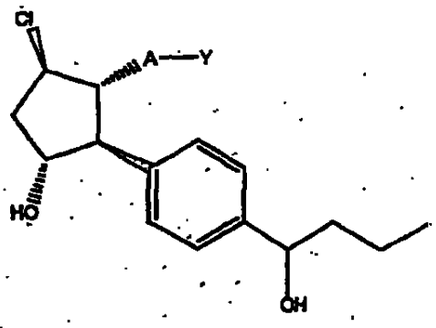
or a pharmaceutically acceptable salt or a prodrug thereof.

51. The compound of claim 2 comprising



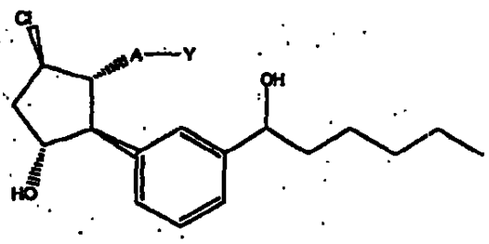
or a pharmaceutically acceptable salt or a prodrug thereof.

52. The compound of claim 2 comprising



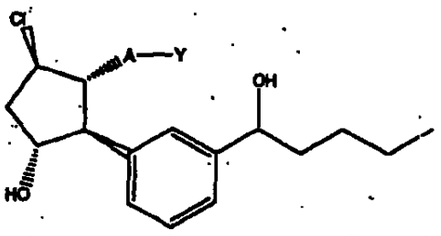
or a pharmaceutically acceptable salt or a prodrug thereof.

53. The compound of claim 2 comprising



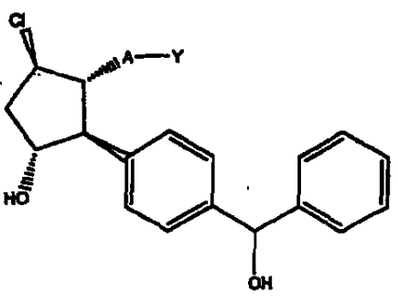
or a pharmaceutically acceptable salt or a prodrug thereof.

54. The compound of claim 2 comprising



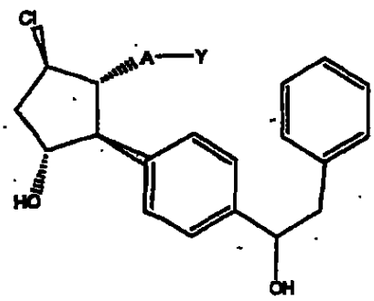
or a pharmaceutically acceptable salt or a prodrug thereof.

55. The compound of claim 2 comprising



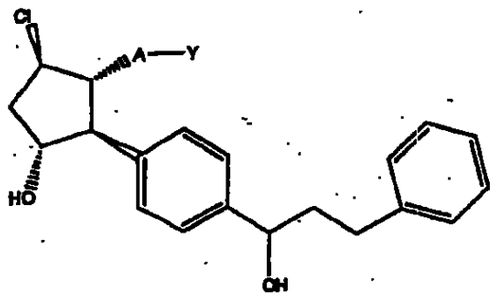
or a pharmaceutically acceptable salt or a prodrug thereof.

56. The compound of claim 2 comprising



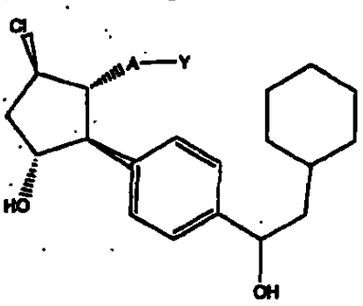
or a pharmaceutically acceptable salt or a prodrug thereof.

57. The compound of claim 2 comprising



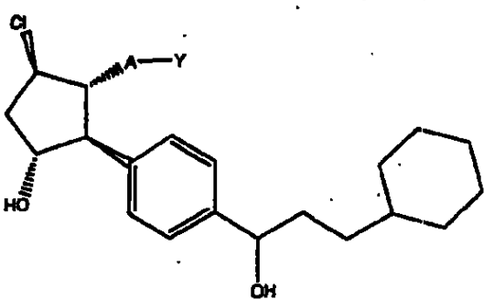
or a pharmaceutically acceptable salt or a prodrug thereof.

58. The compound of claim 2 comprising



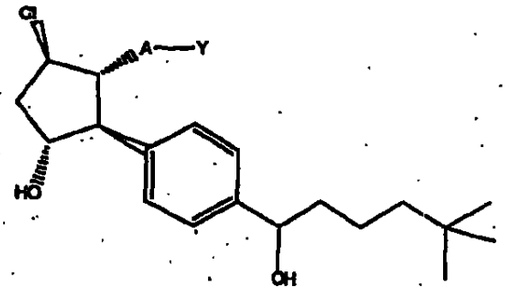
or a pharmaceutically acceptable salt or a prodrug thereof.

59. The compound of claim 2 comprising



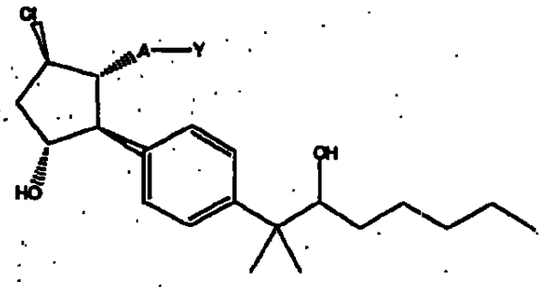
or a pharmaceutically acceptable salt or a prodrug thereof.

60. The compound of claim 2 comprising



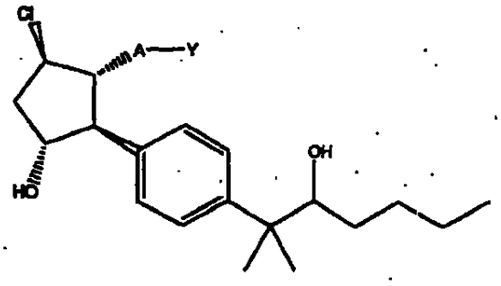
or a pharmaceutically acceptable salt or a prodrug thereof.

61. The compound of claim 2 comprising



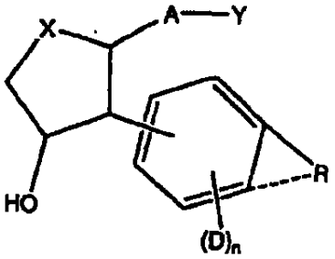
or a pharmaceutically acceptable salt or a prodrug thereof.

62. The compound of claim 2 comprising



or a pharmaceutically acceptable salt or a prodrug thereof.

63. Use of a compound according to any one of claims 1-62 for the manufacture of a medicament for the treatment of glaucoma or the reduction of intraocular pressure, said compound comprising



or a pharmaceutically acceptable salt or a prodrug thereof,

wherein a dashed line represents the presence or absence of a covalent bond;

Y is a carboxylic acid, sulfonic acid, or phosphonic acid; or an amide or ester thereof comprising from 0 to 12 carbon atoms; or Y is a hydroxymethyl, or tetrazolyl functional group;

A is $-(CH_2)_5-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is substituted or unsubstituted phenyl or monocyclic heteroaryl, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O;

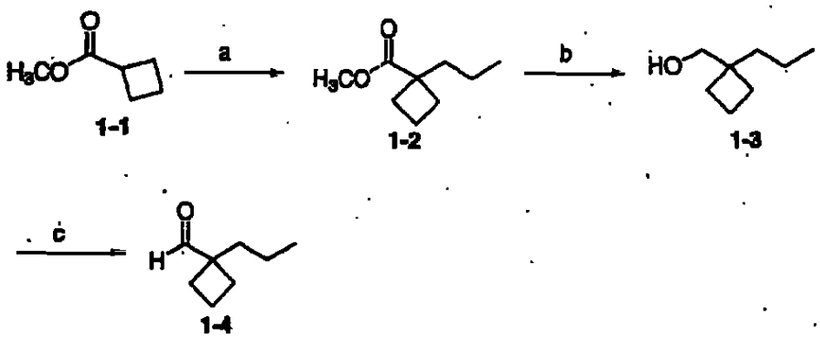
X is C=O, CHF, CF_2, CHCl, or CHOH; wherein if X is CHOH, then OH is in the β-configuration;

R is a hydrocarbyl or a hydroxyhydrocarbyl moiety comprising from 1 to 12 carbon atoms;

D is independently a moiety comprising from 1 to 6 non-hydrogen atoms; and

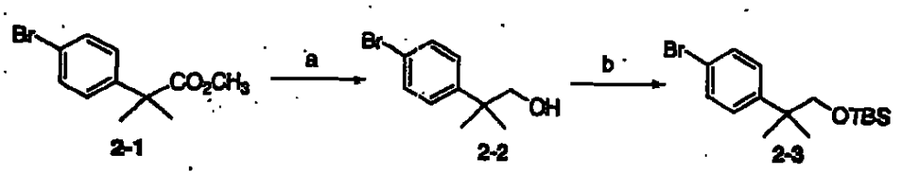
n is an integer from 0 to 4.

64. A liquid comprising a compound according to any one of claims 1-62 wherein said liquid is ophthalmically acceptable.A compound comprising a prostaglandin EP_2 selective agonist wherein the ω-chain comprises a substituted phenyl, wherein at least one substituent consists of hydrocarbyl or non-linear hydroxyhydrocarbyl, wherein said compound is effective in reducing IOP in a monkey by at least 20%.



(a) LDA; propyl iodide; (b) $LiBH_4$; (c) TPAP, NMO, 4Å sieves.

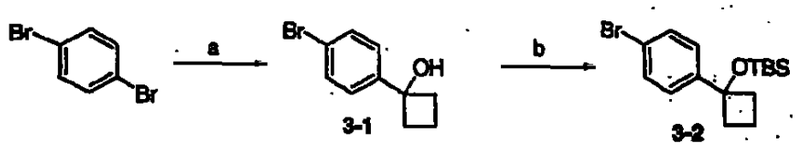
Fig. 2



2-1 2-2 2-3

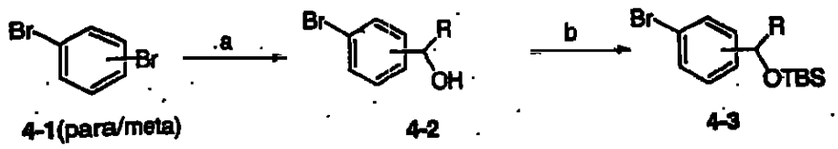
(a) $LiBH_4$; (b)TBSOTf, 2,6-lutidine.

Fig. 3



(a) *n*-BuLi; cyclobutanone; (b)TBSOTf, 2,6-lutidine.

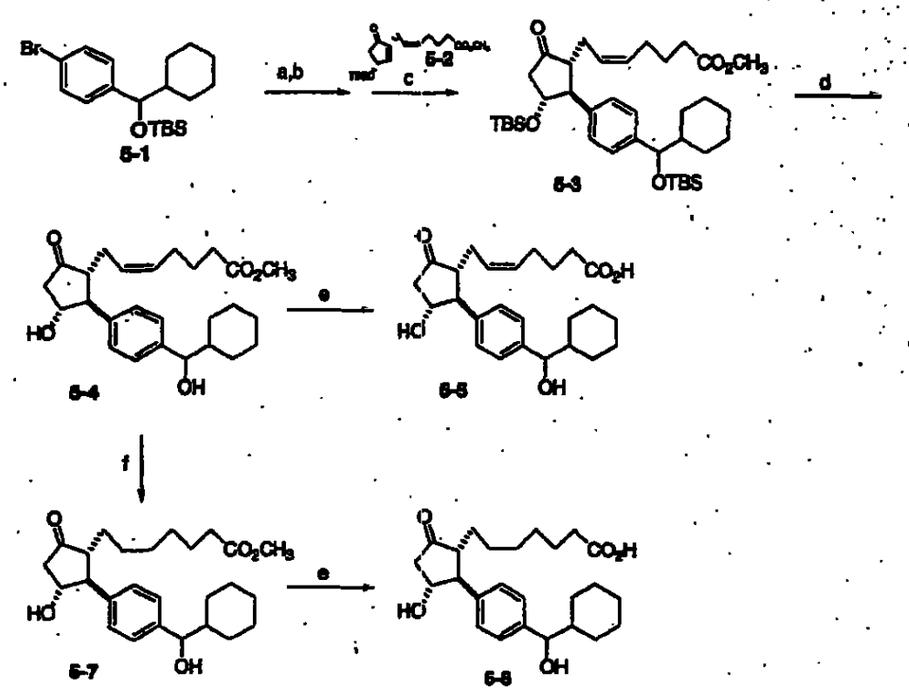
Fig. 4



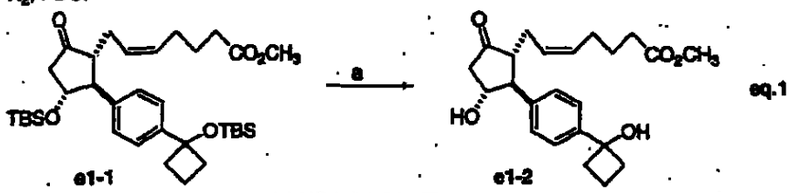
4-1(para/meta) 4-2 4-3

(a) *n*-BuLi; RCHO; (b)TBSOTf, 2,6-lutidine.

Fig. 5

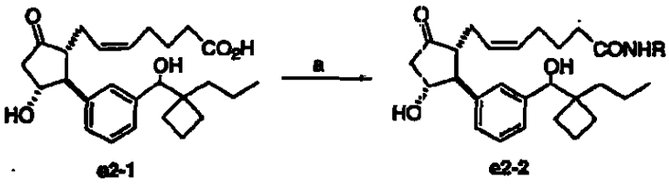


(a) t-BuLi; (b) lithium 2-thienylcuprate; (c) 5-2, THF -78 °C; (d) HF-pyridine, 0 °C; (e) rabbit liver esterase; (f) H_2, Pd/C.



eq.1

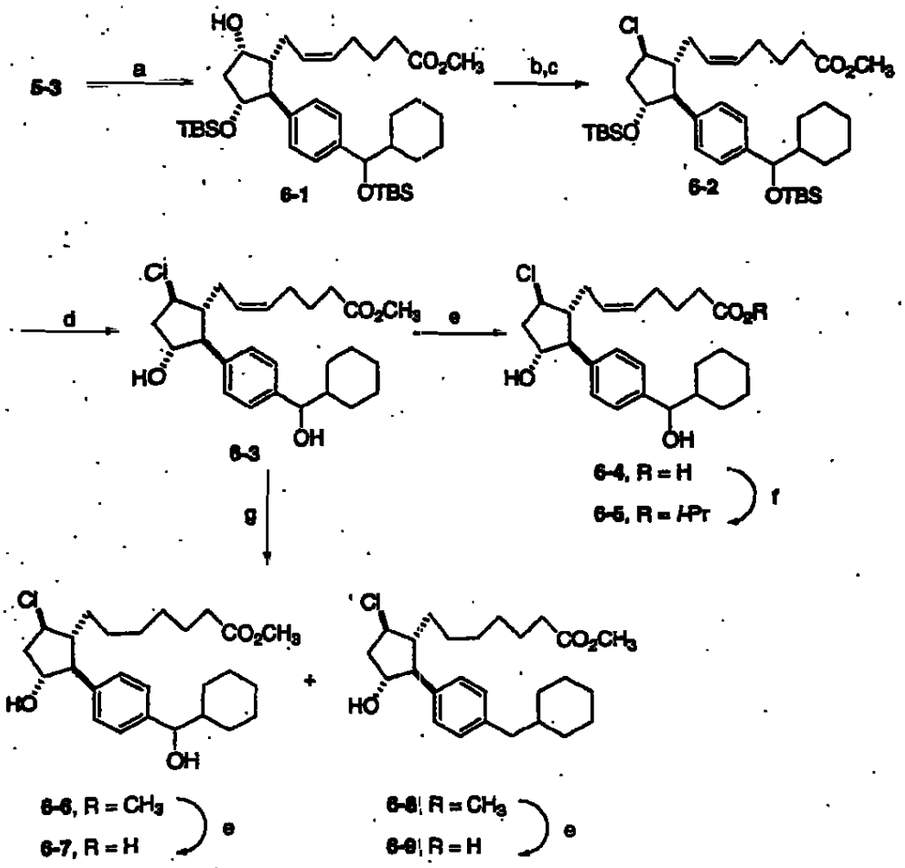
(a) HOAc/H_2O/THF.



eq. 2

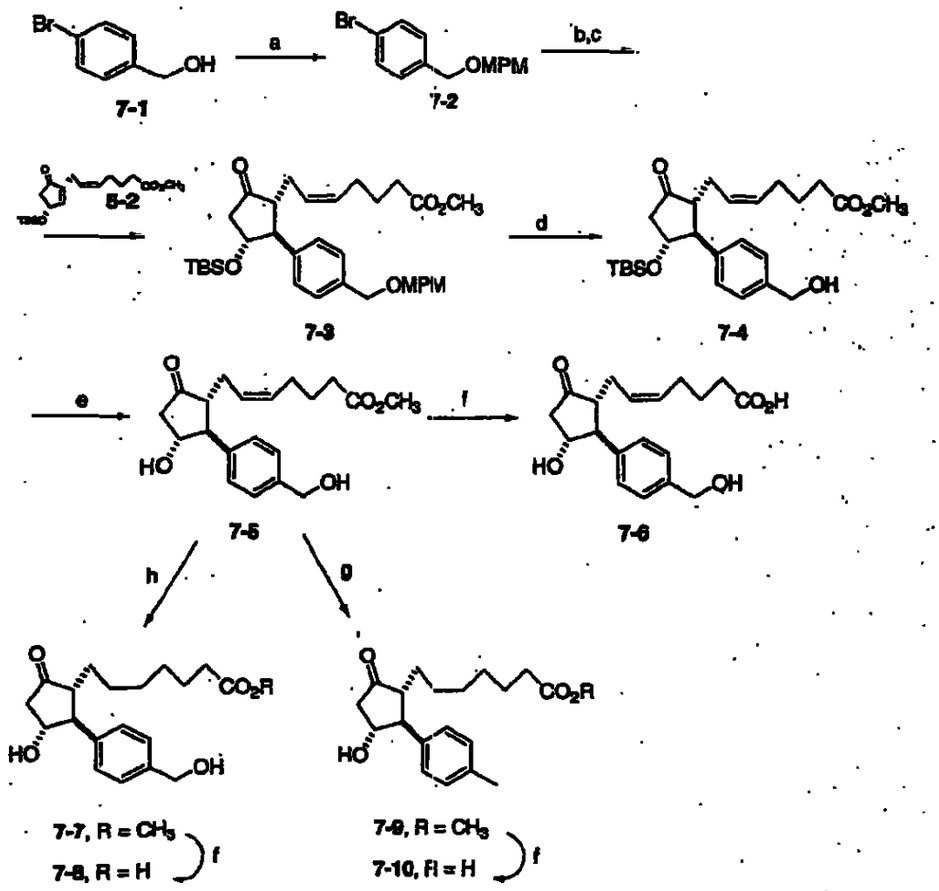
(a) EtOCOCl, TEA;RNH_2 or N-hydroxysuccinimide, EDCI, RNH_2, DMF.

Fig. 6



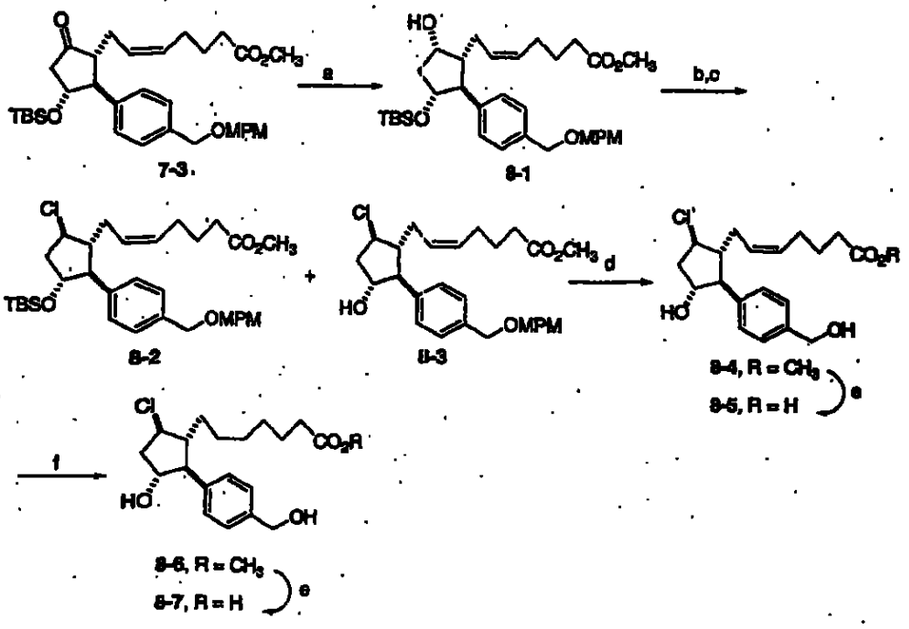
(a) L-Selectride; (b) MsCl, TEA; (c) $(n\text{-Bu})_4NCl$ 40 °C; (d) HF-pyridine, 0 °C; (e) LiOH, H_2O,THF (f) *i*-PrI, DBU; (g) H_2, Pd/C.

Fig. 7



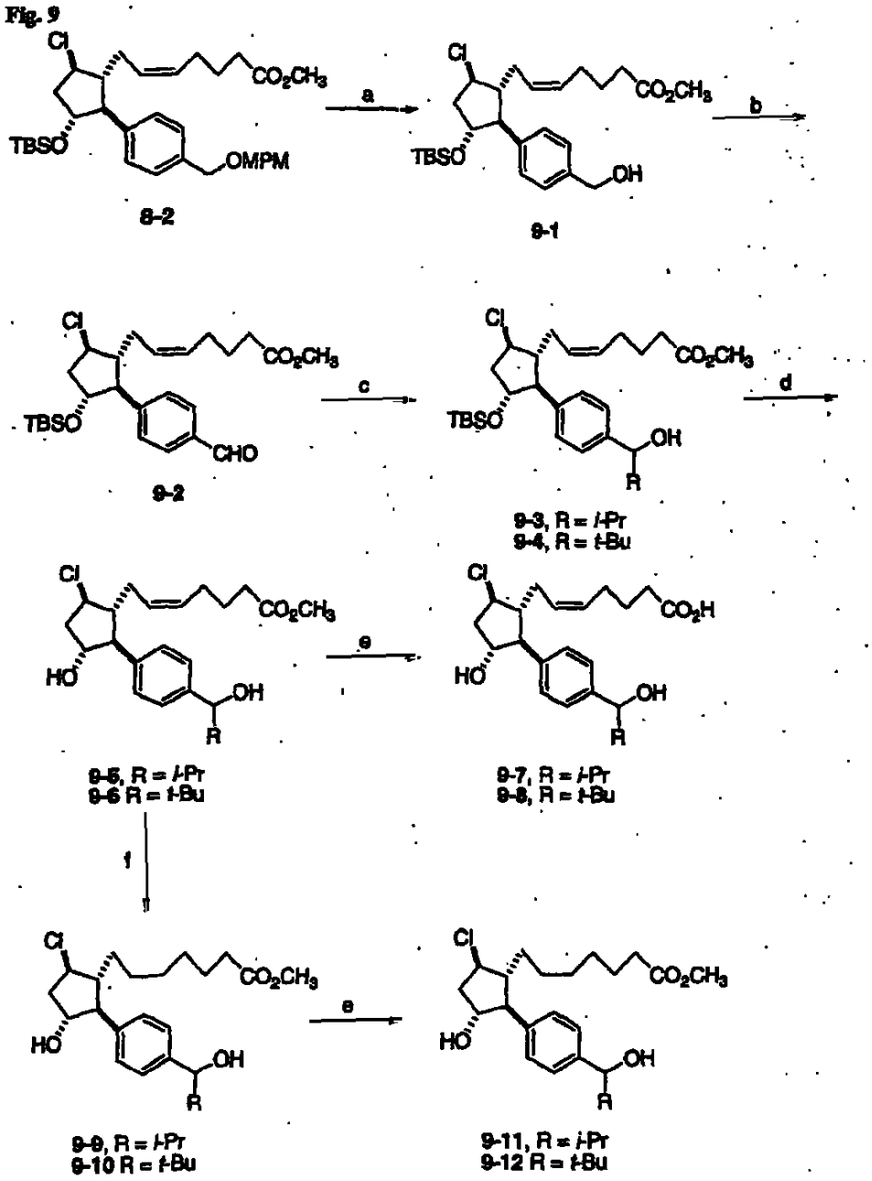
(a) NaH; MPMCl; (b) *t*-BuLi; (c) lithium 2-thienylcuprate; (d) DDQ; (e)HF-pyridine 0 °C; (f) Rabbit Liver Esterase; (g) H_2, Pd/C, EtOAc; (h) Wilkinson's catalyst, H_2, THF.

Fig. 8



(a) L-selectride; H_2O_2; (b) MsCl, Et_3N; (c) $(n\text{-}Bu)_4NCl$ 40 °C; (d) DDQ; (e) 1 M LiOH; (f) H_2, Pd/C, ethyl acetate.

Fig. 9



9-2 9-1

9-3, R = *i*-Pr
9-4, R = *t*-Bu

9-5, R = *i*-Pr
9-6 R = *t*-Bu

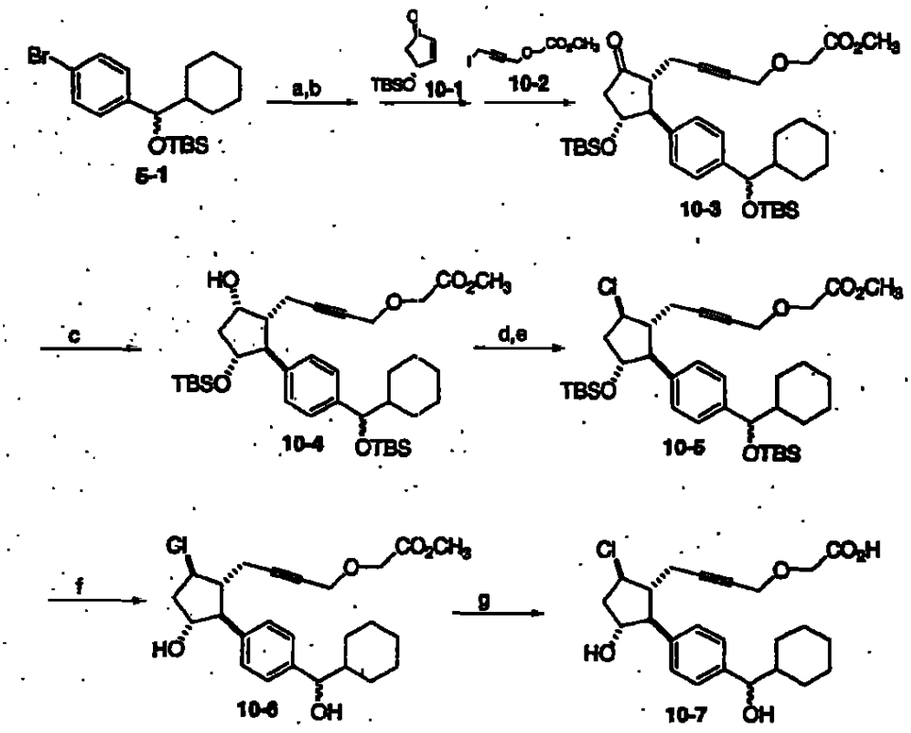
9-7, R = *i*-Pr
9-8, R = *t*-Bu

9-9, R = *i*-Pr
9-10 R = *t*-Bu

9-11, R = *i*-Pr
9-12 R = *t*-Bu

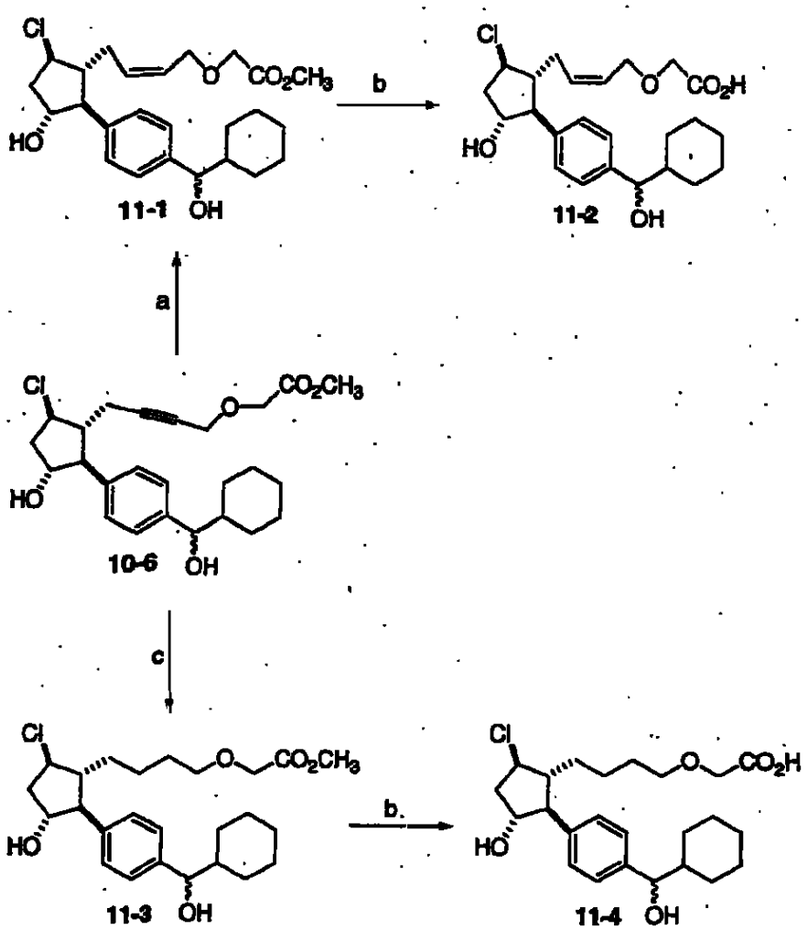
(a) DDQ; (b) TPAP, NMO; (c) *i*-PrMgCl or *t*-BuMgBr; (d) HF-pyridine 0 °C; (e) 1 M LiOH; (f) H_2, Pd/C, ethyl acetate.

Fig. 10



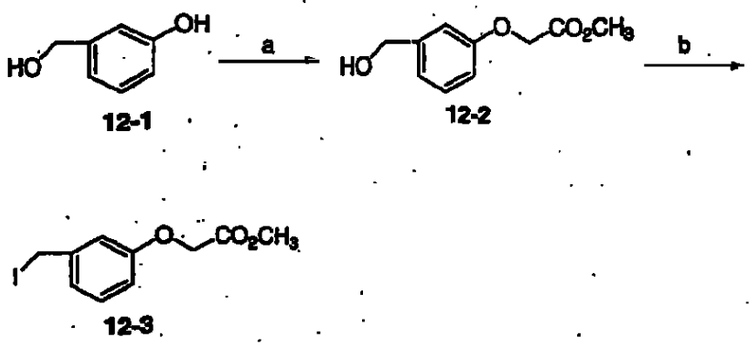
(a) t-BuLi; (b)Me_2Zn; (c) L-selectride; H_2O_2; (d) MsCl, TEA; *(e)* *n*-Bu_4NCl (f) HF-pyridine, 0 °C; (g) Rabbit Liver Esterase.

Fig. 11



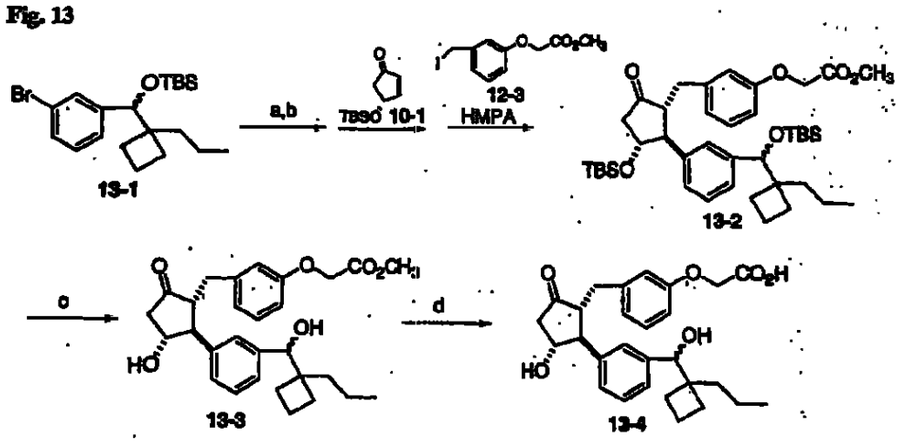
(a) H_2, $NiCl_2$, $NaBH_4$, $H_2NCH_2CH_2NH_2$; (b) rabbit liver esterase; (c) H_2, Pd/C.

Fig. 12



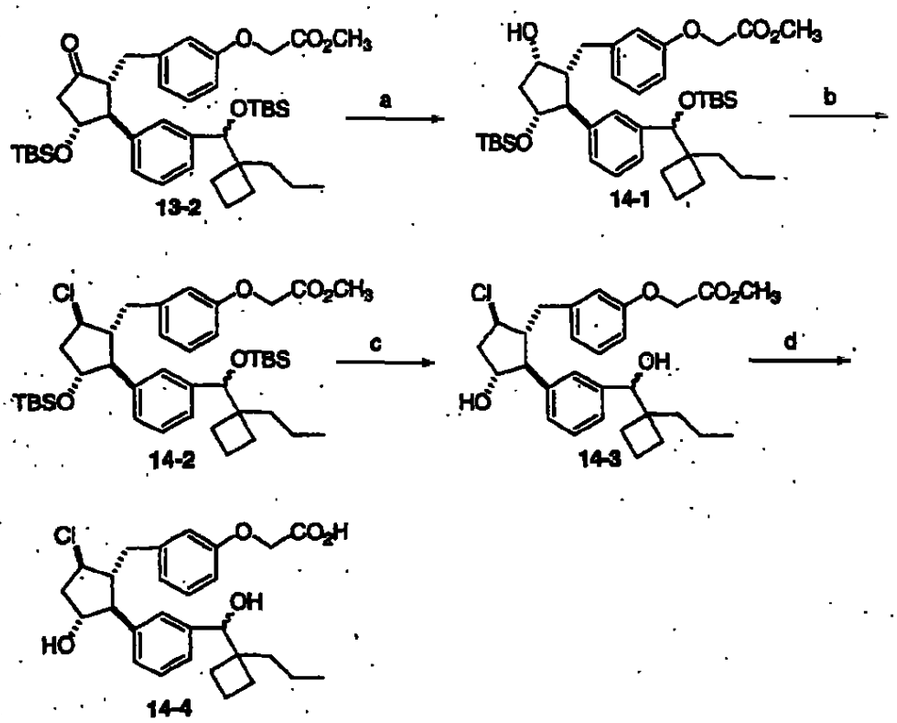
a) K_2CO_3, methyl bromoacetate; (b)Ph_3P, I_2, imidazole, CH_2Cl_2.

Fig. 13



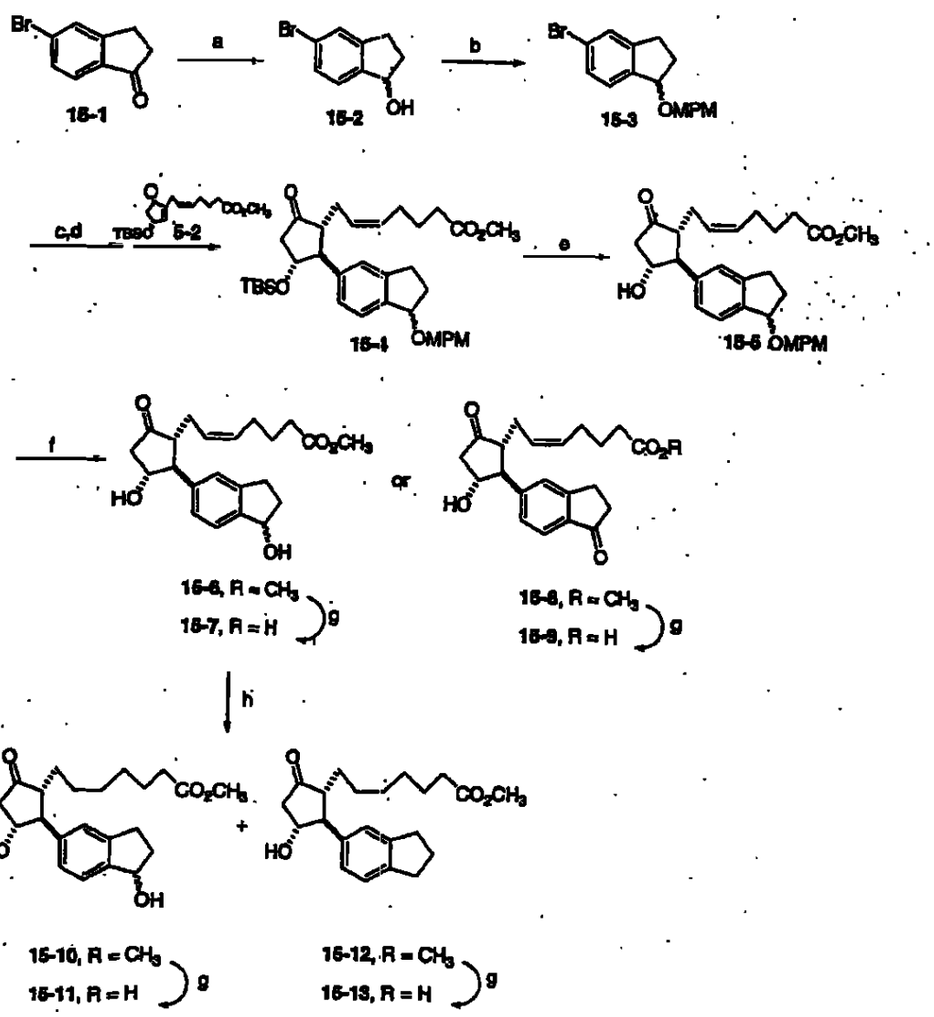
a) t-BuLi; (b)Me_2Zn; (c) HF-pyridine, 0 °C; (d) rabbit liver esterase.

Fig. 14



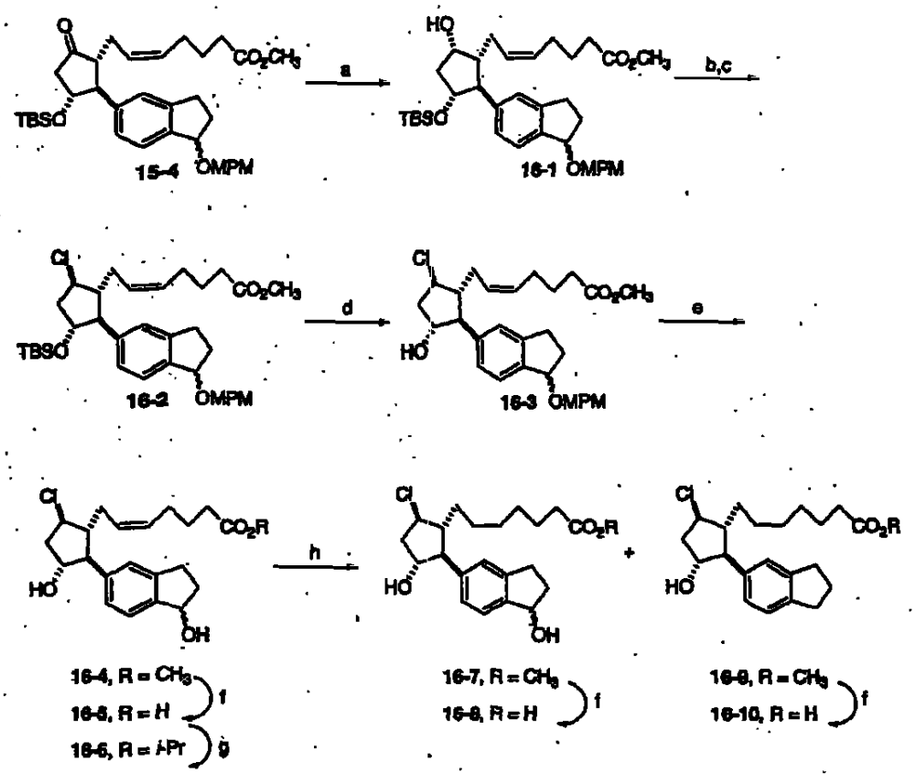
(a) L-Selectride; (b) MsCl, TEA; $(n\text{-}Bu)_4NCl$; (c) HF-pyridine, 0 °C; (d) LiOH, H_2O,THF.

Fig. 15



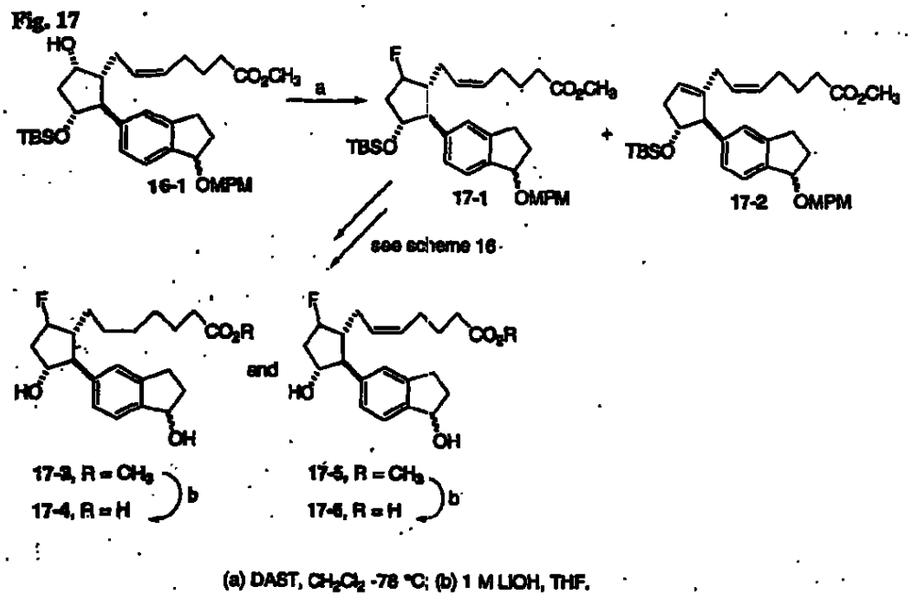
(a) $NaBH_4$; (b) MPMCl, NaH; (c) *t*-BuLi; (d) 2-thienylCuCNLi; (e) HOAc/H_2O/THF; (f) DDQ; (g) rabbit lever esterase; (h) H_2, Pd/C.

Fig. 16



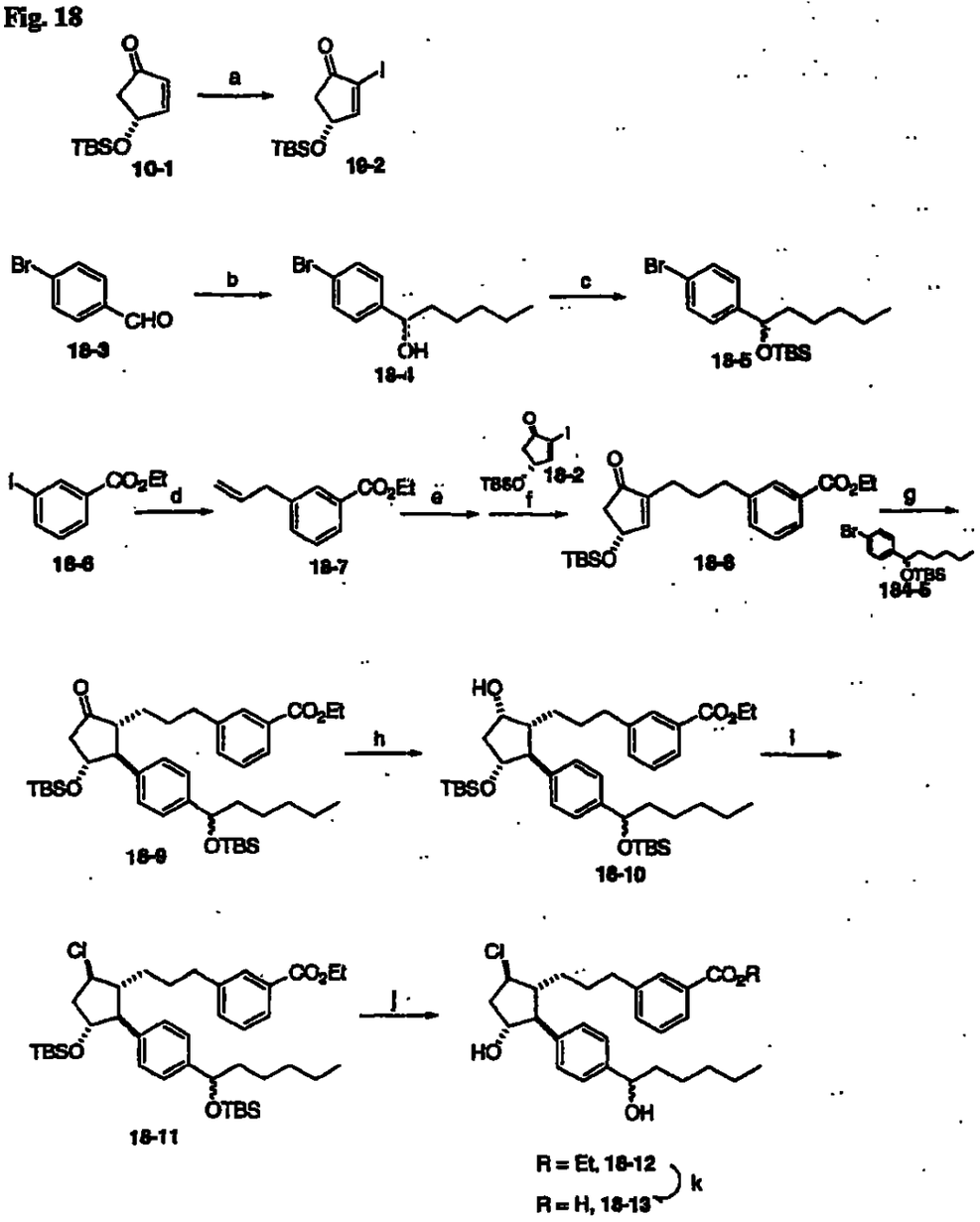
(a) L-selectride; H_2O_2; (b) MsCl, TEA;(c)TBAC 40 °C; (d) HOAc/H_2O/THF; (e) DDQ; (f) rabbit liver esterase; (g) *i*-PrI, DBU (h) H_2, Pd/C.

Fig. 17



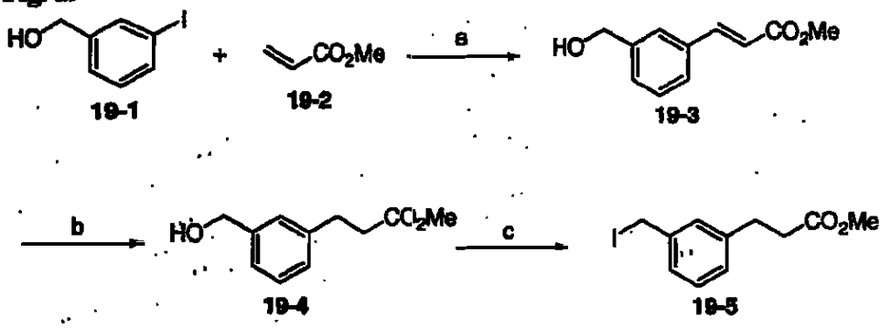
(a) DAST, CH_2Cl_2 -78 °C; (b) 1 M LiOH, THF.

Fig. 18



(a) I_2, pyridine, CH_2Cl_2; (b) *n*-pentylMgBr; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2; (d) *i*-PrMgCl; cat. CuCN, allylbromide; (e) 9-BBN; (f) $PdCl_2(dppf)$, K_3PO_4, DMF; (g) *t*-BuLi; 2-ThienylCuCNLi; (h) L-selectride; (i) MsCl, TEA; TBAC 40 °C (j) HF-pyridine 0 °C; (k) 1 M LiOH, THF.

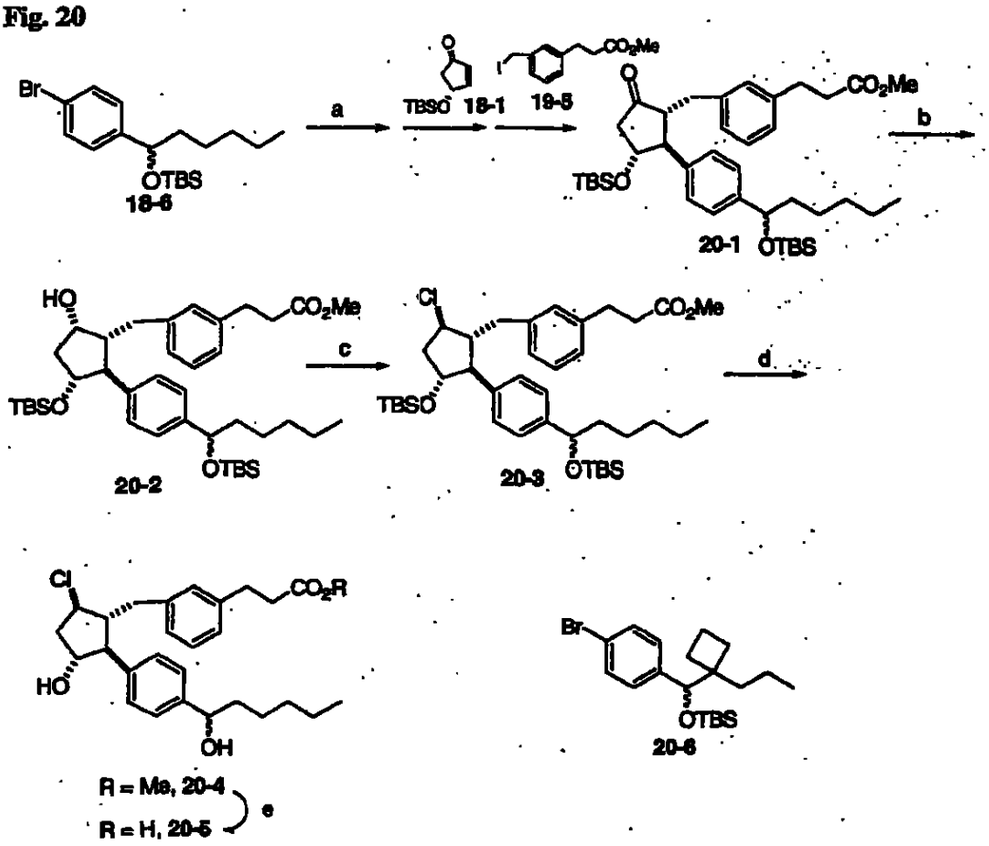
Fig. 19



19-1 19-2 19-3 19-4 19-5

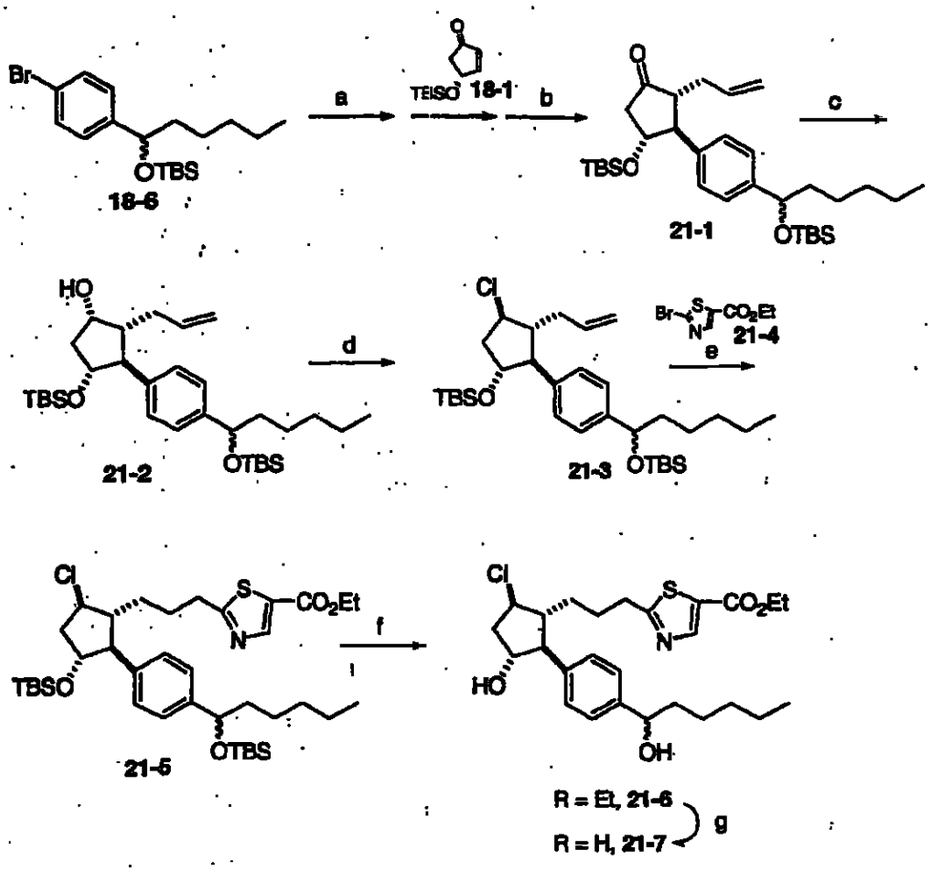
(a) $Pd(OAc)_2$, Et_3N CH_3CN 100 °C; (b) H_2, $(Ph_3P)_3RhCl$, EtOH; (c) Ph_3P, I_2, imidazole, $ClCH_2CH_2Cl$.

Fig. 20



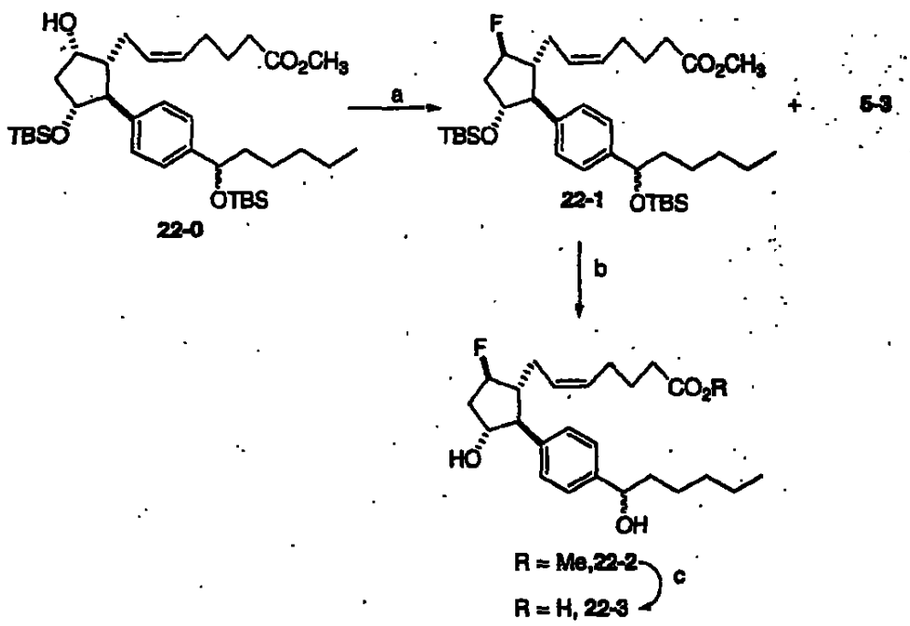
(a) *t*-BuLi; Me_2Zn; (b) L-selectride; (c) MsCl, TEA; TBAC 40 °C; (d)HF·pyridine; (e) aq. LiOH.

Fig. 21



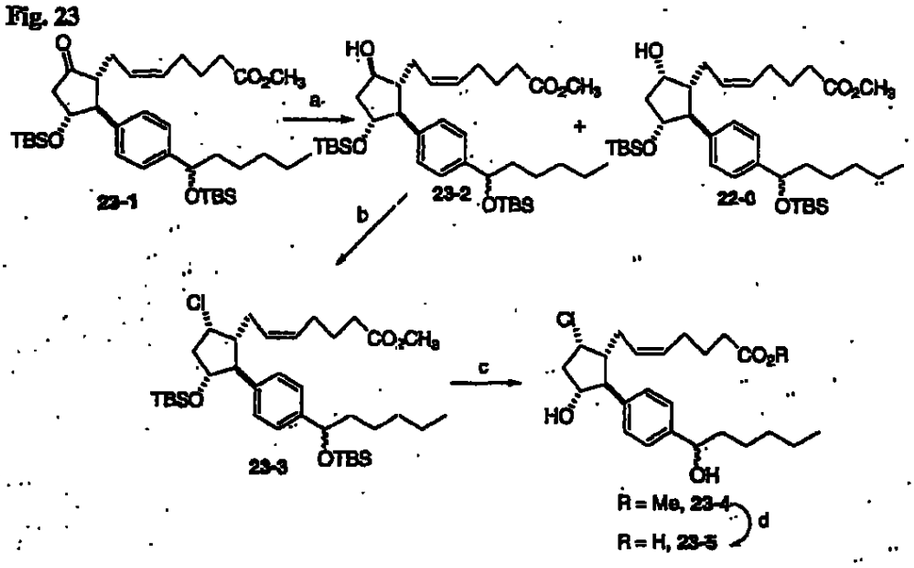
(a) *t*-BuLi; Me_2Zn; (b) allyl bromide, HMPA; (c) L-selectride; (d) MsCl, TEA; TBAC 40 °C; (e) 9-BBN; $PdCl_2(dppf)$, K_3PO_4, DMF 50 °C; (f) HF·pyridine 0 °C; (g) aq.LiOH, THF.

Fig. 22



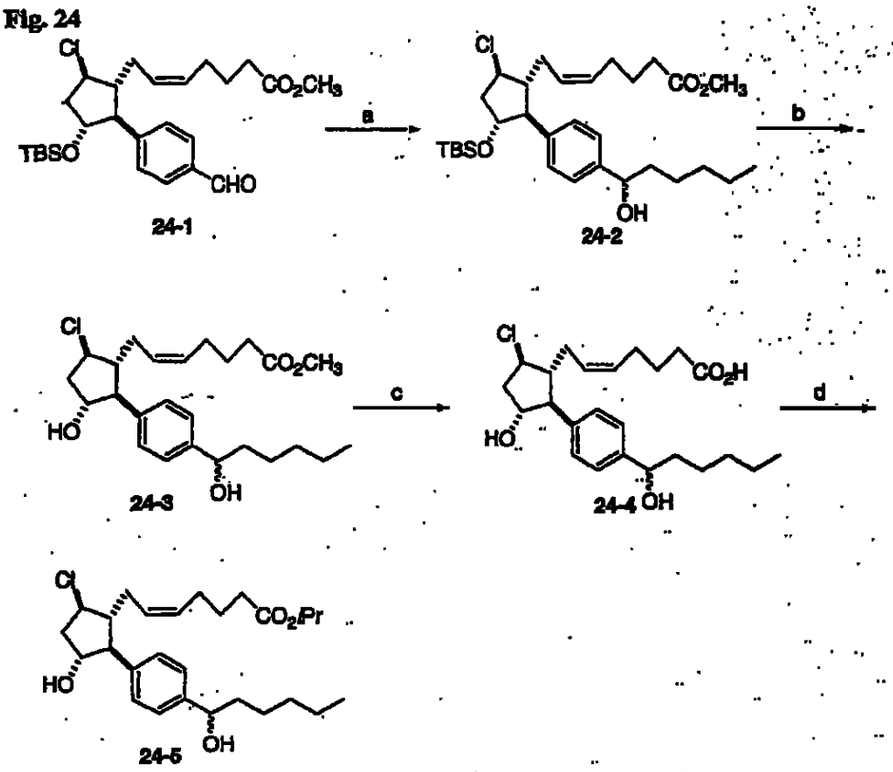
(a) MsCl, TEA; NaCN, DMSO 80 °; (b) HF·pyridine, 0 °C; (c) aq. LiOH, THF.

Fig. 23



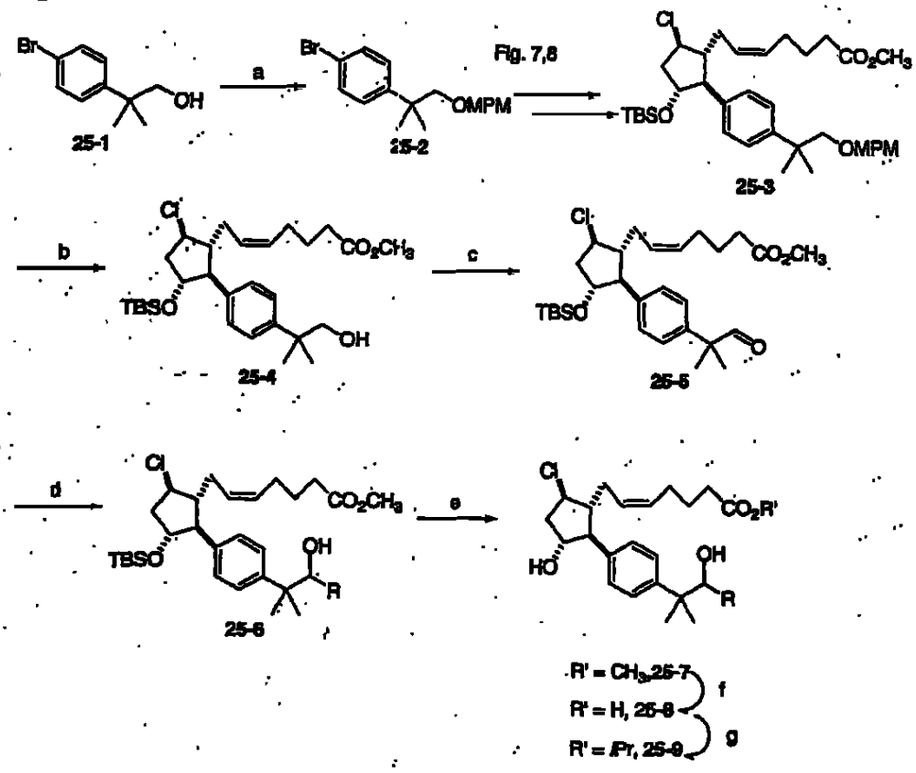
(a) $NaBH_4$; (b) MsCl, TEA; TBAC 80 °C; (c) HF · pyridine, 0 °C; (d) rabbit liver esterase.

Fig. 24



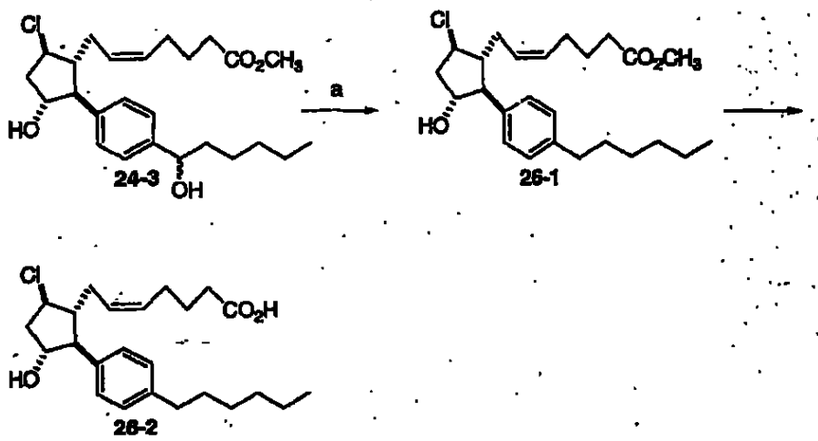
(a)*n*-pentylMgBr; (b) HF-pyridine 0 °C; (c) 1 M LiOH, THF; (d) 2-iodopropane, DBU, acetone.

Fig. 25



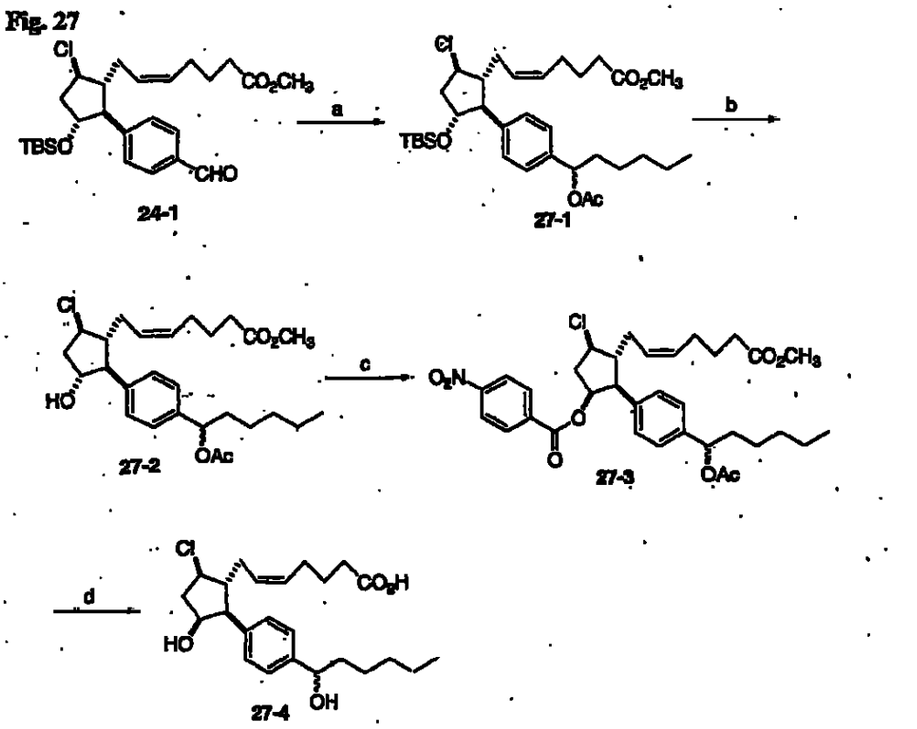
(a) 4-methoxybenzyl chloride, NaH; (b) DDQ; (c) TPAP, NMO; (d) RMgX; (e) HF-pyridine 0 °C; (f) 1 M LiOH, THF; (g) 2-iodopropane, DBU, acetone.

Fig. 26



(a) Et_3SiH, TFA, $ClCH_2CH_2Cl$; (b) aq. LiOH, THF.

Fig. 27



(a)*n*-pentylMgBr;EtOAc; (b) HF-pyridine 0 °C; (c) Ph_3P, diisopropyl azodicarboxylate, 4-nitrobenzoic acid, THF; (d) 1 M LiOH, THF.

PCT

PETITORIO

El abajo firmante pide que la presente solicitud internacional sea tramitada con arreglo al Tratado de Cooperación en materia de Patentes.

Para uso de la Oficina receptora únicamente

Solicitud internacional Nº

Fecha de presentación internacional

Nombre de la Oficina receptora y "Solicitud internacional PCT"

Referencia al expediente del solicitante o del mandatario *(si se desea) (como máximo, 12 caracteres)*

Recuadro Nº I TÍTULO DE LA INVENCIÓN

Recuadro Nº II SOLICITANTE ☐ Esta persona también es inventor.

Nombre y dirección: *(apellido seguido del nombre; si se trata de una persona jurídica, la designación oficial completa. En la dirección deben figurar el código postal y el nombre del país. El país de la dirección indicada en este recuadro es el Estado de domicilio del solicitante si no se indica más abajo el Estado de domicilio.)*

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Irvine, Ca 92612
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Nº de teleimpresora: Ninguno
Nº de registro del solicitante en la Oficina: 51.851

Estado de nacionalidad *(nombre del Estado)*: Estados Unidos

Estado de domicilio *(nombre del Estado)*: Estados Unidos

Esta persona es solicitante para: ☐ todos los Estados designados ☒ todos los Estados designados salvo los Estados Unidos de América ☐ los Estados Unidos de América únicamente ☐ los Estados indicados en el recuadro suplementario

Recuadro Nº III OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)

Nombre y dirección: *(apellido seguido del nombre; si se trata de una persona jurídica, la designación oficial completa. En la dirección deben figurar el código postal y el nombre del país. El país de la dirección indicado en este recuadro es el Estado de domicilio del solicitante si no se indica más abajo el Estado de domicilio.)*

DONDE, Yariv
24386 Antilles Way
Dana Point, CA 92629
Estados Unidos de America

Esta persona es:
☐ solicitante únicamente
☒ solicitante e inventor
☐ inventor únicamente *(si se marca esta casilla, no se debe rellenar lo que sigue.)*

Nº de registro del solicitante en la Oficina:

Estado de nacionalidad *(nombre del Estado)*: Estados Unidos

Estado de domicilio *(nombre del Estado)*: Estados Unidos

Esta persona es solicitante para: ☐ todos los Estados designados ☐ todos los Estados designados salvo los Estados Unidos de América ☒ los Estados Unidos de América únicamente ☐ los Estados indicados en el recuadro suplementario

☐ Los demás solicitantes y/o (demás) inventores se indican en una hoja de continuación.

Recuadro Nº IV MANDATARIO O REPRESENTANTE COMÚN; O DIRECCIÓN PARA LA CORRESPONDENCIA

La persona abajo identificada se nombra/ha sido nombrada para actuar en nombre del/de los solicitante(s) ante las administraciones internacionales competentes como: ☐ mandatario ☐ representante común

Nombre y dirección: *(apellido seguido del nombre; si se trata de una persona jurídica, la designación oficial completa. En la dirección deben figurar el código postal y el nombre del país.)*

JOHNSON, Brent A; BARAN, Robert J; DONOVAN Stephen; GERMAN, Joel; STATHAKIS, Dean G; VOET, Martin A.
c/o Allergan, INC
2525 Dupont Drive
Irvine, CA 92612
Estados Unidos de América

Nº de teléfono: (714) 246-4348
Nº de facsímil: (714) 246-4249
Nº de teleimpresora: Ninguno
Nº de registro del mandatario en la Oficina: 51.851

☐ Dirección para la correspondencia: márquese esta casilla cuando no se nombre/se haya nombrado ningún mandatario o representante común y el espacio de arriba se utilice en su lugar para indicar una dirección especial a la que deba enviarse la correspondencia.

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Continuación del recuadro N° III OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)

Si no se ha de utilizar ninguno de estos subrecuadros, esta hoja no debe ser incluida en el petitorio.

Nombre y dirección: *(apellido seguido del nombre; si se trata de una persona jurídica, la designación oficial completa. En la dirección deben figurar el código postal y el nombre del país. El país de la dirección indicada en este recuadro es el Estado de domicilio del solicitante si no se indica más abajo el Estado de domicilio.)*

NGUYEN, Jeremiah H.
16146 Bamboo Street
La Puente, CA 91744
Estados Unidos de América

Esta persona es:
- [ ] solicitante únicamente
- [x] solicitante e inventor
- [ ] inventor únicamente *(si se marca esta casilla, no se debe rellenar lo que sigue.)*

N° de registro del solicitante en la Oficina

Estado de nacionalidad *(nombre del Estado)*: Estados Unidos

Estado de domicilio *(nombre del Estado)*: Estados Unidos

Esta persona es solicitante para: [ ] todos los Estados designados [ ] todos los Estados designados salvo los Estados Unidos de América [ ] los Estados Unidos de América únicamente [ ] los Estados indicados en el recuadro suplementario

Nombre y dirección: *(apellido seguido del nombre; si se trata de una persona jurídica, la designación oficial completa. En la dirección deben figurar el código postal y el nombre del país. El país de la dirección indicada en este recuadro es el Estado de domicilio del solicitante si no se indica más abajo el Estado de domicilio.)*

Esta persona es:
- [ ] solicitante únicamente
- [ ] solicitante e inventor
- [ ] inventor únicamente *(si se marca esta casilla, no se debe rellenar lo que sigue.)*

N° de registro del solicitante en la Oficina

Estado de nacionalidad *(nombre del Estado)*:

Estado de domicilio *(nombre del Estado)*:

Esta persona es solicitante para: [ ] todos los Estados designados [ ] todos los Estados designados salvo los Estados Unidos de América [ ] los Estados Unidos de América únicamente [ ] los Estados indicados en el recuadro suplementario

Nombre y dirección: *(apellido seguido del nombre; si se trata de una persona jurídica, la designación oficial completa. En la dirección deben figurar el código postal y el nombre del país. El país de la dirección indicada en este recuadro es el Estado de domicilio del solicitante si no se indica más abajo el Estado de domicilio.)*

Esta persona es:
- [ ] solicitante únicamente
- [ ] solicitante e inventor
- [ ] inventor únicamente *(si se marca esta casilla, no se debe rellenar lo que sigue.)*

N° de registro del solicitante en la Oficina

Estado de nacionalidad *(nombre del Estado)*:

Estado de domicilio *(nombre del Estado)*:

Esta persona es solicitante para: [ ] todos los Estados designados [ ] todos los Estados designados salvo los Estados Unidos de América [ ] los Estados Unidos de América únicamente [ ] los Estados indicados en el recuadro suplementario

Nombre y dirección: *(apellido seguido del nombre; si se trata de una persona jurídica, la designación oficial completa. En la dirección deben figurar el código postal y el nombre del país. El país de la dirección indicada en este recuadro es el Estado de domicilio del solicitante si no se indica más abajo el Estado de domicilio.)*

Esta persona es:
- [ ] solicitante únicamente
- [ ] solicitante e inventor
- [ ] inventor únicamente *(si se marca esta casilla, no se debe rellenar lo que sigue.)*

N° de registro del solicitante en la Oficina

Estado de nacionalidad *(nombre del Estado)*:

Estado de domicilio *(nombre del Estado)*:

Esta persona es solicitante para: [ ] todos los Estados designados [ ] todos los Estados designados salvo los Estados Unidos de América [ ] los Estados Unidos de América únicamente [ ] los Estados indicados en el recuadro suplementario

[ ] Los demás solicitantes y/o (demás) inventores se indican en otra hoja de continuación.

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Recuadro Nº VI REIVINDICACIÓN DE PRIORIDAD

Se reivindica la prioridad de las siguientes solicitudes anteriores:

Fecha de presentación de la solicitud anterior *(día/mes/año)*	Número de la solicitud anterior	Si la solicitud anterior es:		
		solicitud nacional: país o miembro de la OMC	solicitud regional:* Oficina regional	solicitud internacional: Oficina receptora
Punto (1) (10.12.04) 10 Diciembre 2004	11/009.298	US		
Punto (2)				
Punto (3)				
Punto (4)				
Punto (5)				

☐ En el recuadro suplementario se incluyen reivindicaciones de prioridad adicionales

Se ruega a la Oficina receptora que prepare y transmita a la Oficina Internacional una copia certificada de la solicitud anterior/de las solicitudes anteriores *(sólo si la solicitud anterior ha sido presentada ante la oficina que a los fines de la presente solicitud internacional es la Oficina receptora)* identificada(s) supra como:

☐ Todos los puntos ☒ Punto (1) ☐ Punto (2) ☐ Punto (3) ☐ Punto (4) ☐ Punto (5) ☐ otros, ver Recuadro suplementario

** Si la solicitud anterior es una solicitud ARIPO, se indicará al menos un Estado miembro del Convenio de París para la Protección de la Propiedad Industrial o un Miembro de la Organización Mundial del Comercio para el que ha sido presentada la solicitud anterior (Regla 4.10.b)ii)):* .....

Recuadro Nº VII ADMINISTRACIÓN ENCARGADA DE LA BÚSQUEDA INTERNACIONAL

Elección de la Administración encargada de la búsqueda internacional *(si dos o más Administraciones encargadas de la búsqueda internacional son competentes para efectuar la búsqueda internacional, indíquese el nombre de la Administración elegida; se puede utilizar el código de dos letras):*

ISA / EP .....

Petición para que se utilicen los resultados de la búsqueda anterior; referencia a esa búsqueda *(si una búsqueda anterior ha sido realizada por o pedida a la Administración encargada de la búsqueda internacional):*

Fecha *(día/mes/año)* Número País *(u Oficina regional)*

Recuadro Nº VIII DECLARACIONES

Las siguientes declaraciones se contienen en los Recuadros Nº VIII.i) a v) *(márquense las casillas indicadas abajo que correspondan, e indíquese el número de cada tipo de declaración en la columna de la derecha):*

		Número de declaraciones
☐ Recuadro Nº VIII.i)	Declaración sobre la identidad del inventor :	
☐ Recuadro Nº VIII.ii)	Declaración sobre el derecho del solicitante, en la fecha de presentación internacional, para solicitar y que le sea concedida una patente :	
☐ Recuadro Nº VIII.iii)	Declaración sobre el derecho del solicitante, en la fecha de presentación internacional, a reivindicar la prioridad de la solicitud anterior :	
☐ Recuadro Nº VIII.iv)	Declaración sobre la calidad de inventor (sólo para la designación de los Estados Unidos de América) :	
☐ Recuadro Nº VIII.v)	Declaración sobre las divulgaciones no perjudiciales o las excepciones a la falta de novedad :	

Recuadro Nº IX LISTA DE VERIFICACIÓN; IDIOMA DE PRESENTACIÓN

La presente solicitud internacional contiene:

a) el siguiente número de hojas en papel:
- petitorio (incluidas las hojas de declaración): 4
- descripción (excluidas las listas de secuencias y los cuadros conexos): 106
- reivindicaciones: 20
- resumen: 1
- dibujos: 27
- Número subtotal de hojas: 158 0
- Listas de secuencias:
- Cuadros conexos:
- *(para ambas enumeraciones, número total de hojas si éstas han sido presentadas en papel, con independencia de que también se presentaran en formato legible por ordenador; ver c) abajo)*
- Número total de hojas: 158 0

b) ☐ sólo en formato legible por ordenador (según la Instrucción 801.a)ii)):
- i) ☐ listas de secuencias
- ii) ☐ cuadros conexos

c) ☐ asimismo en formato legible por ordenador (según la Instrucción 801.a)ii)):
- i) ☐ listas de secuencias
- ii) ☐ cuadros conexos

Tipo y número de soportes (disquete, CD-ROM, CD-R u otros) que contienen las:
- i) ☐ listas de secuencias: .....
- ii) ☐ cuadros conexos: .....

(las copias adicionales se deben indicar en los puntos 9.ii) y/o 10.ii) de la columna de la derecha)

La presente solicitud internacional va acompañada del(los) siguiente(s) documento(s) *(marcar las casillas que procedan e indicar en la columna de la derecha el número de cada documento)*: — Número de documentos

1. ☐ hoja de cálculo de tasas :
2. ☐ poder separado original :
3. ☐ poder general original :
4. ☐ copia del poder general; número de referencia, en su caso: ..... :
5. ☐ declaración explicativa de la ausencia de firma :
6. ☐ documento(s) de prioridad identificado(s) en el Recuadro Nº VI como punto o puntos: ..... :
7. ☐ traducción de la solicitud internacional al *(idioma)*: ..... :
8. ☐ indicaciones separadas relativas a microorganismos depositados o a otro material biológico :
9. ☐ listas de secuencias en formato legible por ordenador *(indicar el tipo y el número de soportes)*
   - i) ☐ copia presentada para la búsqueda internacional según la Regla 13*ter* sólo (y no como parte de la solicitud internacional) :
   - ii) ☐ *(sólo cuando se ha marcado la casilla b)i) o c)i) en la columna de la izquierda)* copias adicionales, incluyendo, cuando proceda, la copia para la búsqueda internacional según la Regla 13*ter* :
   - iii) ☐ junto a la declaración que proceda sobre la identidad de la copia - o copias - respecto de las listas de secuencias mencionadas en la columna de la izquierda :
10. ☐ cuadros conexos, en formato legible por ordenador, a las listas de secuencias *(indicar el tipo y el número de soportes)*
    - i) ☐ copias presentadas para la búsqueda internacional según la Instrucción 802.b-*quater*) sólo (y no como parte de la solicitud internacional) :
    - ii) ☐ *(sólo cuando se ha marcado la casilla b)ii) o c)ii) en la columna de la izquierda)* copias adicionales, incluyendo, cuando proceda, la copia para la búsqueda internacional, según la Instrucción 802.b-*quater*) :
    - iii) ☐ junto a la declaración que proceda sobre la identidad de la copia - o copias - respecto de los cuadros mencionados en la columna de la izquierda :
11. ☐ otros *(especifíquese)*: ..... :

Figura de los dibujos que debe acompañar el resumen:

Idioma de presentación de la solicitud internacional:

Recuadro Nº X FIRMA DEL SOLICITANTE, DEL MANDATARIO O DEL REPRESENTANTE COMÚN

Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio).

Brent A. Johnson, Ph.D.

Para uso de la Oficina receptora únicamente

1. Fecha efectiva de recepción de la pretendida solicitud internacional:
2. Dibujos: ☐ recibidos: ☐ no recibidos:
3. Fecha efectiva de recepción, rectificada en razón de la recepción ulterior, pero dentro de plazo, de documentos o de dibujos que completen la pretendida solicitud internacional:
4. Fecha de recepción, dentro de plazo, de las correcciones requeridas según el Artículo 11.2) del PCT:
5. Administración encargada de la búsqueda internacional especificada por el solicitante: ISA /
6. ☐ Transmisión de la copia para la búsqueda diferida hasta que se pague la tasa de búsqueda.

Para uso de la Oficina Internacional únicamente

Fecha de recepción del ejemplar original por la Oficina Internacional:

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional

(43) Fecha de Publicación Internacional
15 de junio de 2006 (15.06.2006)

PCT

(10) Número de Publicación Internacional
WO 2006/063179 A1

(51) Clasificación Internacional de Patentes[7]:
C07C 405/00 (2006.01) *A61P 27/06* (2006.01)
A61K 31/5575 (2006.01)

(21) No. Solicitud Internacional: PCT/US2005/044501

(22) Fecha de Presentación Internacional:
8 de diciembre de 2005 (08.12.2005)

(25) Idioma de Presentación: Inglés

(26) Idioma de Publicación: Inglés

(30) Datos relativos a la Prioridad:
11/009,298 10 de diciembre de 2004 (10.12.2004) US

(71) Solicitante *(para todos los países destinatarios con excepción de US)*: **ALLERGAN, INC.** [US/US]; 2525 Dupont Drive, Irvine, CA 92612 (US).

(72) Inventores, e
(75) Inventores/Solicitantes *(para US únicamente)*: **DONDE, Yariv** [US/US]; 24386 Antilles Way, Dana Point, CA 92629 (US). **NGUYEN, Jeremiah, H.** [US/US]; 16146 Bamboo Street, La Puente, CA 91744 (US).

(74) Agentes: **JOHNSON, Brent, A.** et al.; c/o Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92612 (US).

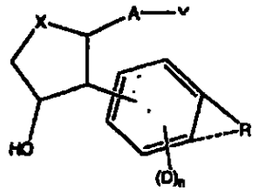
(81) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, *NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD,* SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

(84) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

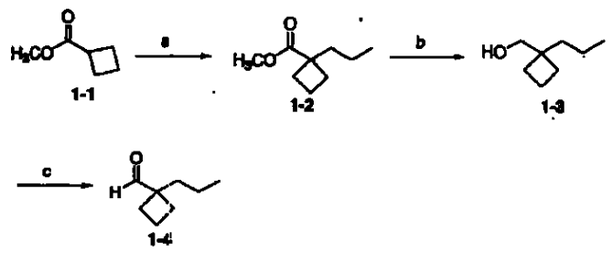
Publicado:
— *sin informe internacional de búsqueda*
— *antes del vencimiento del tiempo límite para modificar las reivindicaciones y para volverse a publicar en el caso de recibo de modificaciones*

[Continúa en la página siguiente]

(54) Título: ANÁLOGOS DE 12-ARIL PROSTAGLANDINA



(I)



(57) Extracto: Se divulgan compuestos que comprenden la fórmula (I), en donde Y, A, X, R, D, y n son como se describen. Igualmente se describe en esta solicitud un compuesto que comprende un agonista selectivo de prostaglandina EP_2, en donde la cadena ω comprende un fenilo sustituido, en donde por lo menos un sustituyente está conformado por un hidrocarbilo o hidroxihidrocarbilo no lineal. Asimismo se describen métodos, composiciones y medicamentos relacionados con ellos.

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Para códigos de dos letras y otras abreviaturas, remítase a las "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT.

ANÁLOGOS DE 12-ARIL PROSTAGLANDINA

Inventores

Yariv Donde y Jeremiah H. Nguyen

CAMPO DE LA INVENCIÓN

Esta invención se refiere a compuestos que son útiles para el tratamiento de enfermedades. En particular, los compuestos objeto de la invención son útiles para el tratamiento de enfermedades o trastornos relacionados con prostaglandinas o con la actividad de receptores de prostaglandina.

ANTECEDENTES DE LA INVENCIÓN

Descripción del Arte Relacionado

Los hipotensores oculares son útiles en el tratamiento de un número de diferentes trastornos hipertensores oculares, tales como episodios hipertensores oculares de trabeculectomía pos-quirúrgicos y pos-láser, glaucoma, y como auxiliares prequirúrgicos.

El glaucoma es una enfermedad del ojo caracterizada por una presión intraocular creciente. Sobre la base de su etiología, el glaucoma se ha clasificado como primario o secundario. Por ejemplo, el glaucoma primario en adultos (glaucoma congénito) puede ser glaucoma de ángulo abierto o glaucoma de ángulo cerrado, agudo o crónico. El glaucoma secundario resulta de enfermedades oculares pre-existentes tales como uveítis, tumor intraocular o una catarata dilatada.

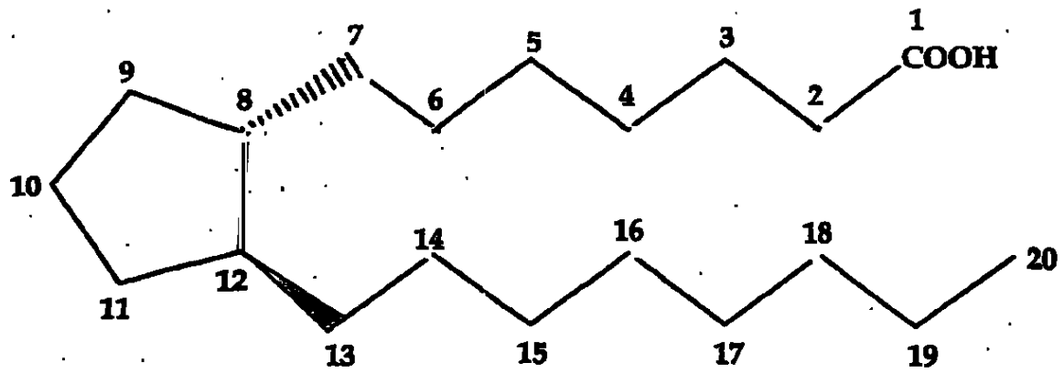
Las causas fundamentales del glaucoma primario son aún desconocidas. La tensión intraocular creciente se debe a la obstrucción de la salida de humor acuoso. En el glaucoma de ángulo abierto, crónico, la cámara anterior y sus estructuras anatómicas parecen normales, pero se impide el drenaje del humor acuoso. En el glaucoma de ángulo cerrado, agudo o crónico, la cámara anterior es poco profunda, el ángulo de filtración se estrecha, y el iris puede obstruir el retículo trabecular en la entrada del canal de Schlemm. La dilatación de la pupila puede empujar la raíz del iris hacia adelante contra el ángulo, y puede producir

bloqueo pupilar y, en consecuencia, precipitar un ataque agudo. Ojos con ángulos estrechos de cámara anterior tienen predisposición a ataques de glaucoma de ángulo cerrado, agudo, de varios grados de gravedad.

El glaucoma secundario es causado por cualquier interferencia del flujo de humor acuoso desde la cámara posterior a la cámara anterior y, por consiguiente, en el canal de Schlemm. La enfermedad inflamatoria del segmento anterior puede impedir el drenaje acuoso ocasionando una sinequia posterior completa en el bombo del iris, y puede obstruir el canal de drenaje con exudados. Otras causas comunes son los tumores intraoculares, cataratas dilatadas, oclusión de la vena retiniana central, trauma al ojo, intervenciones operatorias y hemorragia intraocular.

Considerando en conjunto la totalidad de los tipos, el glaucoma ocurre en alrededor del 2% de todas las personas con una edad superior a 40 años y puede ser asintomático durante años, antes de evolucionar hacia una pérdida rápida de la visión. En casos en donde no es indicada la cirugía, los antagonistas de β-adrenorreceptor tópicos han sido tradicionalmente los medicamentos de elección para tratar el glaucoma.

Se ha informado que ciertos eicosanoides y sus derivados poseen actividad hipotensora ocular, y se los ha recomendado para uso en el manejo del glaucoma. Los eicosanoides y derivados incluyen numerosos compuestos biológicamente importantes, tales como prostaglandinas y sus derivados. Las prostaglandinas pueden describirse como derivados de ácido prostanoico, que tienen la siguiente fórmula estructural:



Se conocen varios tipos de prostaglandinas, dependiendo de la estructura y los sustituyentes que lleva el anillo alicíclico del esqueleto del ácido prostanoico. Una clasificación adicional se basa en el número de enlaces insaturados en la cadena lateral indicados por subíndices numéricos después del tipo genérico de

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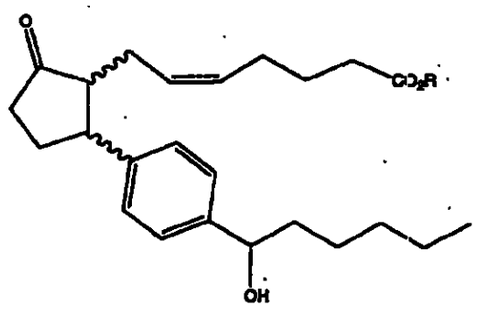
prostaglandina [por ejemplo, prostaglandina E_1 (PGE_1), prostaglandina E_2 (PGE_2)], y en la configuración de los sustituyentes en el anillo alicíclico indicados por una α o β [por ejemplo, prostaglandina $F_{2\alpha}$ ($PGF_{2\beta}$)].

El análogo de prostaglandina E mostrado a continuación se divulga en los siguientes documentos, expresamente incorporados en esta solicitud por referencia: Patente de los Estados Unidos No. 5,462,968; Patente de los Estados Unidos 5,698,598; y Patente de los Estados Unidos No. 6,090,847.



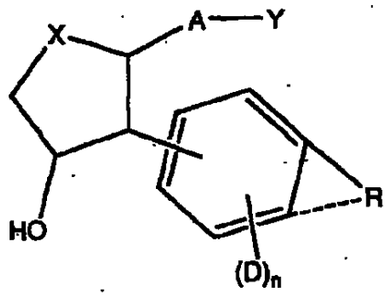
Se cree que agonistas selectivos de prostaglandina EP_2 tienen varias aplicaciones médicas. Por ejemplo, la Patente de los Estados Unidos No. 6,437,146 enseña el uso de agonistas selectivos de prostaglandina EP_2 "para tratar o prevenir la inflamación y el dolor en articulaciones y músculos (por ejemplo, artritis reumatoide, espondilitis reumatoide, osteoartritis, artritis gotosa, artritis juvenil, etc.), afección cutánea inflamatoria (por ejemplo, eritema solar, quemaduras, eccema, dermatitis, etc.), trastorno ocular inflamatorio (por ejemplo, conjuntivitis, etc.), trastorno pulmonar en el cual se encuentra implicada inflamación (por ejemplo, asma, bronquitis, enfermedad del cuidador de aves, pulmón de granjero, etc.), afección del tubo digestivo asociada con inflamación (por ejemplo, úlcera aftosa, enfermedad de Crohn, gastritis atrófica, gastritis varialoforme, colitis ulcerosa, enfermedad celíaca, ileítis regional, síndrome de intestino irritable, etc.), gingivitis, inflamación, dolor y tumescencia luego de una operación o lesión, pirexia, dolor y otros trastornos asociados con inflamación, enfermedad alérgica, lupus eritematoso sistémico, escleroderma, polimiositis, tendinitis, bursitis, periarteritis nodosa, fiebre reumática, síndrome de Sjöngren, enfermedad de Behçet, tiroiditis, diabetes tipo I, complicación diabética (microangiopatía diabética, retinopatía diabética, nefropatía diabética, etc.), síndrome nefrótico, anemia aplásica, miastenia grave, uveítis, dermatitis por contacto, psoriasis, enfermedad de Kawasaki, sarcoidosis, enfermedad de Hodgkin, enfermedad de Alzheimer, disfunción renal (nefritis, síndrome nefrítico, etc.), disfunción hepática (hepatitis, cirrosis, etc.), disfunción gastrointestinal

(diarrea, enfermedad inflamatoria de los intestinos, etc.), choque, osteopatía caracterizada por un metabolismo óseo anormal tal como osteoporosis (especialmente, osteoporosis posmenopáusica), hipercalcemia, hiperparatiroidismo, osteopatías de Paget, osteólisis, hipercalcemia de neoplasia maligna con o sin metástasis ósea, artritis reumatoide, periodontitis, osteoartritis, ostealgia, osteopenia, caquexia por cáncer, calculosis, litiasis (especialmente, urolitiasis), carcinoma sólido, glomerulonefritis proliferativa mesangial, edema (por ejemplo, edema cardíaco, edema cerebral, etc.), hipertensión tal como hipertensión maligna o similar, tensión premenstrual, cálculos urinarios, oliguria tal como la causada por insuficiencia aguda o crónica, hiperfosfaturia, o similares."

La Patente de los Estados Unidos No. 6,710,072 enseña el uso de agonistas de EP2 para el tratamiento o prevención de "osteoporosis, estreñimiento, trastornos renales, disfunción sexual, calvicie, diabetes, cáncer y en trastornos de regulación inmunitaria... varias enfermedades patofisiológicas, incluidas infarto agudo del miocardio, trombosis vascular, hipertensión, hipertensión pulmonar, cardiopatía isquémica, insuficiencia cardiaca congestiva y angina pectoris."

BREVE DESCRIPCIÓN DE LA INVENCIÓN

En esta solicitud se divulgan compuestos que comprenden



o su sal farmacéuticamente aceptable o profármaco,

en donde una línea discontinua representa la presencia o ausencia de un enlace covalente;

Y es un ácido carboxílico, ácido sulfónico, o ácido fosfónico; o una amida o éster de los mismos, que comprende de 0 a 12 átomos de carbono; o Y es un grupo funcional hidroximetilo, o tetrazolilo; A es $-(CH_2)_6-$, *cis*-$CH_2CH{=}CH-(CH_2)_3-$, o $-CH_2C{\equiv}C-(CH_2)_3-$, en donde 1 ó 2 átomos de carbono pueden sustituirse con S u O; o A es $-(CH_2)_m-Ar-(CH_2)_o-$ en donde Ar es fenilo sustituido o no sustituido o

heteroarilo monocíclico, la sumatoria de **m** y **o** va de 1 a 4, y en donde un CH_2 puede sustituirse con S u O;

X es C=O, CHF, CF_2, CHCl, o CHOH; en donde si X es CHOH, entonces OH está en la configuración β;

R es una fracción hidrocarbilo o hidroxihidrocarbilo que comprende de 1 a 12 átomos de carbono;

D es independientemente una fracción que comprende de 1 a 6 átomos diferentes de hidrógeno; y

n es un entero de 0 a 4.

Igualmente se divulga en esta solicitud un compuesto que comprende un agonista selectivo de prostaglandina EP_2, en donde la cadena ω incluye un fenilo sustituido, en donde por lo menos un sustituyente está conformado por hidrocarbilo o hidroxihidrocarbilo no lineal.

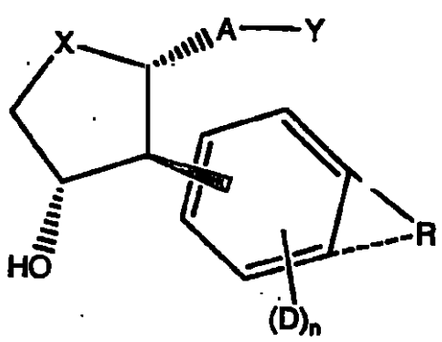
Asimismo se divulgan métodos, composiciones y medicamentos relacionados con el mismo.

BREVE DESCRIPCIÓN DE LAS FIGURAS DE DIBUJOS

Figuras 1-17 ilustran el modo de preparar los compuestos divulgados en esta solicitud.

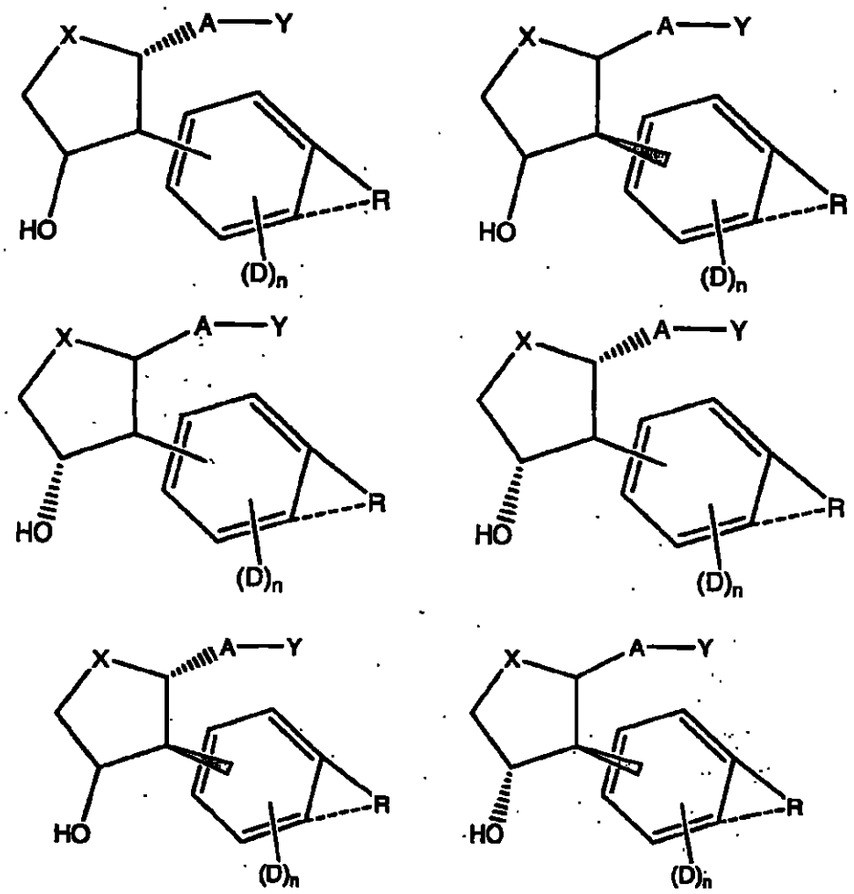
DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Varios de los átomos de carbono en estos compuestos son centros quirales. Sin pretender limitar el ámbito de la invención en modo alguno, o quedar limitados por restricciones teóricas, se cree que son particularmente útiles muchos compuestos y sales farmacéuticamente activas, o profármacos de los mismos, con la estereoquímica mostrada a continuación.



Una persona de habilidad ordinaria en el arte entiende el significado de la estereoquímica asociada con las características estructurales de la cuña sólida/cuña quebrada. Por ejemplo, un libro de texto introductorio de química orgánica (Francis A. Carey, Organic Chemistry, New York: McGraw-Hill Book Company 1987, p. 63) establece que "una cuña indica un enlace que se proyecta del plano del papel hacia el observador" y la cuña quebrada, indicada como una "línea discontinua", "representa un enlace que se aleja del observador."

No obstante, es igualmente ventajoso si uno o más de los enlaces tiene la estereoquímica indicada, mientras que la estereoquímica de los otros enlaces a los centros quirales puede variar. En consecuencia, sin pretender limitar el ámbito de la invención en algún modo, los compuestos que comprenden



y similares; y sus sales y profármacos farmacéuticamente aceptables son particularmente útiles en el contexto divulgado en esta solicitud.

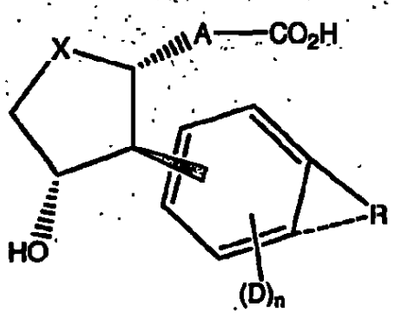
Una "sal farmacéuticamente aceptable" es cualquier sal que conserva la actividad del compuesto precursor y no ocasiona efectos nocivos adicionales o adversos de ningún tipo al sujeto al cual se administra y en el contexto, en el cual

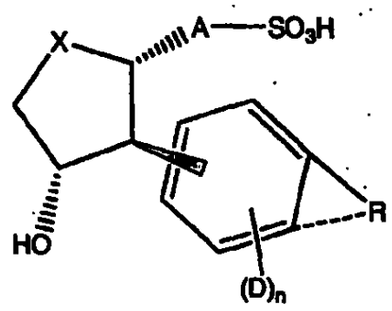
se administra, comparada con el compuesto precursor. Asimismo, una sal farmacéuticamente aceptable se refiere a cualquier sal que, como resultado de la administración de un ácido, puede formar *in vivo* otra sal, o a un profármaco, el cual se convierte en un ácido o sal.

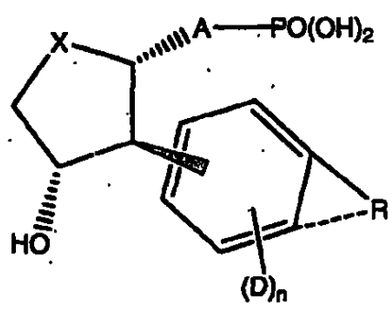
Sales farmacéuticamente aceptables de grupos funcionales ácidos pueden derivarse de bases orgánicas o inorgánicas. La sal puede comprender un ión mono- o polivalente. De particular interés son los iones inorgánicos, litio, sodio, potasio, calcio y magnesio. Las sales orgánicas pueden prepararse con aminas, particularmente sales de amonio tales como mono-, di- y trialquilaminas o etanol aminas. Igualmente pueden formarse sales con cafeína, trometamina y moléculas similares. El ácido clorhídrico o algún otro ácido farmacéuticamente aceptable pueden formar una sal con un compuesto que incluye un grupo básico, tal como un anillo de amina o piridina.

Un "profármaco" es un compuesto que se convierte en un compuesto terapéuticamente activo luego de la administración, y el término debe interpretarse tan ampliamente en esta solicitud como se entiende por lo general en el arte. Sin pretender limitar el ámbito de la invención, la conversión puede ocurrir por hidrólisis de un grupo éster o algún otro grupo biológicamente lábil. General, pero no necesariamente, un profármaco es inactivo o menos activo que el compuesto terapéuticamente activo en el cual se convierte.

Y es un grupo funcional ácido carboxílico, ácido sulfónico, o un ácido fosfónico; o una amida o éster del mismo, que comprende de 0 a 12 átomos de carbono; o **Y** es un grupo funcional hidroximetilo o tetrazolilo. En consecuencia, sin pretender limitar el ámbito de la invención en algún modo, en ciertos compuestos **Y** es un grupo funcional ácido carboxílico, ácido sulfónico, o un ácido fosfónico, es decir, una de las estructuras indicadas a continuación.



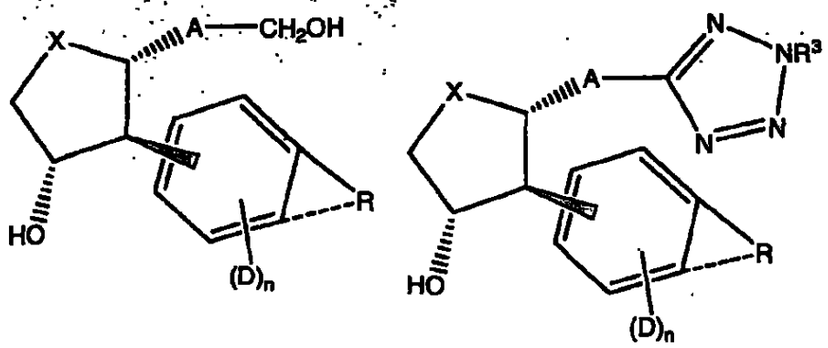




También pueden estar presentes sales de cualquiera de estos ácidos de cualquier forma farmacéuticamente aceptable.

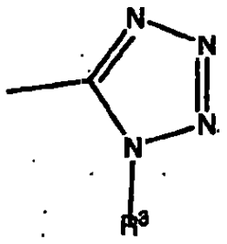
Adicionalmente, se contempla asimismo una amida o éster de uno de los ácidos orgánicos ya indicados, que comprenden de 0 a 12 átomos de carbono. En un éster, una fracción hidrocarbilo reemplaza un hidrógeno de un ácido tal como en un éster de ácido carboxílico, por ejemplo, CO_2R^3. En una amida, un grupo amina reemplaza un OH del ácido. Una amina es una fracción con un nitrógeno central que tiene exactamente tres enlaces a C o H. Ejemplos de amidas incluyen $CON(R^3)_2$, $CON(OR^3)R^3$, $CON(CH_2CH_2OH)_2$ y $CONH(CH_2CH_2OH)$. Fracciones tales $CONHSO_2R^3$ son también amidas del ácido carboxílico, no obstante el hecho de que pueden considerarse igualmente amidas del ácido sulfónico R^3-SO_3H.

Finalmente, sin pretender limitar el ámbito de la invención en algún modo, Y puede ser además un grupo funcional hidroximetilo o tetrazolilo, es decir, compuestos con una estructura tal corno una de las mostradas más adelante.



Cuando R^3 es hidrógeno, el grupo funcional tetrazolilo tiene dos formas tautoméricas, que pueden convertirse rápidamente entre sí en medio acuoso o biológico y, por lo tanto, son equivalentes entre sí. Estos tautómeros se muestran a continuación.

Adicionalmente, si R^3 es C_1C_6 alquilo, fenilo, o bifenilo, son igualmente posibles otras formas isoméricas del grupo funcional tetrazolilo tales como la mostrada a continuación, todas las cuales se considera que están dentro del ámbito del término "tetrazolilo."



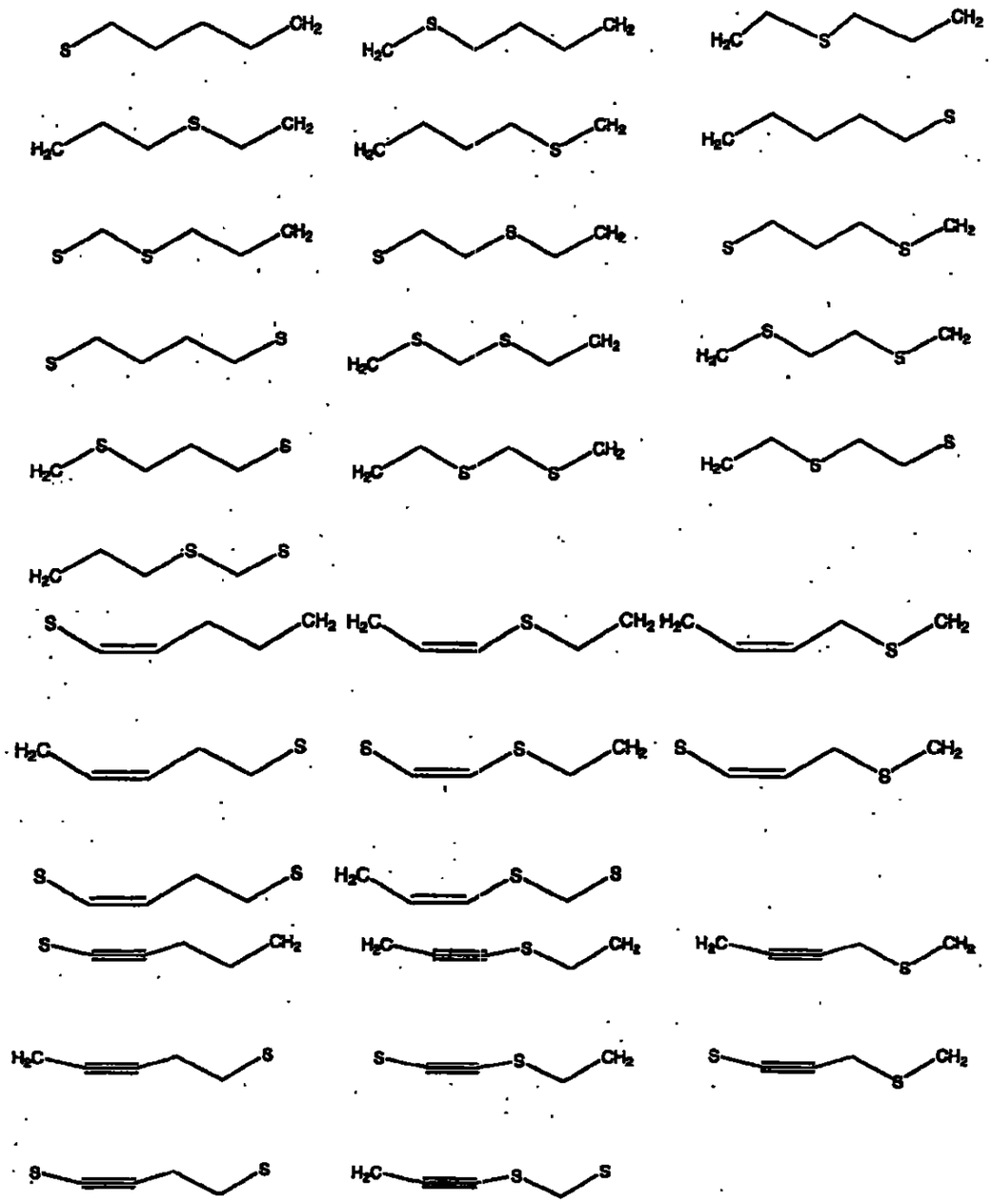
Sin pretender limitar el ámbito de la invención en algún modo, en una incorporación **Y** se selecciona del grupo conformado por $CO_2(R^3)$, $CON(R^3)_2$, $CON(OR^3)R^3$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH, $P(O)(OH)_2$, $CONHSO_2R^3$, $SO_2N(R^3)_2$, SO_2NHR^3 y
tetrazolil-R^3; en donde R^3 es independientemente H, C_1-C_6 alquilo, fenilo, o bifenilo.

En relación con la identidad de A divulgada en las estructuras químicas presentadas en esta solicitud, en el sentido más amplio, **A** es $-(CH_2)_6-$, *cis*-$CH_2CH=CH-(CH_2)_3-$, ó $-CH_2C\equiv C-(CH_2)_3-$, en donde 1 ó 2 átomos de carbono pueden sustituirse con S u O; o A es $-(CH_2)_m-Ar-(CH_2)_o-$ en donde Ar es fenilo

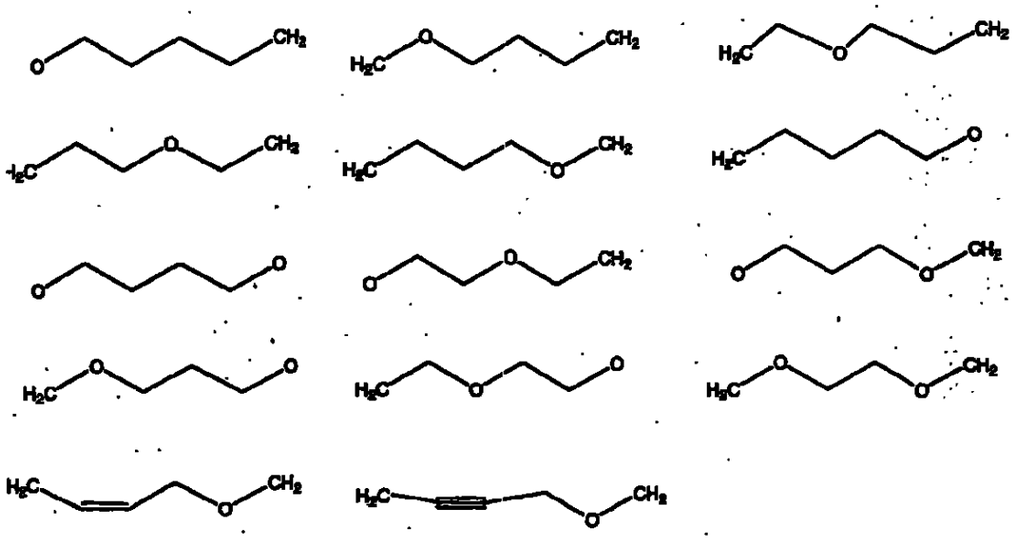
sustituido o no sustituido o heteroarilo monocíclico, la sumatoria de **m** y **o** va de 1 a 3, y en donde un CH_2 puede sustituirse con S u O.

En otras palabras, sin pretender ser limitante, A puede ser $-(CH_2)_6-$, *cis*-$CH_2CH=CH-(CH_2)_3-$, ó $-CH_2C\equiv C-(CH_2)_3-$.

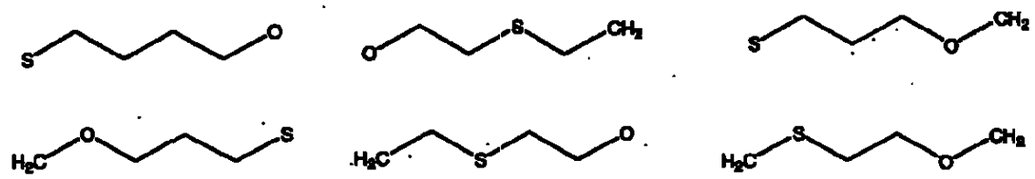
Alternativamente, **A** puede ser un grupo que se relaciona con una de estas tres fracciones en las que cualquier carbono se sustituye con S u O. Por ejemplo, sin pretender limitar el ámbito de la invención en algún modo, **A** puede ser una fracción S sustituida, tal como una de las siguientes o similares.



Alternativamente, sin pretender limitar el ámbito de la invención en algún modo, **A** puede ser una fracción O sustituida, tal como una de las siguientes o similares.



Alternativamente, sin pretender limitar el ámbito de la invención en algún modo, **A** puede tener tanto un O como un S sustituido en la cadena, tal como uno de las siguientes o similares.



Alternativamente, sin pretender limitar el ámbito de la invención en algún modo, en ciertas incorporaciones **A** es $-(CH_2)_m-Ar-(CH_2)_o-$ en donde Ar es fenilo sustituido o no sustituido o heteroarilo monocíclico, la sumatoria de **m** y **o** va de 1 a 4, y en donde un CH_2 puede sustituirse con S u O. En otras palabras, sin pretender limitar el ámbito de la invención en algún modo, **A** comprende de 1 a 4 fracciones CH_2 y Ar, por ejemplo, $-CH_2-Ar-$, $-(CH_2)_2-$ Ar-, $-CH_2-ArCH_2-$, $-CH_2Ar(CH_2)_2-$, $-(CH_2)_2-Ar(CH_2)_2-$ y similares; o

A comprende O, de 0 a 3 fracciones CH_2, y Ar, como en por ejemplo, -O-Ar-, Ar-CH_2-O-, -O-Ar-$(CH_2)_2$-, -O-CH_2- Ar-, -O-CH_2-Ar-$(CH_2)_2$, y similares; o

A comprende S, de 0 a 3 fracciones CH_2, y Ar, como en por ejemplo, -S-Ar-, Ar-CH_2-S-, -S-Ar-$(CH_2)_2$-, -S-CH_2- Ar-, -S-CH_2-Ar-$(CH_2)_2$ y similares.

Ar es fenilo sustituido o no sustituido o heteroarilo monocíclico sustituido o no sustituido. En una incorporación, Ar es fenilo sustituido o no sustituido, tienilo, furilo, o piridinilo. En otra incorporación Ar es fenilo (Ph). En otra incorporación A es $-(CH_2)_2$-Ph. Sin pretender limitar el ámbito de la invención en algún modo, los

sustituyentes pueden tener 4 átomos pesados o menos, o en otras palabras, átomos diferentes de hidrógeno. Se incluirá igualmente cualquier número de átomos de hidrógeno requerido para un sustituyente particular. En consecuencia, el sustituyente puede ser C4 o hidrocarbilo inferior, incluidos C4 o alquilo inferior, alquenil, alquinilo, y similares; C3 o hidrocarbiloxi inferior; CF_3; halo, tal como F, Cl, o Br; hidroxilo; NH_2 y grupos funcionales alquilamina hasta C3; otros sustituyentes que contengan N o S; y similares.

En una incorporación A es $-(CH_2)_m$-Ar-$(CH_2)_o$- en donde Ar es fenilo, la sumatoria de **m** y **o** va de 1 a 3, y en donde un CH_2 puede sustituirse con S u O.

En otra incorporación A es $-CH_2$-Ar-OCH_2-. En otra incorporación A es -CH_2-Ar-OCH_2- y Ar es fenilo.

En otra incorporación **A** es $-(CH_2)_6$-, *cis*-CH_2CH=CH-$(CH_2)_3$-, ó -$CH_2C\equiv C$-$(CH_2)_3$-, en donde 1 ó 2 átomos de carbono pueden sustituirse con S u O; o **A** es -$(CH_2)_2$-Ph- en donde un CH_2 puede sustituirse con S u O.

En otra incorporación A es $-(CH_2)_6$-, *cis*-CH_2CH=CH-$(CH_2)_3$-, ó -$CH_2C\equiv C$-$(CH_2)_3$-, en donde 1 ó 2 átomos de carbono pueden sustituirse con S u O; o **A** es -$(CH_2)_2$-Ph-.

D es una fracción que comprende de 1 a 6 átomos diferentes de hidrógeno, en otras palabras, hay de 1 a 6 átomos que no son hidrógeno, y cualquier número de átomos de hidrógeno requeridos para formar el sustituyente completo. Por ejemplo, un sustituyente metilo tiene 1 átomo de carbono y 3 átomos de hidrógeno. Otros sustituyentes ejemplares incluyen otras fracciones hidrocarbilo que comprenden de 1 a 6 átomos de carbono, incluidos alquilo tal como etilo, propilo, isopropilo, butilo y sus isómeros, pentilo y sus isómeros, hexilo y sus isómeros; hidrocarbilos cíclicos e insaturados con 1 a 6 átomos de carbono; CO_2H y sus sales; alcoxi hasta C_5 tal como metoxi, etoxi, propoxi, isopropoxi, un isómero butoxi, o un isómero pentoxi; ésteres de ácido carboxílico; CN; NO_2; CF_3; F; Cl; Br; I; ésteres de sulfonilo; SO_3H y sus sales; y similares. D puede estar en cualquier posición razonable en el anillo fenilo.

En ciertos compuestos, n es 0. En otros compuestos n es 1, en otros compuestos n es 2, y en otros compuestos n es 3.

Una fracción hidrocarbilo se refiere a una fracción conformada únicamente por carbono e hidrógeno. Sin pretender limitar el ámbito de la invención en algún modo, ejemplos de diferentes tipos de fracción hidrocarbilo son los siguientes.

Un tipo de hidrocarbilo es alquilo que incluye:

a) alquilo lineal tal como metilo, etilo, propilo, n-butilo, n-pentilo, n-hexilo y similares;

b) alquilo ramificado tal como isopropilo, isómeros butilo ramificado (es decir, *sec*-butilo, *terc*-butilo, etc), isómeros pentilo ramificado (es decir, isopentilo, etc), isómeros hexilo ramificado, y fragmentos alquilo ramificados superiores;

c) cicloalquilo tal como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, etc.; y

d) fragmentos alquilo conformados por componentes tanto cíclicos como no cíclicos, lineales o ramificados, los cuales pueden unirse al resto de la molécula en cualquier posición disponible, incluidos átomos de carbono terminales, internos, o de anillo.

En analogía con alquilo, hay un cicloalquilo lineal ramificado; e hidrocarbilo de combinación.

Otro tipo de hidrocarbilo es alquenilo, el cual es similar a alquilo, con la excepción de que está presente un doble enlace.

Otro tipo de hidrocarbilo es alqu(poli)enilo, el cual es similar a alquenilo, excepto que está presente más de un enlace doble.

Otro tipo de hidrocarbilo es alquinilo o un alqu(poli)inilo, el cual es similar a alquenilo o alqu(poli)inilo, excepto que están presentes uno o más enlaces triples.

Otro tipo de hidrocarbilo es arilo, el cual incluye fenilo, naftilo y otros hidrocarbilos aromáticos. Adicionalmente, son también hidrocarbilo las combinaciones de cualquiera de los anteriores en cualquier manera imaginable por aquellas personas de habilidad ordinaria en el arte.

Una fracción hidrocarbilo que comprende una estructura cíclica contiene un cicloalquilo, cicloalquenilo, cicloalquinilo, cicloalquil(poli)enilol, cicloalquil(poli)inilo, arilo, y similares; y puede estar conformada únicamente por el anillo o puede ser una combinación del anillo y uno o más de los fragmentos hidrocarbilo lineal, ramificado o cíclico; o puede ser una estructura policíclica fusionada.

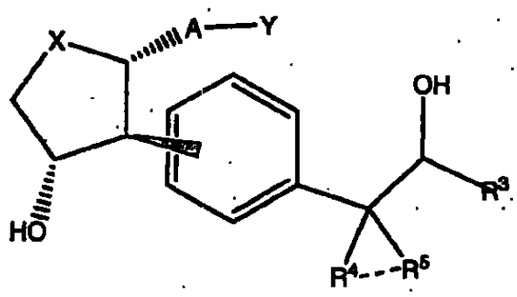
Una fracción hidroxihidrocarbilo está conformada por una combinación de una fracción hidrocarbilo y un grupo hidroxilo. En otras palabras, un átomo de hidrógeno de la fracción hidrocarbilo se sustituye con un grupo hidroxilo. La fracción hidroxihidrocarbilo se une al resto de la molécula en un átomo de carbono.

En consecuencia, sin pretender limitar el ámbito de la invención en algún modo, como R es una fracción hidrocarbilo o hidroxihidrocarbilo que comprende

de 1 a 12 átomos, se contemplan específicamente en esta solicitud incorporaciones con R como cualquiera de las fracciones hidrocarbilo o hidroxicarbilo ya enumeradas. Asimismo R puede ser una fracción diferente, la cual puede considerarse hidrocarbilo o hidroxihidrocarbilo de acuerdo con la descripción dada en esta solicitud.

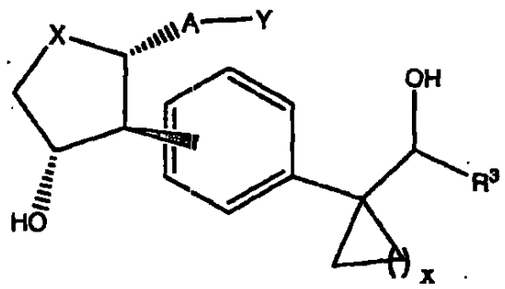
En ciertos compuestos, R es un hidroxihidrocarbilo con el grupo hidroxilo unido al átomo de carbono, que se une asimismo al resto de la molécula. En otras palabras el grupo hidroxilo y el resto de la molécula están en posiciones geminadas en la fracción hidrocarbilo. Este tipo de fracción hidroxihidrocarbilo se designa en esta solicitud como una fracción 1-hidroxihidrocarbilo. El hidroxihidrocarbilo no lineal es un hidroxihidrocarbilo en donde la porción hidrocarbilo es no lineal, es decir, tiene ramificaciones y/o un anillo.

En otros compuestos R es hidroxihidrocarbilo con el grupo hidroxilo unido a un átomo de carbono, el cual se une directamente a la parte restante de la molécula. Estos hidroxihidrocarbilos particulares se denominan 2-hidroxihidrocarbilo en esta solicitud. Por ejemplo, $-C(CH_3)_2CH_2OH$ es 2-hidroxihidrocarbilo. Sin pretender limitar el ámbito de la invención en algún modo, a continuación se muestra una estructura donde R es 2-hidrocarbilo.



Al igual que con las demás estructuras mostradas en esta solicitud, se contemplan igualmente sales farmacéuticamente aceptables y profármacos de compuestos representados por estas estructuras.

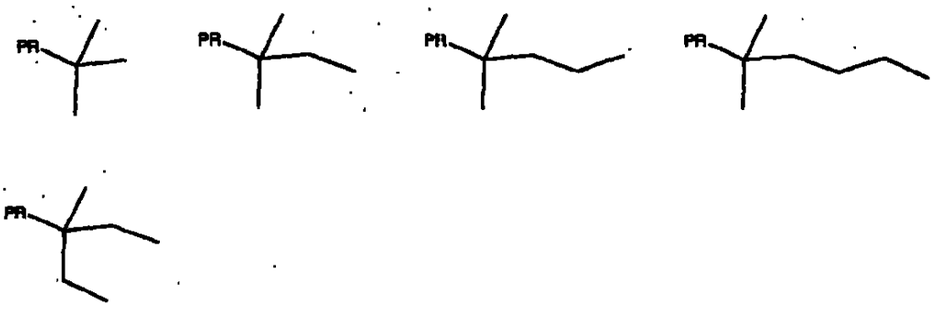
En una incorporación relacionada con la estructura anterior, R^3, R^4, y R^5 son independientemente H ó C_{1-6} alquilo. Como la línea discontinua indica la presencia o ausencia de un enlace, R^4 y R^5 pueden ser dos fracciones separadas. Por ejemplo, sin pretender ser limitantes, R^4 y R^5 pueden ser metilo, y no estaría presente un enlace donde se indica por la línea discontinua. Alternativamente, sin pretender limitar el ámbito de la invención en algún modo, R^4 y R^5 pueden formar un anillo. En otras palabras, es posible un compuesto tal como el mostrado a continuación, en donde X va de 1 a 6.

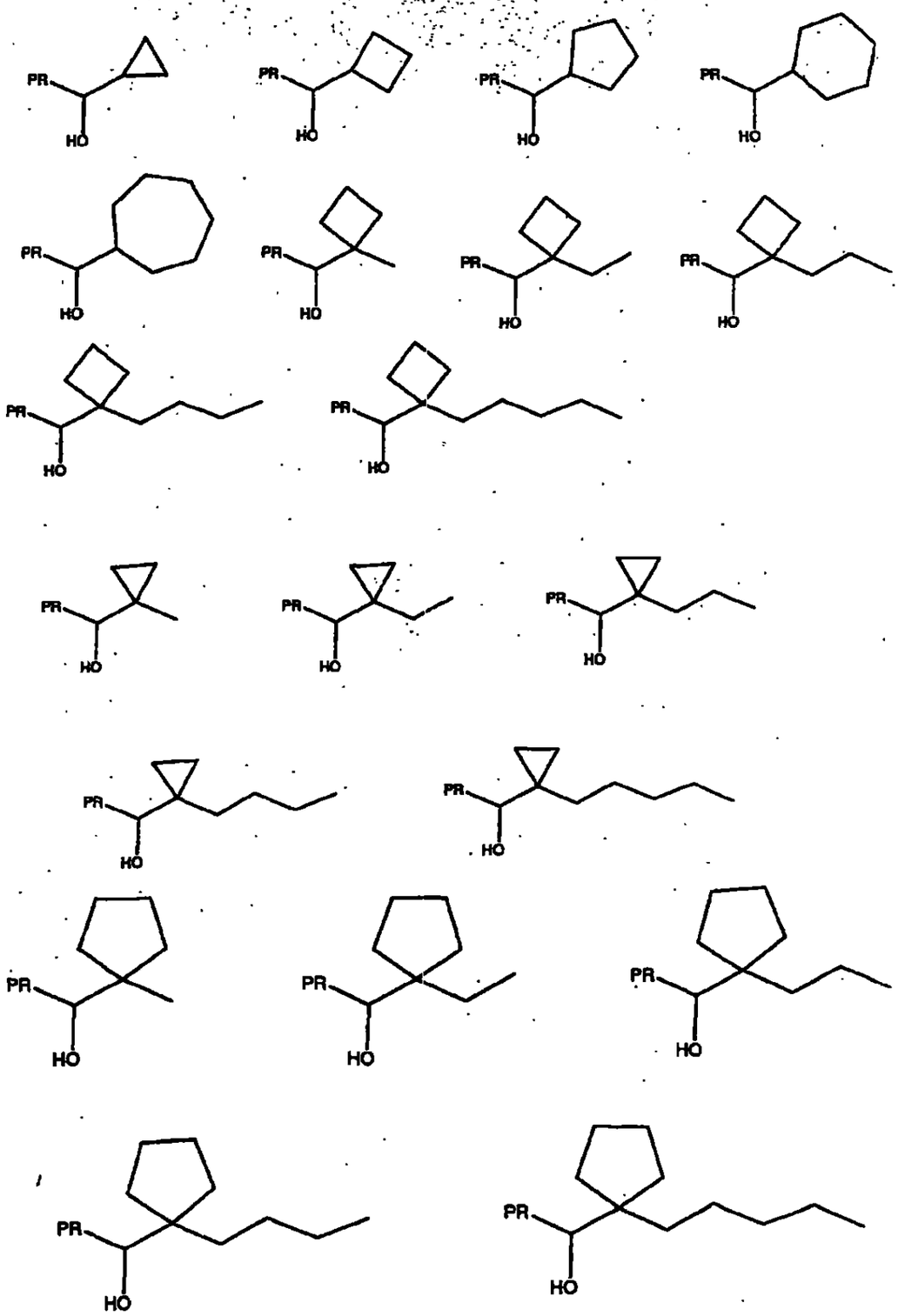


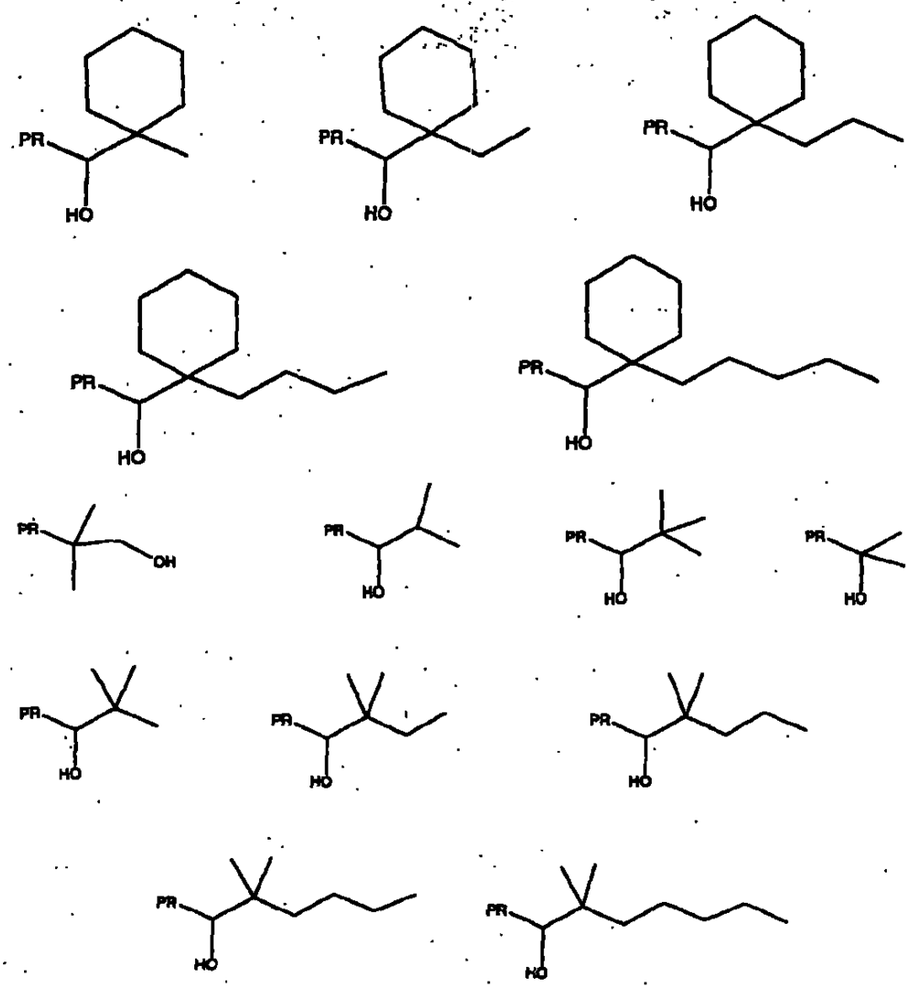
En igual forma se contemplan sales farmacéuticamente aceptables y profármacos de compuestos representados por estas estructuras.

En ciertos compuestos, R comprende de 6 a 9 átomos de carbono y una estructura cíclica. En otros compuestos, R comprende de 1 a 5 átomos de carbono. En ciertos compuestos R es hidroxialquilo con 1 a 5 átomos de carbono. En otros compuestos R es una fracción 1-hidroxihidrocarbilo que comprende de 6 a 9 átomos de carbono y una estructura cíclica. En otros compuestos R es una fracción 1-hidroxihidrocarbilo que comprende de 6 a 9 átomos de carbono y una estructura cíclica, que incluye de 4-7 átomos de carbono. En otras palabras, la estructura cíclica [que forma] parte de R es un fragmento ciclobutilo, ciclopentilo, ciclohexilo, o cicloheptilo. La estructura cíclica [que forma] parte de R puede ser también un fragmento cicloalquenilo o cicloalquinilo, tal como ciclopenteno o ciclohexeno. En otros compuestos R es una fracción hidrocarbilo que comprende de 1 a 5 átomos de carbono. En otras palabras, R es metilo, etilo, propilo, isopropilo, un isómero butilo tal como *t*-butilo, o un isómero pentilo. En ciertos compuestos R es *t*-butilo.

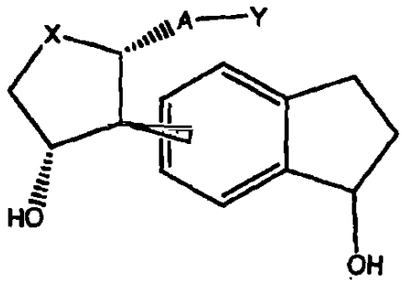
En esta solicitud se contemplan específicamente ciertos grupos R. Éstos se muestran a continuación, donde PR representa la parte restante de la molécula.



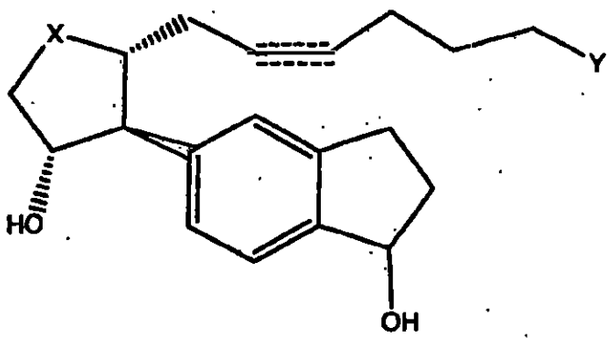

PR
HO



Como existe una línea discontinua entre R y el anillo fenilo, son posibles estructuras cíclicas con dos átomos de carbono del anillo fenilo. En consecuencia, sin pretender limitar el ámbito de la invención en algún modo, son posibles compuestos tales como los representados por la siguiente estructura.

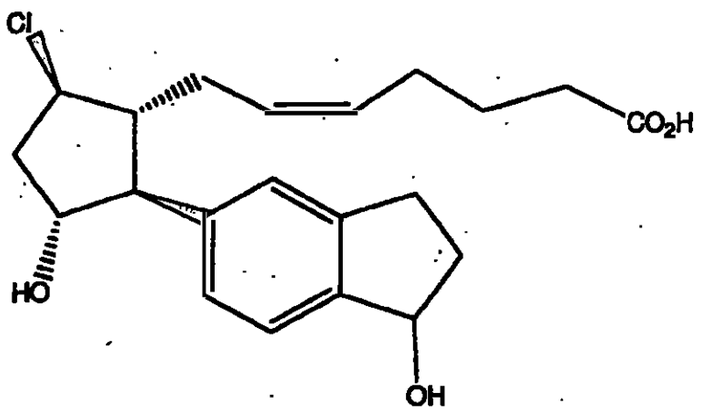


Se contemplan igualmente sales farmacéuticamente aceptables y profármacos de



o su sal farmacéuticamente aceptable o profármaco.

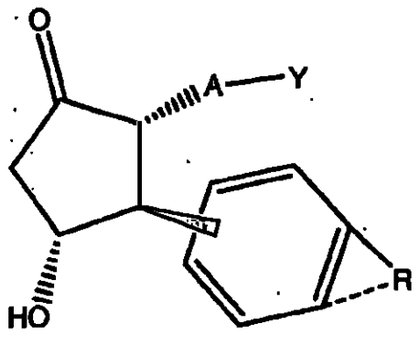
Otros compuestos útiles comprenden



o su sal farmacéuticamente aceptable o profármaco.

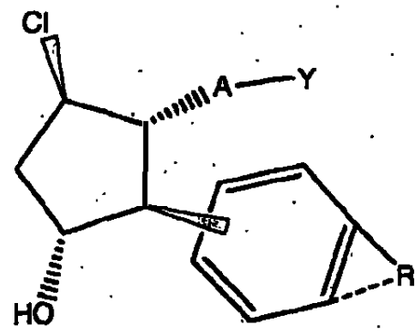
Aquellas personas de habilidad ordinaria en el arte entienden que cualquier valor que se refiera al número de átomos, fracciones, etc., en una molécula pequeña será un entero, es decir 0, 1, 2, 3, etc.

Ciertos compuestos útiles comprenden



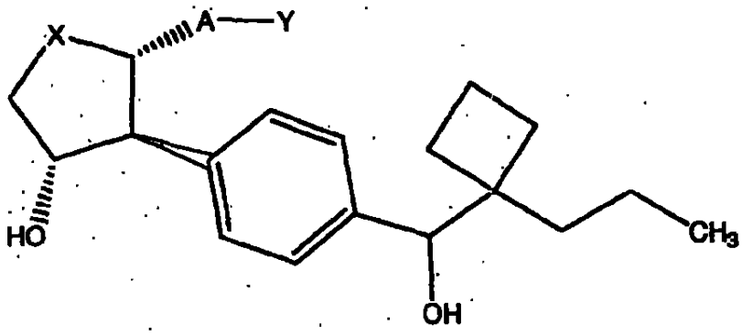
o su sal farmacéuticamente aceptable o profármaco.

Otros compuestos útiles comprenden



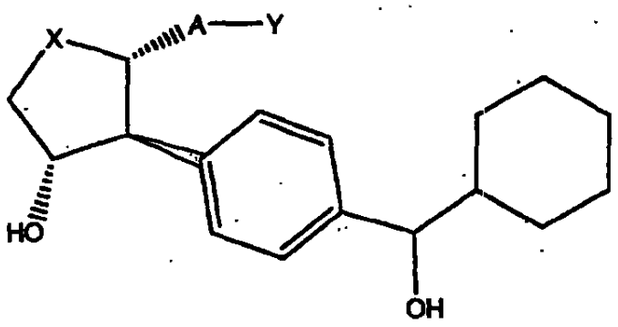
o su sal farmacéuticamente aceptable o profármaco.

Otros ejemplos útiles de compuestos comprenden



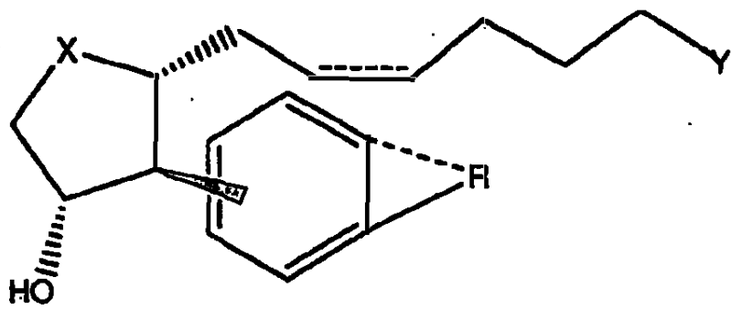
o su sal farmacéuticamente aceptable o profármaco.

Otros compuestos comprenden



o su sal farmacéuticamente aceptable o profármaco.

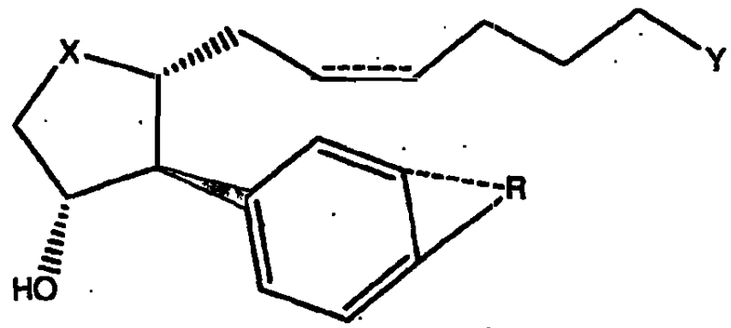
Otras incorporaciones comprenden



o su sal farmacéuticamente aceptable o profármaco,

en donde una línea discontinua indica la presencia o ausencia de un enlace.

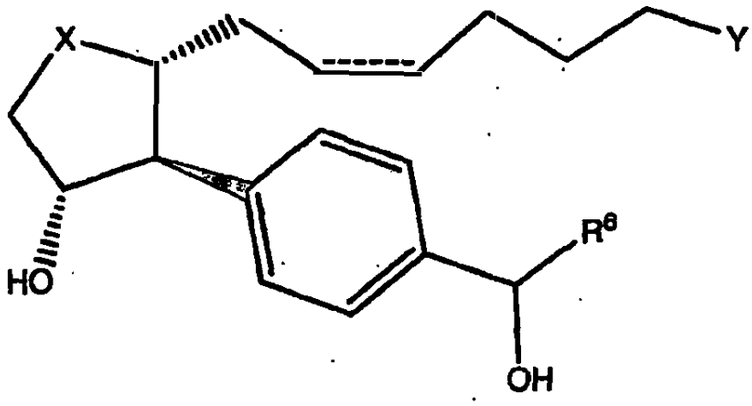
Otros compuestos comprenden



en donde X es C=O ó CHCl; y

R es alquilo con 3 a 6 átomos de carbono.

Otros compuestos comprenden

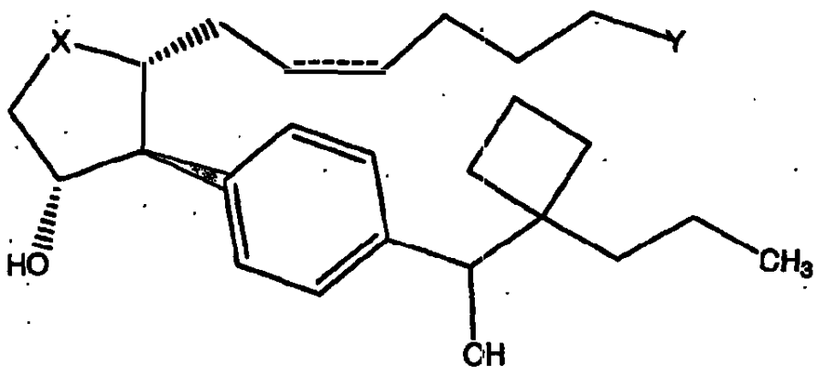


o su sal farmacéuticamente aceptable o profármaco,

en donde R^6 es cicloalquilo que comprende de 3 a 10 átomos de carbono; y

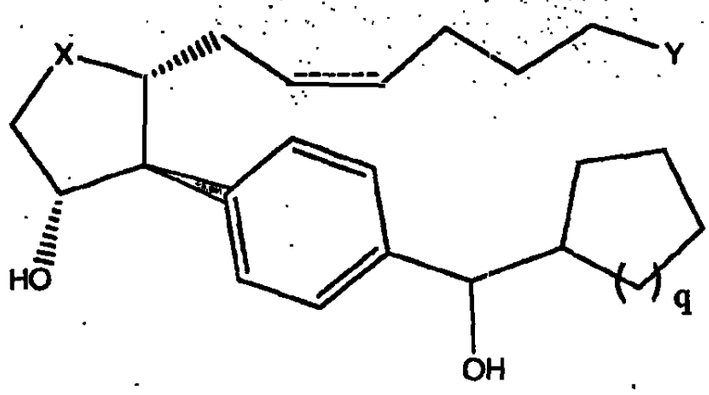
X es C=O ó CHCl.

Otros compuestos comprenden



o su sal farmacéuticamente aceptable o profármaco.

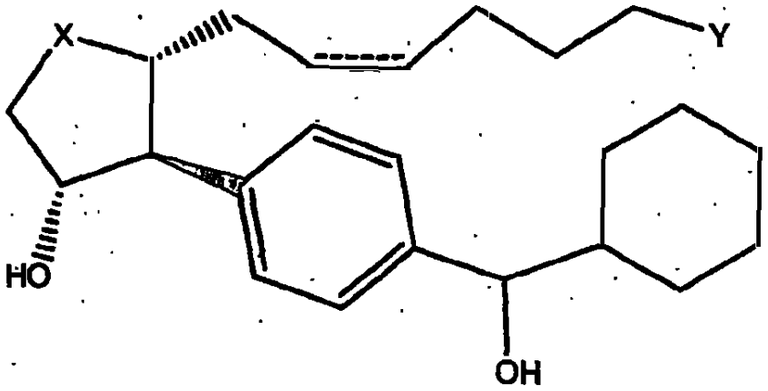
Otras incorporaciones comprenden



o su sal farmacéuticamente aceptable o profármaco

en donde **q** es un entero con un valor de desde 0 a 3.

Otros compuestos comprenden



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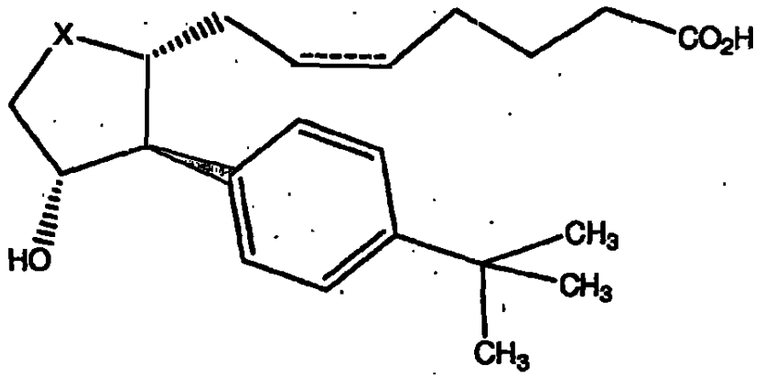
Otros compuestos comprenden



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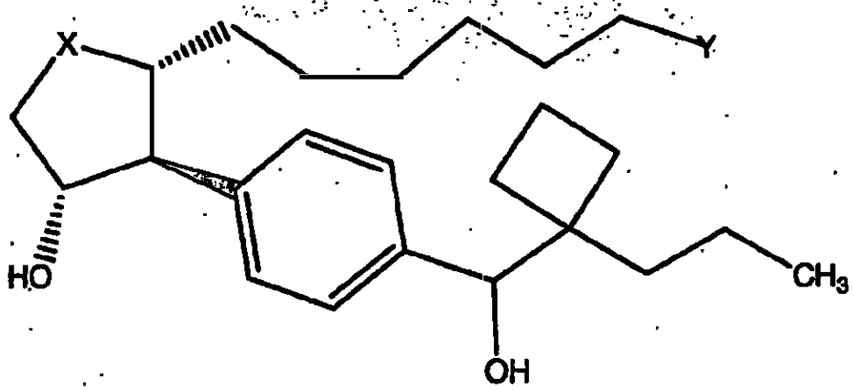
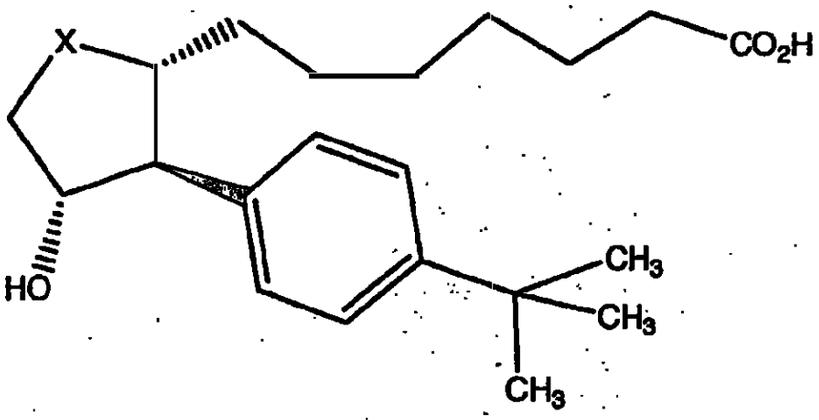
Otros compuestos útiles comprenden



o su sal farmacéuticamente aceptable o profármaco.

Otras incorporaciones útiles comprenden



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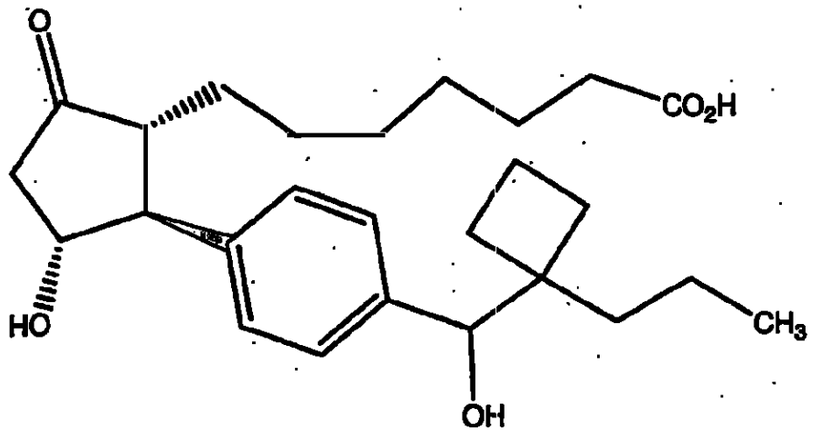
Otro compuesto útil es



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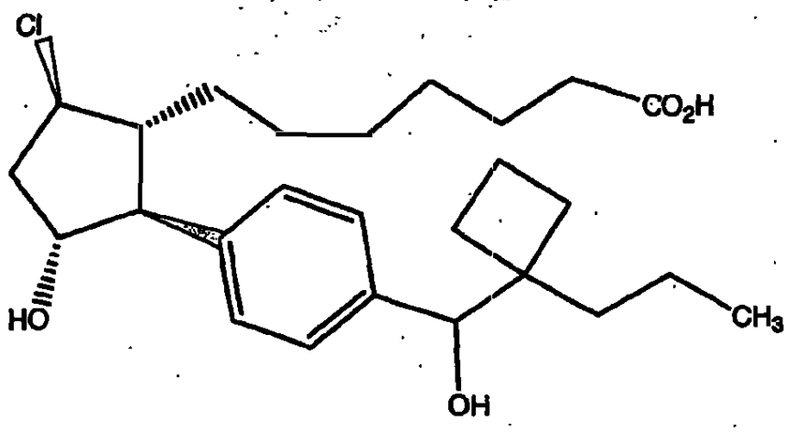

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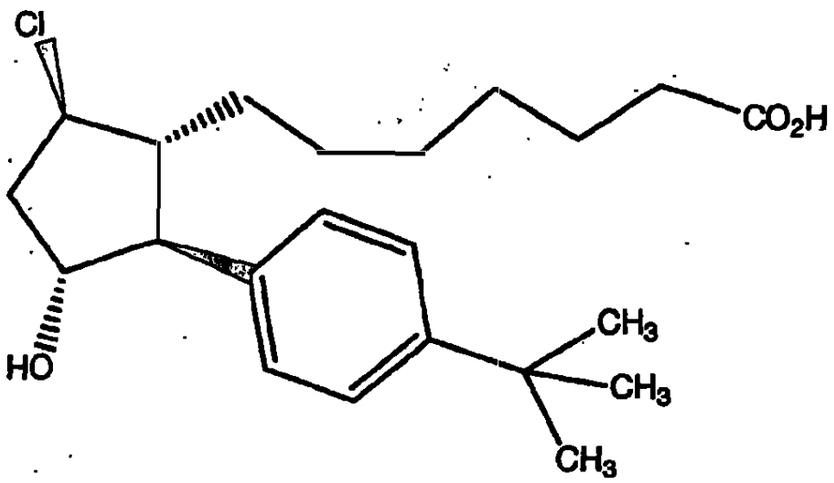

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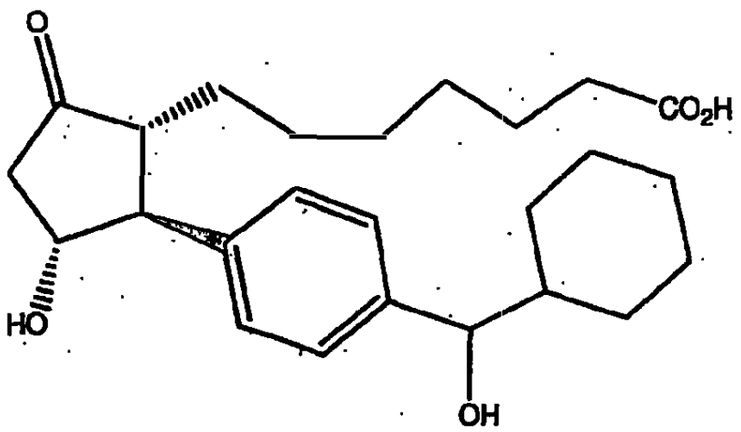

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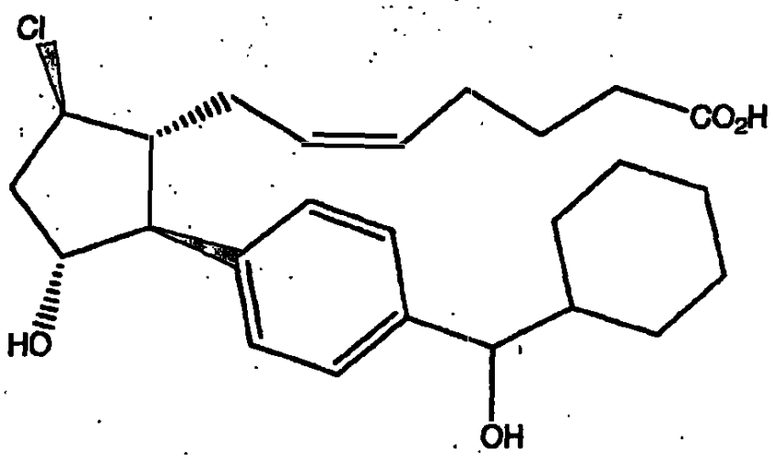
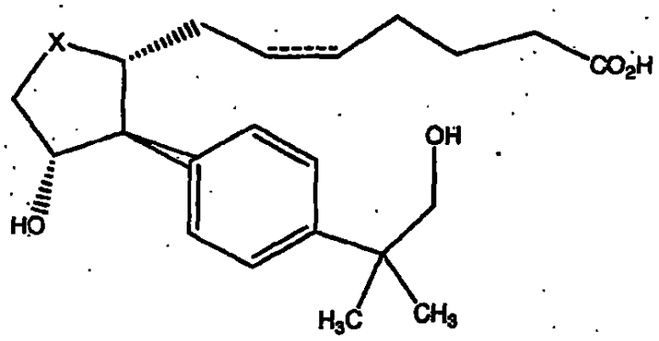


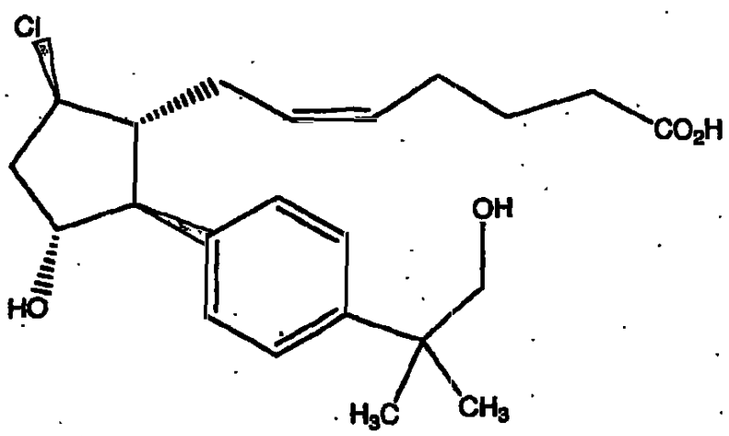
o su sal farmacéuticamente aceptable o profármaco.

Ciertos compuestos comprenden



o su sal farmacéuticamente aceptable o profármaco.

Otros compuestos comprenden



o su sal farmacéuticamente aceptable o profármaco.

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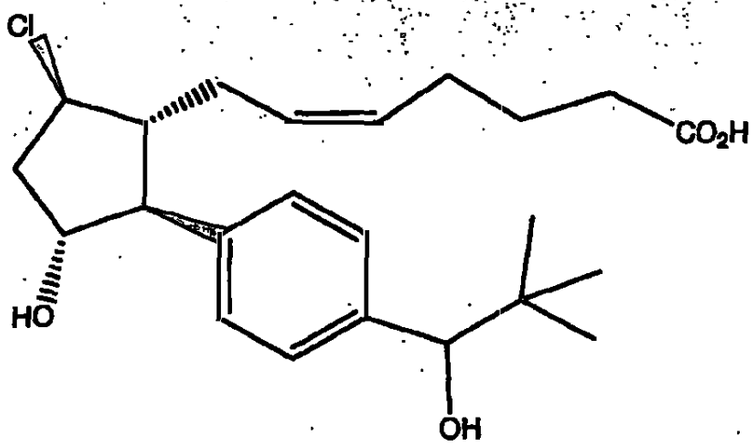

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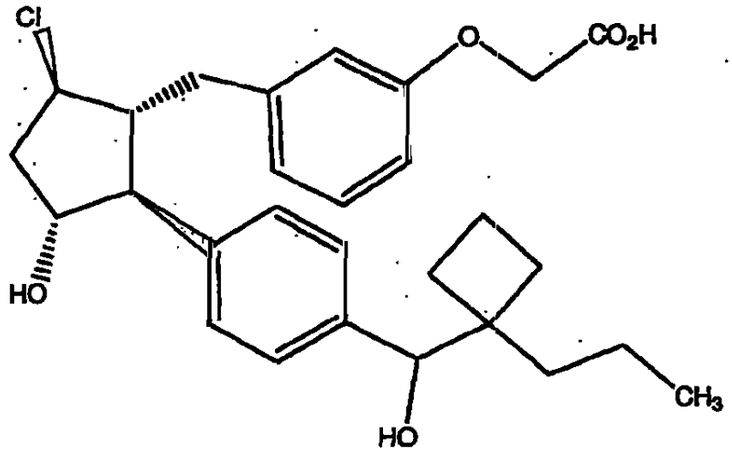
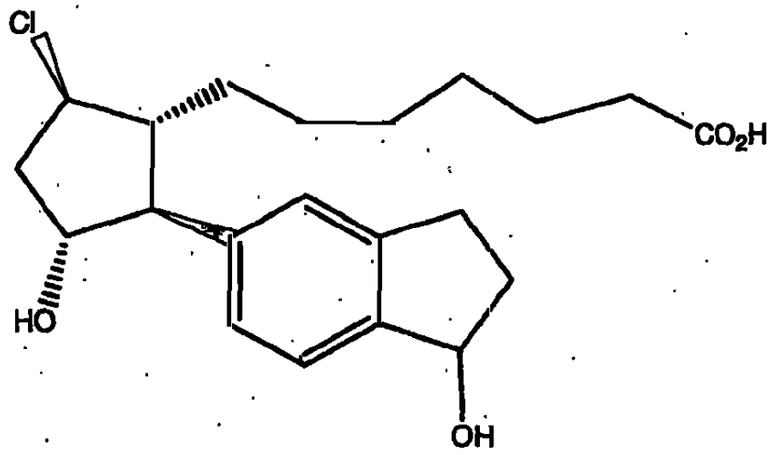


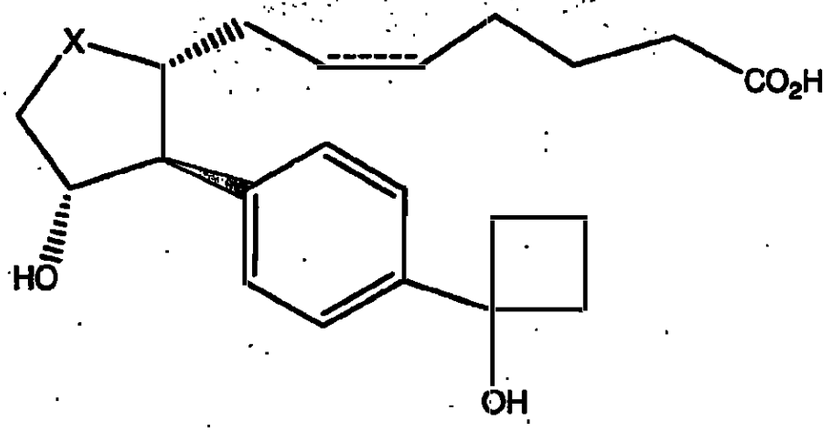
o su sal farmacéuticamente aceptable o profármaco.

Otro compuesto útil es



o su sal farmacéuticamente aceptable o profármaco.

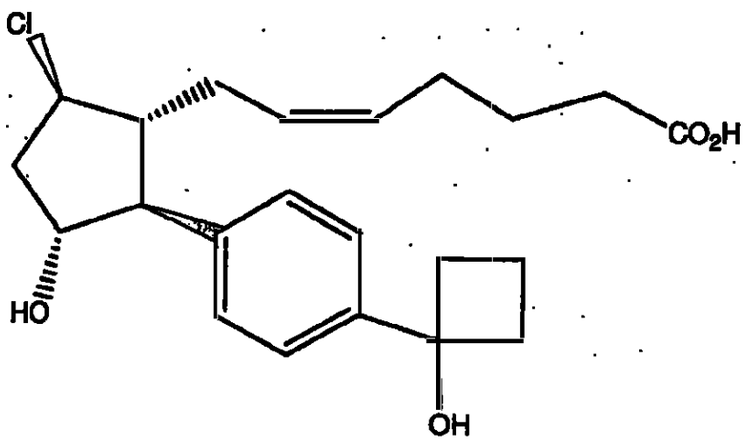
Otros compuestos comprenden



o su sal farmacéuticamente aceptable o profármaco

en donde X es C=O ó CHCl.

Otro compuesto útil es



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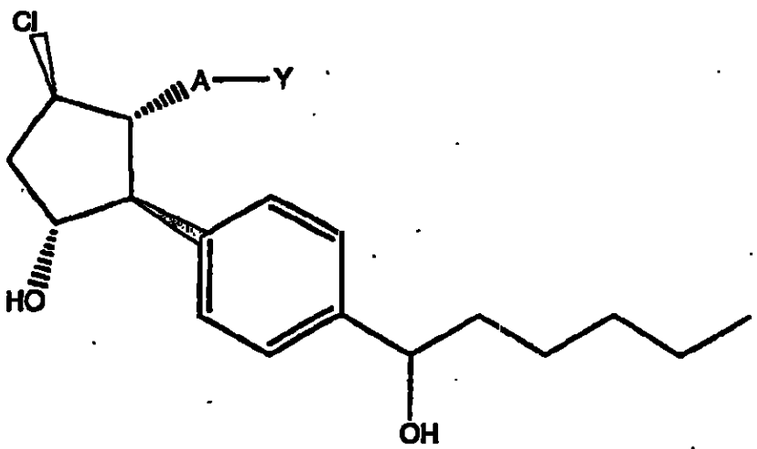
Otro compuesto útil es



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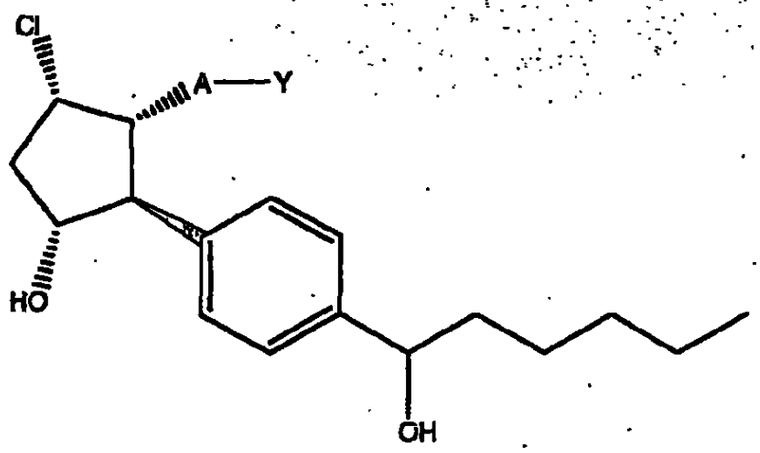

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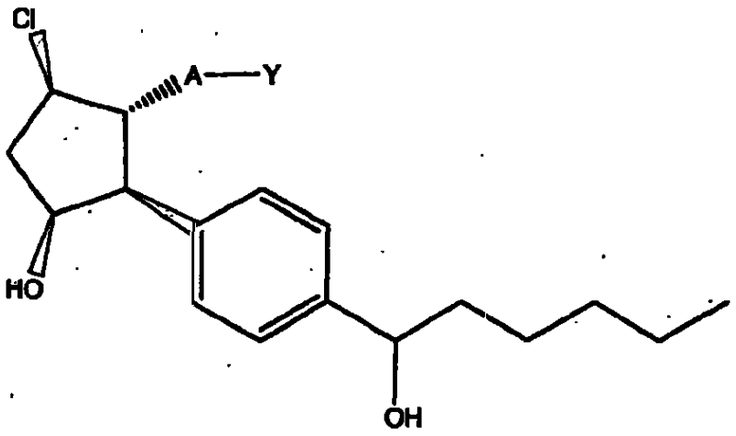
Otro compuesto útil es



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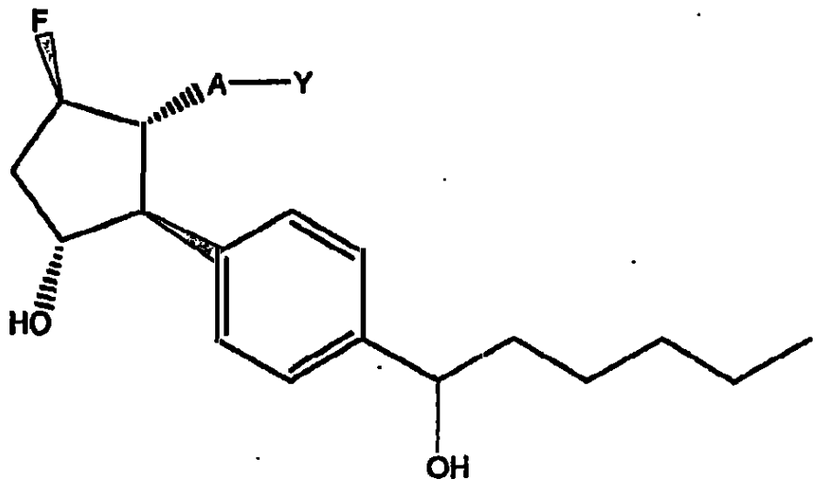
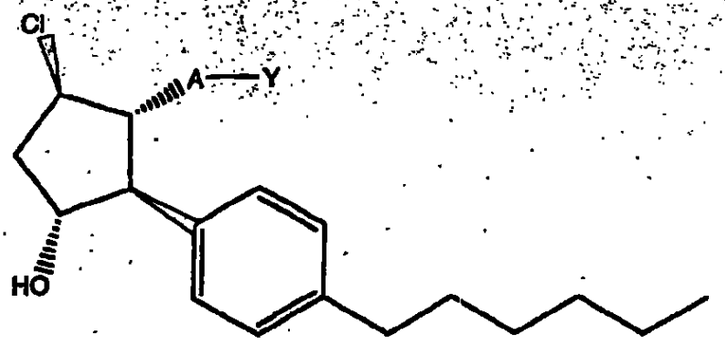


o su sal farmacéuticamente aceptable o profármaco.

Otro compuesto útil es



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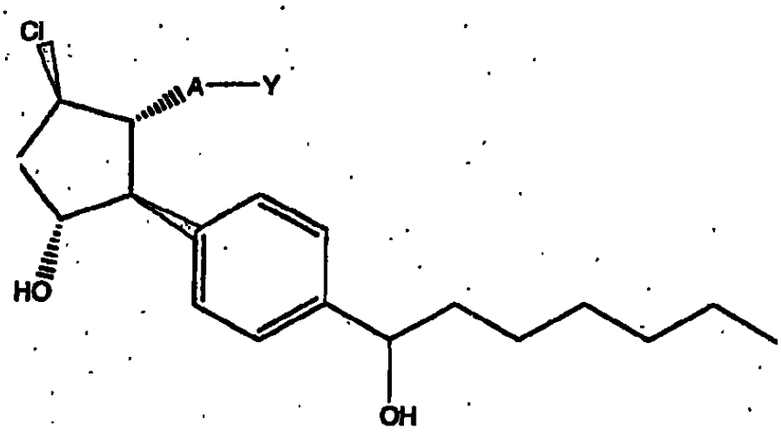

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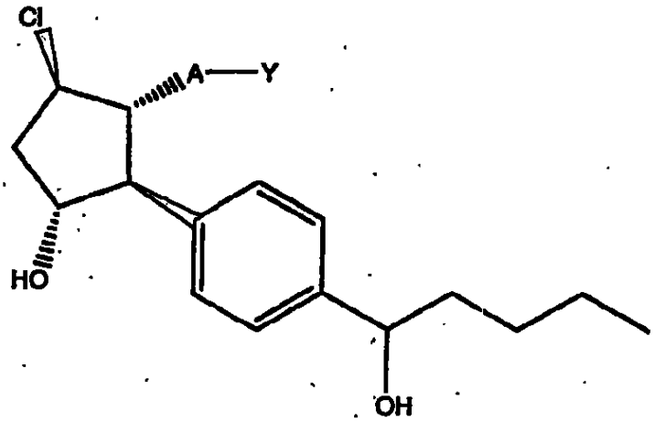
Otro compuesto útil es



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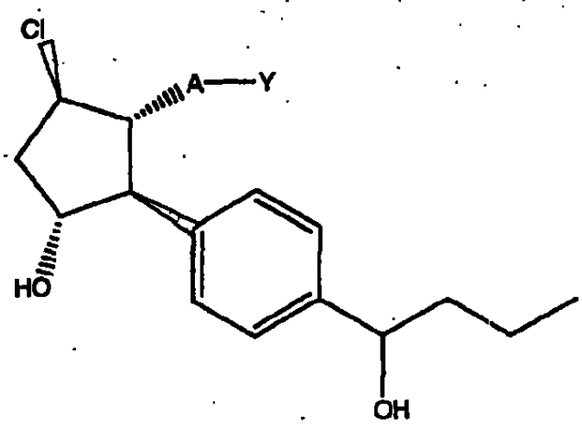
Otro compuesto útil es



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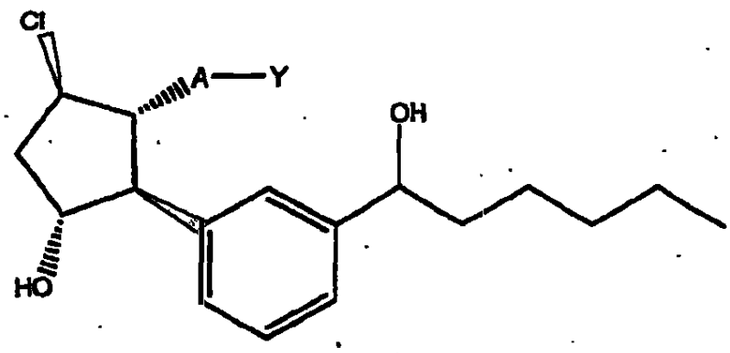

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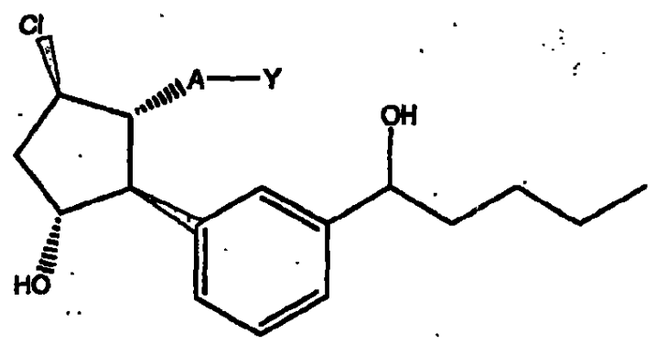

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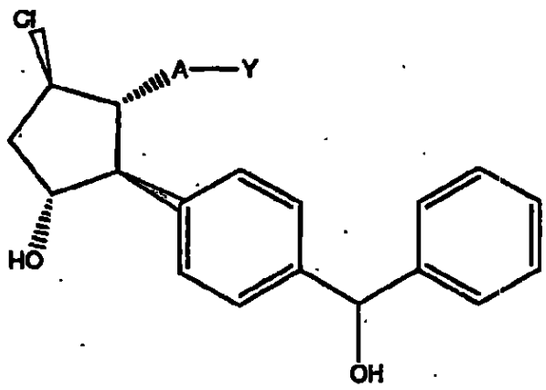

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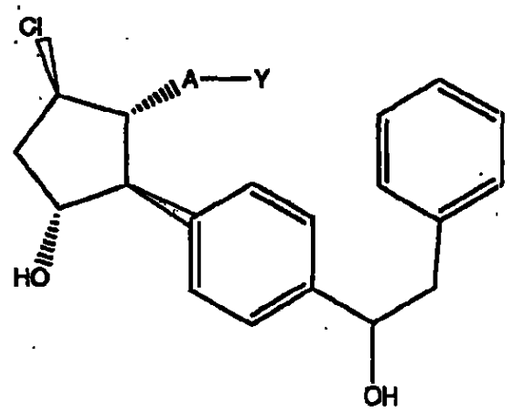

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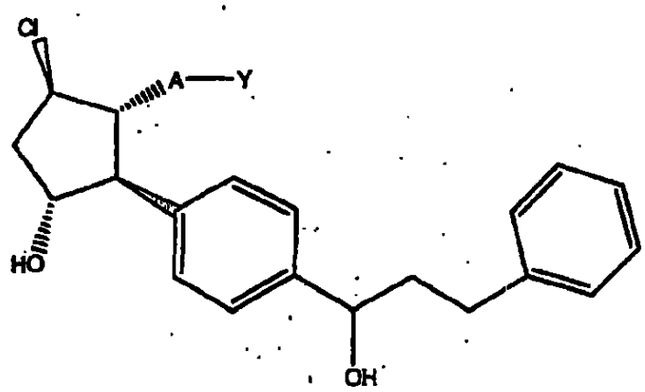

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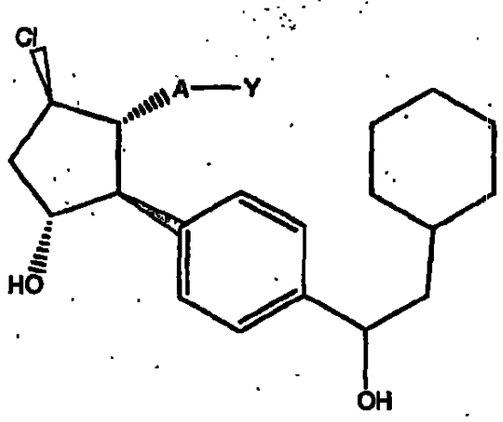
Otro compuesto útil es



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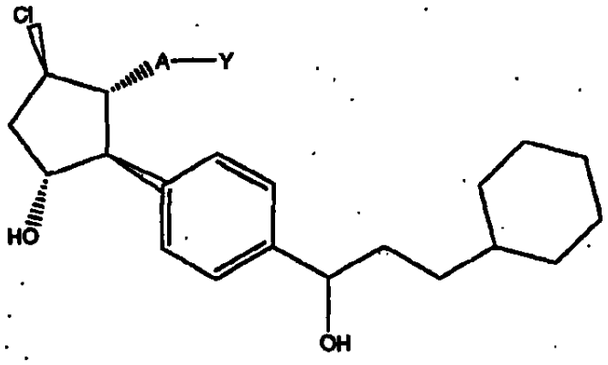
Otro compuesto útil es



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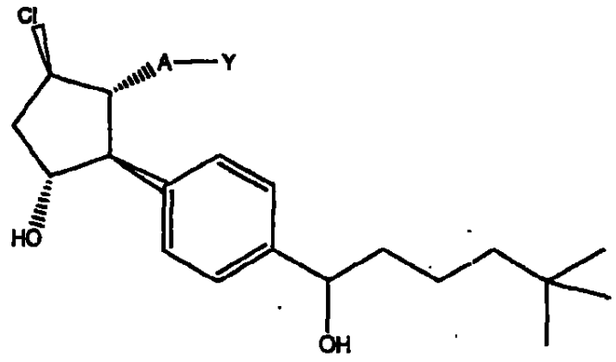
Otro compuesto útil es



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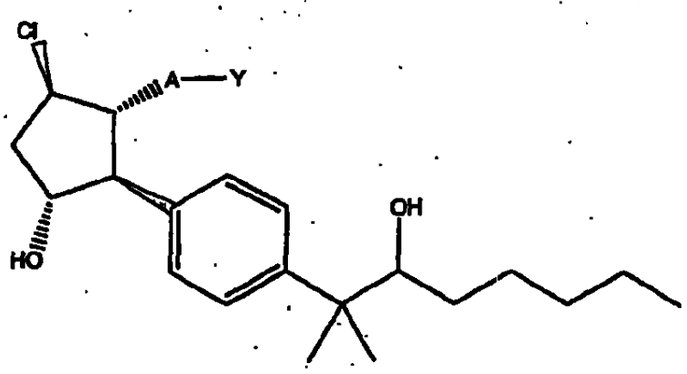

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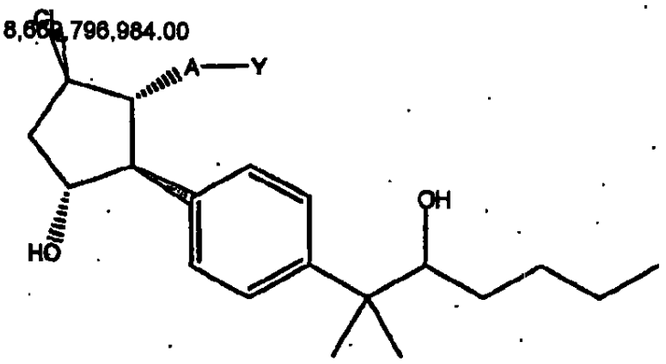
Otro compuesto útil es



o su sal farmacéuticamente aceptable o profármaco.

Estos compuestos pueden usarse en composiciones, métodos, o medicamentos contemplados para cualquier otro compuesto divulgado en esta solicitud.

Otros compuestos comprenden

éster metílico de ácido (Z)-7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil)-hept-5-enoico (5-4);

ácido (Z)-7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil}-hept-5-enoico (5-5);

éster metílico de ácido 7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil}-heptanoico (5-7);

ácido 7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil}-heptanoico (5-8);

éster metílico de ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5- enoico;

ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico;

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éster metílico de ácido 7-((1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico;
ácido 7-((1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico;
éster metílico de ácido (Z)-7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-hept-5-enoico;
ácido (Z)-7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-hept-5-enoico;
éster metílico de ácido 7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-heptanoico;
ácido 7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-heptanoico;
éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-hept-5-enoico;
ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-hept-5-enoico;
éster metílico de ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-heptanoico;
ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-heptanoico;
éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-5-oxo-ciclopentil}-hept-5-enoico (**e1-2**);
éster metílico de ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-5-oxo-ciclopentil}-heptanoico;
ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-5-oxo-ciclopentil}-heptanoico;
éster metílico de ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico;
ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico (**e2-1**);
éster metílico de ácido 7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico;
ácido 7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico;
(2-hidroxi-etil)-amida de ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico (**e2-2, R = 2-hidroxietilo**);

etil amida de ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico (**e2-2, R = etilo**);

etil amida de ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico (**e2-2, R** = H);

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-hept-5-enoico (**6-3**);

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-hept-5-enoico (**6-4**);

éster isopropílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-hept-5-enoico (**6-5**);

éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-heptanoico (**6-6**);

éster metílico de ácido 7-[(1R,2S,3R,5R)-5-cloro-2-(4-ciclohexilmetil-fenil)-3-hidroxi-ciclopentil]-heptanoico (**6-8**);

ácido 7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-heptanoico (**6-7**);

ácido 7-[(1R,2S,3R,5R)-5-cloro-2-(4-ciclohexilmetil-fenil)-3-hidroxi-ciclopentil]-heptanoico (**6-9**);

éster metílico de ácido (Z)-7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-hept-5-enoico;

ácido (Z)-7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil-metil]-fenil}-ciclopentil)-hept-5-enoico;

éster metílico de ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico;

ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico;

éster metílico de ácido (Z)-7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-hept-5-enoico;

ácido (Z)-7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-hept-5-enoico;

éster metílico de ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico;

ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico;

éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-hept-5-enoico;

ácido (Z)-7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-hept-5-enoico;

éster metílico de ácido 7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-heptanoico;

ácido 7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-heptanoico;

éster isopropílico de ácido (Z)-7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-hept-5-enoico;

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-hept-5-enoico;

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-hept-5-enoico;

éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-heptanoico;

ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-heptanoico;

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-hept-5-enoico;

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-hept-5-enoico;

éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-heptanoico;

ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-heptanoico;

éster isopropílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-heptanoico;

éster metílico de ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-hept-5-enoico (**7-5**);

ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-hept-5-enoico (**7-6**);

éster metílico de ácido 7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-heptanoico (**7-7**);

éster metílico de ácido 7-((1R,2S,3R)-3-hidroxi-5-oxo-2-*p*-tolil-ciclopentil)-heptanoico (**7-9**);
ácido 7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-heptanoico (**7-8**);
éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-hept-5-enoico (**8-4**);
ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-hept-5-enoico (**8-5**);
éster metílico de ácido 7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-heptanoico (**8-6**);
ácido 7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-heptanoico (**8-7**);
éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-hept-5-enoico (**9-5**);
éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-hept-5-enoico (**9-6**);
ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-hept-5-enoico (**9-7**);
ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-hept-5-enoico (**9-8**);
éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-heptanoico (**9-9**);
éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-heptanoico (**9-10**);
ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-heptanoico (**9-11**);
ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-heptanoico (**9-12**);
éster metílico de ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-but-2-iniloxi)-acético (**10-6**);
ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-but-2-iniloxi)-acético (**10-7**);
éster metílico de ácido ((Z)-4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-but-2-eniloxi)-acético (**11-1**);

ácido ((Z)-4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-but-2-eniloxi)-acético (**11-2**);

éster metílico de ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-butoxi)-acético (**11-3**);

ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-butoxi)-acético (**11-4**);

éster metílico de ácido [3-((1R,2S,3R)-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentilmetil)-fenoxi]-acético (**13-3**);

ácido [3-((1R,2S,3R)-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentilmetil)-fenoxi]-acético (**13-4**);

éster metílico de ácido [3-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentilmetil)-fenoxi]-acético (**14-3**);

ácido [3-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentilmetil)-fenoxi]-acético (**14-4**);

éster metílico de ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-hept-5-enoico (**15-6**);

ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-hept-5-enoico (**15-7**);

éster metílico de ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-5-oxo-2-(1-oxo-indan-5-il)-ciclopentil]-hept-5-enoico (**15-8**);

ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-5-oxo-2-(1-oxo-indan-5-il)-ciclopentil]-hept-5-enoico (**15-9**);

éster metílico de ácido 7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-heptanoico (**15-10**);

éster metílico de ácido 7-((1R,2S,3R)-3-hidroxi-2-indan-5-il-5-oxo-ciclopentil)-heptanoico (**15-12**);

ácido 7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-heptanoico (**15-11**);

ácido 7-((1R,2S,3R)-3-hidroxi-2-indan-5-il-5-oxo-ciclopentil)-heptanoico (**15-13**);

éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico (**16-4**);

ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico (**16-5**);

éster isopropílico de ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico (**16-6**);

éster metílico de ácido 7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico (**16-7**);

éster metílico de ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-indan-5-il-ciclopentil)-heptanoico (**16-9**);

ácido 7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico (**16-8**);

ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-indan-5-il-ciclopentil)-heptanoico (**16-10**);

éster metílico de ácido 7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico (**17-3**);

ácido 7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico (**17-4**);

éster metílico de ácido (Z)-7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico (**17-5**);

ácido (Z)-7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico (**17-6**);

ácido 3-(3-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-benzoico (**18-13**);

éster etílico de ácido 3-(3-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-benzoico;

ácido 5-(3-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-tiofen-2-carboxílico (**102**);

éster metílico de ácido 5-(3-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-tiofen-2-carboxílico;

éster isopropílico de ácido 5-(3-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-tiofen-2-carboxílico;

ácido 3-(3-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentilmetil}-fenil)-propiónico (**20-5**);

éster metílico de ácido 3-(3-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentilmetil}-fenil)-propiónico;

ácido 3-[3-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentilmetil)-fenil]-propiónico (**104**);

éster metílico de ácido 3-[3-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil-ciclopentilmetil)-fenil]-propiónico;

ácido 2-(3-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-tiazol-5-carboxílico (**21-7**);

éster etílico de ácido 2-(3-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-tiazol-5-carboxílico;

ácido (Z)-7-{(1R,2S,3R,5R)-5-fluoro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (**22-3**);

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-fluoro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico;

ácido (Z)-7-{(1R,2S,3R,5S)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (**23-5**);

éster metílico de ácido (Z)-7-{(1R,2S,3R,5S)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico;

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (**110**);

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (**24-4**);

éster isopropílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico;

ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-heptanoico (**114**);

éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-heptanoico;

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(3-ciclohexil-1-hidroxi-propil)-fenil]-3-hidroxi-ciclopentil }-hept-5-enoico (**115**);

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(3-ciclohexil-1-hidroxi-propil)-fenil]-3-hidroxi-ciclopentil}-hept-5- enoico;

ácido 7-{(1R,2S,3R,5R)-5-cloro-2-[4-(3-ciclohexil-1-hidroxi-propil)-fenil]-3-hidroxi-ciclopentil}-heptanoico (**116**);

éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-2-[4-(3-ciclohexil-1-hidroxi-propil)-fenil]-3-hidroxi-ciclopentil}-heptanoico;

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(2-ciclohexil-1-hidroxi-etil)-fenil]-3-hidroxi-ciclopentil}-hept-5-enoico (**117**);

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(2-ciclohexil-1-hidroxi-etil)-fenil]-3-hidroxi-ciclopentil}-hept-5-enoico;

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-butil)-fenil]-ciclopentil}-hept-5-enoico;

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-butil)-fenil]-ciclopentil}-hept-5-enoico (**126**);

éster isopropílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-butil)-fenil]-ciclopentil}-hept-5-enoico;

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-pentil)-fenil]-ciclopentil}-hept-5-enoico;

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-pentil)-fenil]-ciclopentil}-hept-5-enoico (**127**);

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(hidroxi-fenil-metil)-fenil]-ciclopentil}-hept-5-enoico;

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(hidroxi-fenil-metil)-fenil]-ciclopentil}-hept-5-enoico (**128**);

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[3-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico;

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[3-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (**129**);

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[3-(1-hidroxi-pentil)-fenil]-ciclopentil}-hept-5-enoico;

ácido (Z)-7-{(1R;2S,3R,5R)-5-cloro-3-hidroxi-2-[3-(1-hidroxi-pentil)-fenil]-ciclopentil}-hept-5-enoico (**130**);

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-heptil)-fenil]-ciclopentil}-hept-5-enoico;

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-heptil)-fenil]-ciclopentil}-hept-5-enoico (**131**);

éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-hexil)-fenil]-ciclopentil}-hept-5-enoico;

ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-hexil)-fenil]-ciclopentil}-hept-5-enoico (**132**);

ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-2-(4-hexil-fenil)-3-hidroxi-ciclopentil]-hept-5-enoico (**26-2**);

éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-2-(4-hexil-fenil)-1-hidroxi-ciclopentil]-hept-5-enoico;

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éster isopropílico de ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-2-(4-hexil-fenil)-3-hidroxi-ciclopentil]-hept-5-enoico; y
ácido (Z)-7-{(1R,2S,3S,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (211217).

Un agonista selectivo de prostaglandina EP_2 es un compuesto que es más activo en un receptor de prostaglandina EP_2 que en cualquier otro receptor de prostaglandina.

Una incorporación es un compuesto que comprende un agonista selectivo de prostaglandina EP_2 en donde la cadena ω contiene un fenilo sustituido, en donde por lo menos un sustituyente está conformado por hidrocarbilo o hidroxihidrocarbilo no lineal, en donde dicho compuesto es efectivo en reducir en por lo menos 20% la presión intraocular (IOP, ***Intraocular Pressure***) en un mono.

Reducir IOP en un mono, tal como se emplea en esta solicitud, tiene como finalidad significar reducir la IOP utilizando el método descrito en esta solicitud.

En una incorporación, el compuesto tiene un valor IC_{50} menor de 1 μM. En otra incorporación, el compuesto es más de 100 veces más activo en el receptor EP_2 que en cualquier otro receptor. En otra incorporación, el compuesto es más de 1.000 veces más activo en el receptor EP_2 que en cualquier otro receptor.

La cadena ω tiene el significado normalmente entendido en el arte. En prostaglandina E_2, la cadena ω está en la tercera posición del anillo ciclopentanona, donde la posición 1 es el carbonilo y la cadena α está en la posición 2. No obstante, el significado del término cadena α debe adaptarse de acuerdo con variaciones sintéticas que se hacen a la prostaglandina E_2. Una persona de habilidad ordinaria en el arte puede distinguir fácilmente la cadena ω en análogos sintéticos y derivados de la prostaglandina E_2. Por ejemplo, sin pretender limitar el ámbito de la invención en algún modo, la cadena ω podría estar en la tercera posición en un 1-clorociclopentano con la cadena α en la posición 2.

Un fenilo sustituido, en donde por lo menos un sustituyente está conformado por hidrocarbilo o hidroxihidrocarbilo no lineal, puede tener sustituyentes adicionales diferentes de hidrocarbilo o hidroxihidrocarbilo no lineal, es decir, por lo menos un sustituyente es hidrocarbilo hidroxihidrocarbilo no lineal y por lo menos un sustituyente no lo es. Los compuestos divulgados en esta solicitud son útiles para la prevención o tratamiento de glaucoma o hipertensión ocular en mamíferos, o para la fabricación de un medicamento para el tratamiento

de glaucoma o hipertensión ocular. También son útiles para el tratamiento de aquellas enfermedades divulgadas en el arte como sensibles al tratamiento con un agonista de prostaglandina EP_2, tal como las enumeradas previamente.

Aquellas personas de habilidad en el arte entenderán fácilmente que para la administración o la fabricación de medicamentos, los compuestos divulgados en esta solicitud pueden mezclarse con excipientes farmacéuticamente aceptables, los cuales son ***per se*** bien conocidos en el arte. Específicamente, un fármaco que se va a administrar en forma sistémica puede confeccionarse como un polvo, píldora, tableta o similar, o como una solución, emulsión, suspensión, aerosol, jarabe o elíxir apropiado para administración oral o parenteral, o inhalación.

Para formas farmacéuticas sólidas o medicamentos, vehículos sólidos no tóxicos incluyen, pero no se limitan a, grados farmacéuticos de mannitol, lactosa, almidón, estearato de magnesio, sacarina sódica, los polialquilen glicoles, talco, celulosa, glucosa, sacarosa y carbonato de magnesio. Las formas farmacéuticas sólidas pueden no recubrirse o recubrirse por técnicas conocidas para retrasar la desintegración y absorción en el tubo digestivo y proporcionar así una acción sostenida durante un período más prolongado. Por ejemplo, puede emplearse un material de retardo tal como gliceril monoestearato o gliceril diestearato. Pueden recubrirse asimismo mediante la técnica descrita en las Patentes de los Estados Unidos No. 4,256,108; 4,166,452; y 4,265,874, para formar tabletas terapéuticas osmóticas de liberación controlada. Formas farmacéuticas para administración líquida pueden contener, por ejemplo, un solución o suspensión de uno o más de los compuestos actualmente útiles y coadyuvantes farmacéuticos opcionales en un vehículo, tal como por ejemplo, agua, solución salina, dextrosa acuosa, glicerol, etanol y similares, para formar así una solución o suspensión. Si se desea, la composición farmacéutica a administrarse puede contener además cantidades menores de sustancias auxiliares no tóxicas, tales como agentes humectantes o emulsionantes, agentes amortiguadores de pH y similares. Ejemplos típicos de tales agentes auxiliares son acetato de sodio, monolaurato de sorbitán, trietanolamina, acetato de sodio, oleato de trietanolamina, etc. Se conocen métodos actuales de preparar tales formas farmacéuticas, o serán evidentes, a aquellas personas expertas en el arte; por ejemplo, véase Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 16 Edition, 1980. La composición de la formulación que se va a administrar, en cualquier

La administración parenteral se caracteriza generalmente por inyección, ya sea subcutánea, intramuscular o intravenosa. Los inyectables pueden prepararse en formas convencionales, como soluciones líquidas o suspensiones, formas sólidas apropiadas para solución o suspensión en líquido antes de la inyección, o como emulsiones. Excipientes apropiados son, por ejemplo, agua, solución salina, dextrosa, glicerol, etanol y similares. Además, si se desea, las composiciones farmacéuticas inyectables a administrarse pueden contener asimismo cantidades menores de sustancias auxiliares no tóxicas, tales como agentes humectantes o emulsionantes, agentes amortiguadores de pH y similares.

Naturalmente, la cantidad del compuesto o compuestos administrados actualmente útiles depende del efecto o efectos terapéuticos deseados, del mamífero específico que se está tratando, de la gravedad y naturaleza de la dolencia del mamífero, de la forma de administración, de la potencia y farmacodinámica del compuesto o compuestos particulares empleados, y del médico que lo/los prescriben. La posología terapéuticamente efectiva del compuesto o compuestos actualmente útiles está preferiblemente en el rango de alrededor de 0.5 o alrededor de 1 a alrededor 100 mg/kg/día.

Un líquido que es oftálmicamente aceptable se formula de tal modo que pueda administrarse tópicamente al ojo. La comodidad debe maximizarse tanto como sea posible, aunque a veces las consideraciones de formulación (por ejemplo, la estabilidad del fármaco) puedan requerir menos de una comodidad óptima. En el caso de que no pueda maximizarse la comodidad, el líquido debe formularse de tal manera que el líquido sea tolerable al paciente para uso oftálmico tópico. Además, un líquido oftálmicamente aceptable debe empacarse para uso único, o contener un preservante para evitar la contaminación durante usos múltiples.

Para aplicación oftálmica, a menudo se preparan soluciones o medicamentos usando una solución salina fisiológica como vehículo principal. Las soluciones oftálmicas deben mantenerse preferiblemente en un pH amplio con un sistema amortiguador apropiado. Las formulaciones pueden contener además preservantes, estabilizantes y tensoactivos convencionales, farmacéuticamente aceptables.

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Preservantes que pueden emplearse en las composiciones farmacéuticas de la presente invención incluyen, pero no se limitan a, cloruro de benzalconio, clorobutanol, imerosal, acetato fenilmercúrico y nitrato fenilmercúrico. Un tensoactivo útil es, por ejemplo, Tween 80. Análogamente, pueden usarse varios vehículos útiles en las preparaciones oftálmicas de la presente invención. Estos vehículos incluyen, pero no se limitan a, alcohol polivinílico, povidona, hidroxipropilmetilcelulosa, poloxámeros, carboximetilcelulosa, hidroxietilcelulosa y agua purificada. Según sea necesario o se estime conveniente, pueden agregarse ajustadores de tonicidad. Éstos incluyen, pero no se limitan a, sales, particularmente cloruro de sodio, cloruro de potasio, mannitol y glicerina, o cualquier otro ajustador de tonicidad apropiado, oftálmicamente aceptable.

Pueden utilizarse varios amortiguadores y medios para ajustar el pH, siempre que la preparación resultante sea oftálmicamente aceptable. En consecuencia, los amortiguadores incluyen amortiguadores de acetato, amortiguadores de citrato, amortiguadores de fosfato y amortiguadores de borato. Según se requiera, pueden usarse ácidos o bases para ajustar el pH de estas formulaciones.

En la misma línea, un antioxidante oftálmicamente aceptable para uso en la presente invención incluye, pero no se limita a, metabisulfito de sodio, tiosulfato de sodio, acetilcisteína, hidroxianisol butilado e hidroxitolueno butilado.

Otros componentes excipientes que pueden incluirse en las preparaciones oftálmicas son agentes quelantes. Un agente quelante útil es edetato disódico, aunque pueden usarse también otros agentes quelantes en su lugar o en combinación con él.

Los ingredientes se emplean usualmente en las siguientes cantidades:

Ingrediente	**Cantidad (% p/v)**
Ingrediente activo	alrededor de 0.001-5
preservante	0-0.10
vehículo	0-40
ajustador de tonicidad	1-10
amortiguador	0.01-10
ajustador de pH	en cantidad suficiente para (q.s.) pH 4.5-7.5
antioxidante	según se necesite

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tensoactivo	según se necesite
agua purificada	según se necesite para obtener 100%

Para uso tópico, se emplean cremas, ungüentos, geles, soluciones o suspensiones, etc., que contienen el compuesto divulgado en esta solicitud. Generalmente las formulaciones tópicas pueden estar conformadas por un vehículo farmacéutico, un co-disolvente, un emulsificante, un intensificador de penetración, sistema preservante y emoliente.

La dosis actual del compuesto activo de la presente invención depende del compuesto específico y de la afección a tratarse; la selección de la dosis apropiada se encuentra perfectamente d entro del conocimiento del artesano experto.

Ejemplo 1

Éster metílico de ácido 1-propil-ciclobutanocarboxílico (1-2). Éster 1-1 (2.043 g, 15.9 mmol) se agregó a una solución a -78 °C de LDA (8 mL, 16 mmol, 2 M en heptano/THF/etil benceno) en THF (16 mL), enjuagando con 1 mL THF. La reacción se agitó durante 30 minutos a -78 °C y luego se dejó calentar a temperatura de la sala. A continuación, mediante cánula, se agregó la solución de enolato a una solución de yoduro de n-propilo (4.087 g, 24 mmol) en 8 mL DMSO. La temperatura interna se mantuvo entre 16-20 °C enfriando con un baño helado. Luego de 1 hora, se retiró el disolvente y el residuo se diluyó con H_2O (150 mL). La mezcla resultante se extrajo con hexanos (2 x 120 mL) y la solución orgánica combinada se lavó con 2% HCl (100 mL) y salmuera (100 mL). Entonces la solución orgánica se secó (Na_2SO_4), se filtró y se evaporó. El producto crudo se combinó con el producto crudo de otro ciclo de reacción (comenzando con 14.858 g, 116 mmol de 1-1) y el producto combinado se purificó por destilación simple bajo presión reducida para proporcionar 1-2 (9.744 g, 49%).

(1-Propil-ciclobutil)-metanol (1-3). $LiBH_4$ (524 mg, 24 mmol) y metanol (1 mL) se agregaron a una solución a 0 °C de 1-2 (1.935 g, 11.4 mmol) en éter (22 mL). Luego de 1 hora a 0 °C y 1.5 horas a temperatura de la sala, se agregaron lentamente 41 mL 2 M NaOH y la mezcla resultante se agitó durante 1 hora. Seguidamente la mezcla se extrajo con diclorometano (3 x 40 mL) y la solución combinada de diclorometano se lavó con una solución de NH_4Cl saturado y

salmuera (150 mL cada uno). Entonces la solución orgánica se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (diclorometano) produjo 1-3 (1.229 g, 87%).

1-Propil-ciclobutanocarbaldehído (1-4). Una mezcla helada de N-óxido de 4-metilmorfolina (NMO) (1.683 g, 14.4 mmol), 1-3 (1.229 g, 9.59 mmol) y mallas moleculares de 4Å (5.5 g) en diclorometano (20 mL) se trató con perrutenato de tetrapropilamonio (TPAP) (179 mg, 0.51 mmol). La mezcla se agitó a 0 °C durante 5 minutos y, a continuación, se dejó calentar a temperatura de la sala. Después de 1 hora, la mezcla se filtró a través de una almohadilla de gel de sílice (diclorometano) y se evaporó el diclorometano. El producto crudo se combinó con el producto crudo de otro lote (iniciando con 4.986 g, 38.9 mmol de 1-3) y el producto combinado se purificó mediante destilación bajo presión reducida, seguido por cromatografía de destello en gel de sílice (15% éter/pentano) para producir 1-4 (2.649 g, 43%).

2-(4-Bromo-fenil)-2-metil-propan-1-ol (2-2). $LiBH_4$ (387 mg, 17.8 mmol) y metanol (0.75 mL) se agregaron a una solución a 0 °C de 2-1 (2.07 g, 8.05 mmol) en éter (75 mL). Pasados 30 minutos a 0 °C y 1.5 hora a temperatura de la sala, la reacción se extinguió mediante la lenta adición de 40 mL 2 M NaOH. Las capas se separaron y la capa acuosa se extrajo posteriormente con diclorometano (3 x 40 mL). La solución orgánica combinada se lavó con salmuera y luego se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (20% acetato de etilo/hexanos) produjo 2-2 (1.780 g, 97%).

[2-(4-Bromo-fenil)-2-metil-propoxi]-*terc*-butil-dimetil-silano (2-3). TBSOTf (2.9 mL, 12.6 mmol) se agregó a una solución a 0 °C de 2-2 (1.893 g, 8.26 mmol) y 2,6-lutidina (2.9 mL, 24.9 mmol) en diclorometano (24 mL). La reacción se dejó calentar a temperatura de la sala y después de 1 hora, se agregaron 50 mL de solución de $NaHCO_3$ saturado. La mezcla resultante se extrajo con acetato de etilo (3 x 60 mL) y la solución de acetato de etilo combinada se lavó con salmuera. Entonces la solución se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (hexanos) produjo 2-3 (2.767 g, 98%).

1-(4-Bromo-fenil)-ciclobutanol (3-1). *n*-Butil litio (1.2 mL 1.92 mmol, 1.6 M/hexanos) se agregó a una solución a -78 °C de 1,4-dibromobenceno (489 mg, 2.07 mmol) en THF (4.2 mL). Después de 30 minutos, se agregó mediante cánula una solución de ciclobutanona (141 mg, 2.01 mmol) en 1 en THF, enjuagando con 0.5 mL THF. La reacción se dejó calentar a temperatura de la sala y luego de 2

horas, se agregó una solución de NH_4Cl saturado. La mezcla resultante se extrajo con acetato de etilo (3 x 30 mL) y la solución de acetato de etilo combinada se lavó con salmuera. Entonces la solución se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (5% → 10% acetato de etilo/hexanos) produjo 3-1 (235 mg, 54%).

[1-(4-Bromo-fenil)-ciclobutoxi]-*terc*-butil-dimetil-silano (3-2). TBSOTf (360 µL, 1.57 mmol) se agregó a una solución a 0 °C de **3-1** (235 mg, 1.04 mmol) y trietilamina (450 µL, 3.23 mmol) en diclorometano (3 mL). La reacción se dejó calentar a temperatura de la sala y luego de 1 hora, se agregó una solución de $NaHCO_3$ saturado. La mezcla resultante se extrajo con acetato de etilo (3 x 30 mL) y la solución de acetato de etilo combinada se lavó con salmuera. Seguidamente la solución se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (hexanos) produjo 3-2 (329 mg, 93%).

Procedimiento representativo para la reacción de dibromobenceno con aldehídos: (4-Bromo-fenil)-ciclohexil-metanol (4-2, R = ciclohexilo, sustitución para). *n*-BuLi (14.4 mL, 23 mmol) se agregó a una solución a -78 °C de 1,4-dibromobenceno (5.442 g, 23.1 mmol) en THF (48 mL). La mezcla resultante se agitó durante 30 minutos y luego se agregó mediante cánula una solución de ciclohexanocarboxaldehído (2.9 mL, 24.1 mmol) en THF (10 mL). La solución turbia resultante se dejó calentar a temperatura de la sala y se continuó agitando durante 2 horas. A continuación se agregó una solución de NH_4Cl saturado (200 mL) y la mezcla se extrajo con acetato de etilo (3 x 100 mL). La solución de acetato de etilo combinada se lavó con salmuera (150 mL) y luego se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (10% acetato de etilo/hexanos → 15% → 20%) produjo el alcohol del título (5.095 g, 18.9 mmol, 82%).

Procedimiento representativo para la protección TBS de alcoholes de cadena inferior: [(4-Bromo-fenil)-ciclohexil-metoxi]-*terc*-butil-dimetil-silano (4-3, R = ciclohexilo, sustitución para). Una solución helada de **4-2** (5.095 g, 18.9 mmol) se trató con 2,6-lutidina (2.9 mL, 24.9 mmol) y TBSOTf (5.2 mL, 22.6 mmol). Luego de 2 horas, se agregaron 100 mL de una solución de $NaHCO_3$ saturado y la mezcla resultante se extrajo con 50 mL diclorometano. La solución de diclorometano se lavó con 1 M HCl (100 mL) y 100 mL salmuera y luego se secó

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(Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice produjo el éter TBS del título (6.772 g, 17.7 mmol, 94%).

[(4-Bromo-fenil)-(1-propil-ciclobutil)-metoxi]-*terc*-butil-dimetil-silano (4-3, R = 1-propilciclobutilo, sustitución para). Este compuesto se preparó usando la secuencia representativa (figura 4), iniciando con 1,4-dibromobenceno y aldehído **1-4**.

[(3-Bromo-fenil)-(1-propil-ciclobutil)-metoxi]-*terc*-butil-dimetil-silano (4-3, R = 1-propilciclobutilo, sustitución meta). Este compuesto se preparó usando la secuencia representativa (figura 4), iniciando con 1,3-dibromobenceno y aldehído **1-4**.

Procedimiento representativo para acoplamiento de 2 componentes: Éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[(*terc*-butil-dimetil-silaniloxi)-ciclohexil-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico (5-3). *n*-BuLi (1.1 mL, 1.76 mmol, 1.6 M/hexanos) se agregó a una solución a -78 °C de tiofeno (195 mg, 2.32 mmol) en éter (2 mL). La reacción se dejó a agitar a 0 °C durante 1 hora y luego se volvió a enfriar a -78 °C. La solución resultante del tiofeno de litio se transfirió mediante cánula a una mezcla de CuCN (226 mg) en éter (2 mL). La suspensión resultante se dejó agitar a temperatura de la sala durante 30 minutos y a -78 °C durante 30 minutos.

En otro matraz, se agregó *t*-buLi (2.3 mL, 3.91 mmol) a una solución a -78 °C de **5-1** (747 mg, 1.95 mmol) en éter (2 mL). La suspensión se agitó durante 1 hora y luego se transfirió mediante cánula a la mezcla de 2-tienilcianocuprato de litio, enjuagando con 1 mL éter. La mezcla resultante se agitó durante 15 minutos a 0 °C y luego se volvió a enfriar a -78 °C. Una solución de enona 5-2 (578 mg, 1.64 mmol, obtenida de Nissan Chemical Industries, LTD, Chemicals Division 3-7-1 Kanda-Nishiki-cho, Chiyoda-ku, Tokio 101-0054, Japón) en éter (2 mL) se agregó entonces mediante cánula, enjuagando con 1 mL éter. La reacción se agitó durante 1 hora a -78 °C, 1 hora a 0 °C y durante 15 minutos a temperatura de la sala.

Seguidamente la reacción se extinguió mediante la adición de una solución al 10% de NH_4OH concentrado en NH_4Cl saturado. La mezcla resultante se extrajo con acetato de etilo (3x) y la solución de acetato de etilo combinada se lavó con salmuera. La solución orgánica se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (4% acetato de etilo/hexanos → 5%) produjo la cetona del título (760 mg, 71%).

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Procedimiento representativo para desprotección TBS con HF-piridina: éster metílico de ácido (Z)-7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil}-hept-5-enoico (5-4). HF-piridina (1.8, mL) se agregó a una solución de CH_3CN (9 mL) helada de **5-3** (196 mg, 0.30 mmol). La reacción se agitó durante 1 hora y luego se extinguió mediante la adición de una solución de $NaHCO_3$ saturado. La mezcla resultante se extrajo con diclorometano y la solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (50% acetato de etilo/hexanos) produjo el tiol del título **5-4** (117 mg, 91%).

Procedimiento representativo para hidrólisis de éster metílicoes con esterasa de hígado de conejo: Ácido (Z)-7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil}-hept-5-enoico (5-5). Una mezcla de **5-4** (46 mg, 0.11 mmol) y esterasa de hígado de conejo (8 mg) en CH_3CN (0.45 mL)/pH 7.2 amortiguador de fosfato (9 mL) se agitó de un día para otro. La mezcla se co-evaporó con CH_3CN y el residuo se purificó por cromatografía de destello en gel de sílice (5% metanol/diclorometano) para producir el ácido del título **5-5** (36 mg, 80%). 300 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.3-7.1 (4 H, m) 5.3-5.2 (2 H, m) 5.5-4.5 (3 H, s amplio) 4.4-4.3 (2 H, m) 3.0-2.7 (2 H, m) 2.6-0.8 (21 H, m traslapante).

Procedimiento representativo para hidrogenación de la cadena superior: Éster metílico de ácido 7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil}-heptanoico (5-7). Una mezcla de éster **5-4** (67 mg, 0,16 mmol) y 5% Pd/C (49 mg) en metanol (12 mL) se agitó bajo 1 atmósfera de H_2 durante 4 horas. La mezcla se filtró a través de celita y se evaporó el disolvente. La purificación por cromatografía de destello en gel de sílice (50% acetato de etilo/hexanos) produjo el éster del título (15 mg, 22%).

Ácido 7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil}-heptanoico (5-8). Se siguió el procedimiento representativo usando esterasa de hígado de conejo.

Éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico. Se siguió una secuencia análoga a la utilizada para preparar **5-4** (figura 4, 5), a partir de **[(4-bromo-fenil)-(1-propil-ciclobutil)-metoxi]-*terc*-butil-dimetil-silano (4-3)**.

Ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico. Se siguió el procedimiento

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representativo utilizando esterasa de hígado de conejo, a partir del éster metílico correspondiente.

Éster metílico de ácido 7-((1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico. Se siguió una secuencia análoga a la utilizada para preparar 5-7 (figura 5).

Ácido 7-((1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico. Se siguió el procedimiento representativo utilizando esterasa de hígado de conejo, a partir del éster metílico correspondiente.

Éster metílico de ácido (Z)-7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-hept-5-enoico. Se siguió una secuencia análoga a la utilizada para preparar **5-4** (figura 5), a partir de 1-bromo-4-*terc*-butilbenceno en lugar de **5-1**.

Ácido (Z)-7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-hept-5-enoico. Se siguió el procedimiento representativo utilizando esterasa de hígado de conejo, a partir del éster metílico correspondiente.

Éster metílico de ácido 7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-heptanoico. Se siguió el procedimiento de hidrogenación representativo.

Ácido 7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-heptanoico. Se siguió el procedimiento representativo utilizando esterasa de hígado de conejo, a partir del éster metílico correspondiente.

Éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-hept-5-enoico. Se siguió una secuencia análoga a la utilizada para preparar **5-4** (figura 2, 5), iniciando con **2-3** en lugar de **5-1**.

Ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-hept-5-enoico. Se siguió el procedimiento representativo utilizando esterasa de hígado de conejo, a partir del éster metílico correspondiente.

Éster metílico de ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-heptanoico. Se siguió el procedimiento de hidrogenación representativo, usando acetato de etilo como disolvente y agitando de un día para otro.

Ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-heptanoico. Se utilizó el procedimiento representativo utilizando esterasa de hígado de conejo, a partir del éster metílico correspondiente.

Éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-5-ox -ciclopentil}-hept-5-enoico (e1-2). Se siguió una secuencia análoga

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a la utilizada para preparar **5-4** [a partir de **3-2** en lugar de **5-1** (figura 3, 5)] con la excepción del paso de desprotección TBS, lo cual se hizo usando el siguiente procedimiento (véase ecuación 1): Una mezcla de **e1-1** (46 mg, 0.075 mmol) en AcOH/H_2O/THF 3:1:1 (0.6 mL) se dejó agitar a temperatura de la sala. Luego de 2 días, se agregó una solución de $NaHCO_3$ saturado y la mezcla resultante se extrajo con diclorometano (3 x 25 mL). La solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (50% acetato de etilo/hexanos) produjo el diol del título **e1-2** (6 mg, 21%).

Ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-5-oxo-ciclopentil}-hept-5-enoico. Se siguió el procedimiento representativo utilizando esterasa de hígado de conejo, iniciando con **e1-2**.

Éster metílico de ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-5-oxo-ciclopentil}-heptanoico. Se siguió el procedimiento de hidrogenación representativo, usando acetato de etilo como disolvente y agitando de un dia para otro.

Ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-5-oxo-ciclopentil}-heptanoico. Se siguió el procedimiento representativo utilizando esterasa de hígado de conejo, a partir del éster metílico correspondiente.

Éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico. Se siguió una secuencia análoga a la utilizada para preparar **5-4** (figura 4,5), a partir de **[(3-bromo-fenil)-(1-propil-ciclobutil)-metoxil-*terc*-butil-dimetil-silano (4-3)**.

Ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico (e2-1). Se siguió el procedimiento representativo utilizando esterasa de hígado de conejo, a partir del éster metílico correspondiente.

Éster metílico de ácido 7-{(1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico. Se empleó el procedimiento de hidrogenación representativo.

Ácido 7-{(1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico. Se siguió el procedimiento representativo utilizando esterasa de hígado de conejo, a partir del éster metílico correspondiente.

Procedimiento representativo para la formación de amida secundaria: (2-Hidroxi-etil)-amida de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-

ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico (e2-2, R = 2-hidroxietilo, ecuación 2). DMF (0.5 mL) y N-hidroxisuccinimida (12 mg, 0.10 mmol) se agregaron a ácido **e2-1** (8 mg, 0.02 mmol). La mezcla se agitó durante 5 minutos y se agregó clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDCI) (39 mg, 0.20 mmol). Esta mezcla se agitó durante 4 horas a temperatura de la sala y se agregó 2-aminoetanol (6 µL, 0.10 mmol). Luego de agitar de un día para otro, la reacción se diluyó con acetato de etilo y la mezcla resultante se lavó con H_2O (3 x 15 mL) y salmuera. A continuación se secó la solución orgánica (Na_2SO_4), se filtró y se evaporó. La purificación del residuo por cromatografía de destello en gel de sílice (5% → 7% metanol/diclorometano) produjo la amida del título (5.4 mg, 63%).

Etilamida de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico (e2-2, R = etilo). Se siguió un procedimiento análogo al utilizado más arriba.

Etilamida de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico (e2-2, R = H). Diclorometano (0.2 mL) y trietilamina (15 µL, 0.11 mmol) se agregaron a **e2-1** (8 mg, 0.02 mmol). La reacción se agitó durante 10 minutos, se enfrió en un baño helado y se agregó cloroformiato de etilo (7 µL, 0.073 mmol). Luego de 1 hora a 0 °C, se agregó NH_4OH_{aq} concentrado (10 µL, 0.26 mmol). La reacción se agitó de un día para otro a temperatura de la sala y luego se agregó 0.5 M HCl (5 mL). La mezcla resultante se extrajo con acetato de etilo (3 x 25 mL) y la solución de acetato de etilo combinada se lavó con solución $NaHCO_3$ saturado y salmuera. Seguidamente la solución se secó (Na_2SO_4), se filtró y se evaporó. La purificación del residuo por cromatografía de destello en gel de sílice (5% metanol/diclorometano) produjo la amida del título (2.2 mg, 28%).

Procedimiento representativo para la reducción de la C9 cetona: Éster metílico de ácido (Z)-7-{(1R,2S,3R,5S)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[(*terc*-butil-dimetil-silaniloxi)-ciclohexil-metil]-fenil}-5-hidroxi-ciclopentil)-hept-5-enoico (6-1). L-selectride (300 µL, 0.3 mmol, 1 M/THF) se agregó a una solución a -78 °C de cetona **5-3** (159 mg, 0.24 mmol) en 12 mL THF. La reacción se agitó durante 30 minutos a -78 °C y luego se agregó 3% H_2O_2 (7 mL). La reacción se agitó durante 2 horas a temperatura de la sala y luego se vertió en solución de NH_4Cl saturado. La mezcla se extrajo con acetato de etilo (3 x 50 mL) y la solución de acetato de etilo combinada se lavó con salmuera y luego se secó

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(Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (8% acetato de etilo/hexanos) produjo el alcohol del título (149 mg, 93%).

Procedimiento representativo para la conversión del alcohol C9 en el cloruro C9: Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-t(*terc*-butil-dimetil-silaniloxi)-ciclohexil-metil]-fenil}-5-cloro-ciclopentil)-hept-5-enoico (6-2). MsCl (125 µL, 1.62 mmol) se agregó a una solución de **6-1** (117 mg, 0.18 mmol) y trietilamina (250 µL, 1.79 mmol) en 1,2-dicloroetano (0.5 mL). La reacción se agitó durante 3 horas y luego se extinguió mediante la adición de $NaHCO_3$ saturado. La mezcla se extrajo con diclorometano (3 x 40 mL) y la solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó para producir el mesilato crudo (196 mg).

Una mezcla del mesilato crudo y (n-Bu)$_4$NCl (214 mg, 0.077 mmol) en tolueno (1.8 mL) se agitó a 40 °C de un día para otro. La mezcla se filtró entonces a través de gel de sílice, lavando con acetato de etilo y el acetato de etilo se evaporó. El residuo se purificó por cromatografía de destello en gel de sílice para producir el cloruro del título 6-2 (24 mg, 20%) junto con un compuesto que contenía mono TBS (36 mg, 36%).

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-244-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-hept-5-enoico (6-3). HF-piridina (0.60 mL) se agregó a una solución CH_3CN a 0 °C del cloruro **6-2** (24 mg, 20%) y el derivado mono TBS (36 mg, 36%). La reacción se agitó durante 1 hora, y luego se extinguió mediante la adición de una solución de $NaHCO_3$ saturado. La mezcla se extrajo con diclorometano (3 x 30 mL) y la solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (20% acetato de etilo/hexanos) produjo el diol del título 6-3 (37 mg, 93%).

Procedimiento representativo para hidrólisis del éster metílico C1 con LiOH: ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-hept-5-enoico (6-4). LiOH acuoso (0.75 mL, 0.75 mmol, 1 M) se agregó a una solución del éster **6-3** (32 mg, 0.07 mmol) en THF (4 mL). La reacción se agitó de un día para otro y luego se agregó 1 M HCl. La mezcla resultante se extrajo con diclorometano y la solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (3% metanol/diclorometano) seguida por cromatografía

preparativa de capa fina (5% metanol/diclorometano) produjo el ácido del título (26 mg, 83%). 300 MHz ^{1}H NMR ($CDCL_3$, ppm) δ 7.3-7.2 (4 H, m) 5.41-5.35 (2 H, m) 4.42-4.36 (1 H, m) 4.34 (1 H, d, *J* = 7.3 Hz) 4.2-4.1 (1 H, m) 2.7-0.8 (23 H, m's traslapantes).

Éster isopropílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-hept-5-enoico (6-5). Se empleó un procedimiento análogo al utilizado para preparar **16-6**.

Éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-heptanoico (6-6) y éster metílico de ácido 7-[(1R,2S,3R,5R)-5-cloro-2-(4-ciclohexilmetil-fenil)-3-hidroxi-ciclopentil]-heptanoico (6-8). Se empleó el procedimiento de hidrogenación representativo, iniciando con **6-3** (52 mg, 0.12 mmol), 5% Pd/C (32 mg) en 6 mL metanol. La purificación por cromatografía de destello en gel de sílice (50% acetato de etilo/hexanos) produjo **6-6** (18 mg, 35%) y el producto desoxigenado **6-8** (27 mg, 52%).

Ácido 7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-heptanoico (6-7). Se empleó el procedimiento representativo de hidrólisis mediada por LiOH.

Ácido 7-[(1R,2S,3R,5R)-5-cloro-2-(4-ciclohexilmetil-fenil)-3-hidroxi-ciclopentil] -heptanoico (6-9). Se empleó el procedimiento representativo de hidrólisis mediada por LiOH.

Éster metílico de ácido (Z)-7-((1R,2S,3R,SR)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-hept-5-enoico. Se siguió una secuencia análoga a la utilizada para preparar **6-3** (figura 6).

Ácido (Z)-7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-hept-5-enoico. Se empleó el procedimiento representativo de hidrólisis mediada por LiOH, iniciando con el éster metílico correspondiente.

Éster metílico de ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico. Se siguió una secuencia análoga a la utilizada para preparar **6-6** (figura 6).

Ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico. Se empleó el procedimiento representativo de hidrólisis mediada por LiOH, iniciando con el éster metílico correspondiente.

Éster metílic de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-hept-5-enoico. Se siguió una secuencia análoga a la utilizada para preparar **6-3** (figura 6).

Ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-hept-5-enoico. Se empleó el procedimiento representativo de hidrólisis mediada por LiOH, iniciando con el éster metílico correspondiente.

Éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico. Se siguió una secuencia análoga a la utilizada para preparar **6-6** (figura 6).

Ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico. Se empleó el procedimiento representativo de hidrólisis mediada por LiOH, iniciando con el éster metílico correspondiente.

Éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-hept-5-enoico. Se siguió una secuencia análoga a la utilizada para preparar **6-3** (figura 6).

Ácido (Z)-7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-hept-5-enoico. Se empleó el procedimiento representativo de hidrólisis mediada por LiOH, iniciando con el éster metílico correspondiente.

Éster metílico de ácido 7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-heptanoico. Se siguió el procedimiento de hidrogenación representativo, agitando la reacción de un día para otro.

Ácido 7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-heptanoico. Se empleó el procedimiento representativo de hidrólisis mediada por LiOH, iniciando con el éster metílico correspondiente.

Éster isopropílico de ácido (Z)-7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-hept-5-enoico. Se siguió un procedimiento análogo al utilizado para preparar **16-6**.

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-hept-5-enoico. Se siguió una secuencia análoga a la utilizada para preparar **6-3** con la excepción del paso de desprotección TBS, el cual se realizó utilizando un procedimiento análogo al utilizado para preparar **e1-2**.

Ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-hept-5-enoico. Se empleó el procedimiento representativo de hidrólisis mediada por LiOH, iniciando con el éster metílico correspondiente.

Éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-heptanoico. Se siguió el procedimiento de hidrogenación representativo, usando acetato de etilo como disolvente y agitando de un día para otro.

Ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-heptanoico. Se empleó el procedimiento representativo de hidrólisis mediada por LiOH, iniciando con el éster metílico correspondiente.

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-hept-5-enoico. Se siguió una secuencia análoga a la utilizada para preparar **6-3** (figura 2,5,6), a partir de **2-3** en lugar de **5-1**.

Ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-hept-5-enoico. Se empleó el procedimiento representativo de hidrólisis mediada por LiOH, iniciando con el éster metílico correspondiente.

Éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-heptanoico. Se siguió el procedimiento de hidrogenación representativo, usando acetato de etilo como disolvente y agitando de un día para otro.

Ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-heptanoico. Se empleó el procedimiento representativo de hidrólisis mediada por LiOH, iniciando con el éster metílico correspondiente.

Éster isopropílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-heptanoico. Se siguió un procedimiento análogo al utilizado para preparar **16-6**, a partir del ácido correspondiente.

4-Bromobencil (4-metoxibencil) éter (7-2). Una solución de alcohol 4-bromobencílico (2.011g, 10.7 mmol) en THF (42 mL) se agregó a una mezcla de NaH (663 mg, 16.6 mmol, 60% en aceite) en DMF (13 mL). La mezcla se agitó durante 1.5 h y se agregó cloruro 4-metoxibencílico (MPMCl, 2 mL, 14.8 mmol). Luego de 24 horas, se agregaron 100 mL de solución de NH_4Cl saturado. La mezcla resultante se extrajo con acetato de etilo (3 x 60 mL) y la solución de acetato de etilo combinada se lavó con agua y salmuera. Seguidamente la solución se secó (Na_2SO_4), se filtró y se evaporó. La purificación del residuo por cromatografía de desteilo en gel de sílice (5% acetato de etilo/hexanos) produjo **7-2** (2.43 g, 98%).

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Éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-(*terc*-butil-dimetil-silaniloxi)-2-[4-(4-metoxi-benciloximetil)-fenil]-5-oxo-ciclopentil}-hept-5-enoico (7-3). Se siguió el procedimiento representativo de acoplamiento de 2 componentes, como se describe para **5-3**, y tuvo como resultado **7-3** (1.548 g, 73%).

Procedimiento representativo para desprotección DDQ de éteres MPM: éster metílico de ácido (Z)-7-[(1R,2S,3R)-3-(*terc*-butil-dimetil-silaniloxi)-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-hept-5-enoico (7-4): DDQ (24 mg, 0.10 mmol) se agregó a una mezcla de **7-3** (47 mg, 0.08 mmol) en diclorometano (1.6 mL)/H_2O (80 µL). Luego de 1.5 horas, se agregaron 10 mL de una solución de $NaHCO_3$ saturado. La mezcla resultante se extrajo con acetato de etilo (3 x 30 mL) y la solución de acetato de etilo combinada se lavó con salmuera. Seguidamente la solución se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (25% acetato de etilo/hexanos) produjo **7-4** (25 mg, 67%).

Éster metílico de ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-hept-5-enoico (7-5). Se utilizó el procedimiento de desprotección de HF-piridina representativo para producir **7-5** (165 mg, 65%).

Ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-hept-5-enoico (7-6). Se utilizó el procedimiento representativo de esterasa de hígado de conejo.

Éster metílico de ácido 7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-heptanoico (7-7). Una mezcla de **7-5** (17 mg, 0.05 mmol) y catalizador de Wilkinson (12 mg, 0.01 mmol) en 1 mL THF se agitó durante 5 horas bajo una 1 atmósfera H_2 (balón). La mezcla se filtró entonces a través de celita y se evaporaron los volátiles. La purificación del residuo por cromatografía de destello en gel de sílice (65% acetato de etilo/hexanos) produjo **7-7** (11 mg, 62%).

Éster metílico de ácido 7-((1R,2S,3R)-3-hidroxi-5-oxo-2-*p*-tolil-ciclopentil)-heptanoico (7-9). Se utilizó el procedimiento representativo H_2, Pd/C, reemplazando metanol con acetato de etilo como disolvente y agitando de un día para otro. Esto proporcionó **7-9** (43 mg, 79%).

Ácido 7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-heptanoico (7-8). Se utilizó el procedimiento representativo de esterasa de hígado de conejo.

Ácido 7-((1R,2S,3R)-3-hidroxi-5-ox -2-*p*-tolil-ciclopentil)-heptanoico (7-10). Se utilizó el procedimiento representativo de esterasa de hígado de conejo.

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5S)-3-(*terc*-butil-dimetil-silaniloxi)-5-hidroxi-2-[4-(4-metoxi-benciloximetil)-fenil]-ciclopentil}-hept-5-enoico (8-1). Se utilizó el procedimiento representativo L-selectride.

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-5-cloro-2-[4-(4-metoxi-benciloximetil)-fenil]-ciclopentil}-hept-5-enoico (8-2) y éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(4-metoxi-benciloximetil)-fenil]-ciclopentil}-hept-5-enoico (8-3). Se utilizó el procedimiento representativo, el cual produjo **8-2** (365 mg, 39%) y **8-3** (290 mg, 38%).

Éster metílico de ácido (Z)-7-[(1R,2S,3R,SR)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-hept-5-enoico (8-4). Se utilizó el procedimiento representativo DDQ, el cual resultó en **8-4** (184 mg, 84%).

Ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-hept-5-enoico (8-5). Se utilizó el procedimiento representativo de hidrólisis LiOH.

Éster metílico de ácido 7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-heptanoico (8-6). Se utilizó el procedimiento representativo H_2, Pd/C usando acetato de etilo como disolvente.

Ácido 7-[(1R,2S,3R,SR)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-heptanoico (8-7). Se utilizó el procedimiento representativo de hidrólisis LiOH.

Éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-5-cloro-2-(4-hidroximetil-fenil)-ciclopentil]-hept-5-enoico (9-1). Se utilizó el procedimiento representativo DDQ.

Éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-5-cloro-2-(4-formil-fenil)-ciclopentil]-hept-5-enoico (9-2). Una mezcla helada de **9-1** (43 mg, 0.089 mmol), mallas moleculares de 4Å (56 mg) y NMO (16 mg, 0.14 mmol) en diclorometano (0.5 mL) se trató con TPAP (3 mg, 0.009 mmol). La mezcla se agitó durante 5 minutos a 0 °C y luego durante 1 hora a temperatura de la sala. La mezcla se filtró entonces a través de una almohadilla de gel de sílice, lavando con acetato de etilo. Los disolventes se evaporaron y el residuo se purificó por cromatografía de destello en gel de sílice (10% acetato de etilo/hexanos) para producir **9-2** (34 mg, 79%).

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-5-cloro-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-hept-5-enoico (9-3). Cloruro de *i*-propilmagnesio (335 µL, 0.67 mmol, 2 M/THF) se agregó a una solución helada de **9-2** (161 mg 0.34 mmol) en THF (1.4 mL). La reacción se agitó durante 3 horas a 0 °C y luego se extinguió mediante la adición de 20 mL de solución de NH_4Cl saturado. La mezcla se extrajo con acetato de etilo (3 x 30 mL) y la solución de acetato de etilo combinada se lavó con salmuera. Seguidamente la solución se secó (Na_2SO_4), se filtró y se evaporó. La purificación del residuo por cromatografía de destello en gel de sílice (5% → 7% → 9% acetato de etilo/hexanos) produjo **9-3** (76 mg, 43%).

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-5-cloro-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-hept-5-enoico (9-4). Se siguió el procedimiento anterior usando *t*-BuMgCl en lugar de cloruro de *i*-propilmagnesio para producir 9-4 (60 mg, 62%).

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-hept-5-enoico (9-5). Se siguió el procedimiento representativo de desprotección de HF-piridina para producir **9-5** (45 mg, 81%).

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-hept-5-enoico (9-6). Se siguió el procedimiento representativo de desprotección de HF-piridina para producir **9-6** (84 mg, 96%).

Ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-hept-5-enoico (9-7). Se siguió el procedimiento representativo de hidrólisis mediada por LiOH.

Ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-hept-5-enoico (9-8). Se siguió el procedimiento representativo de hidrólisis mediada por LiOH.

Éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-heptanoico (9-9). Se siguió el procedimiento de hidrogenación representativo empleando acetato de etilo como el disolvente.

Éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-heptanoico (9-10). Se siguió el procedimiento de hidrogenación representativo empleando acetato de etilo como el disolvente.

Ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-heptanoico (9-11). Se empleó el procedimiento representativo de hidrólisis mediada por LiOH.

Ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-heptanoico (9-12). Se empleó el procedimiento representativo de hidrólisis mediada por LiOH.

Procedimiento representativo de acoplamiento de tres componentes: éster metílico de ácido [4-((1R,2S,3R)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[(*terc*-butil-dimetil-silaniloxi)-ciclohexil-metil]-fenil}-5-oxo-ciclopentil)-but-2-iniloxi]-acético (10-3). *t*-BuLi (3.3 mL, 5.6 mmol, 1.7 M/pentano) se agregó a una solución THF a -78 °C (4.0 mL) de **5-1** (990 mg, 2.58 mmol). Luego de 30 minutos, se agregó Me_2Zn (1.5 mL, 3.0 mmol, 2 M/tolueno) y el matraz se puso en un baño helado durante 15 minutos. La reacción se volvió a enfriar a -78 °C y se agregó una solución de enona **10-1** (387 mg, 1.83 mmol, obtenida de Evotec OAI, 151 Milton Park, Abington, Oxon, OX 144SD, UK) en THF (2.0 mL) mediante bomba de jeringa durante 1.75 horas, enjuagando con 0.5 mL THF. La reacción se dejó agitar durante 30 minutos y luego se agregó HMPA (2.8 mL, 16.1 mmol) seguido por yoduro **10-2** (2.487 g, 9.3 mmol, preparado de acuerdo con la Solicitud de Patente de los Estados Unidos Serie Número 861,957, presentada el 3 de junio de 2004). La reacción se agitó a -40 °C durante 19 horas y luego se extinguió mediante la adición de solución de NH_4Cl saturado (40 mL). Se agregó un poco de H_2O a los sólidos disueltos y la mezcla se extrajo con diclorometano (3 x 30 mL). La solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice produjo la cetona del título (563 mg, 0.86 mmol, 47%).

Éster metílico de ácido [4-((1R,2S,3R,5S)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[*terc*-butil-dimetil-silaniloxi)-ciclohexil-metil]-fenil}-5-hidroxi-ciclopentil)-but-2-iniloxi]-acético (10-4). L-selectride (0.76 mL, 0.76 mmol, 1 M/THF) se agregó a una solución THF a -78 °C (20 mL) de **10-3** (415 mg; 0.63 mmol). La reacción se agitó durante 1 hora y luego se agregó 3% H_2O_2 (14 mL). La mezcla resultante se agitó a temperatura de la sala durante 45 minutos y luego se agregó una solución de NH_4Cl saturado (60 mL). La mezcla resultante se extrajo con acetato de etilo (3 x 40 mL) y la solución de acetato de etilo combinada se lavó con salmuera. Seguidamente la solución se secó (Na_2SO_4), se filtró y se evaporó. La purificación

por cromatografía de destello en gel de sílice (25% acetato de etilo/hexanos) produjo el alcohol del título (255 mg, 0.39 mmol, 61 %).

Éster metílico de ácido [4-((1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[(*terc*-butil-dimetil-silaniloxi)-ciclohexil-metil]-fenil}-5-cloro-ciclopentil)-but-2-iniloxi]-acético (10-5). MsCl (0.13 mL, 1.7 mmol) se agregó a una solución de diclorometano (2 mL) del alcohol (255 mg, 0.39 mmol) y trietilamina (0.27 mL, 1.9 mmol). Luego de 2.5 horas, se agregaron 20 mL de una solución de $NaHCO_3$ saturado y la mezcla resultante se extrajo con diclorometano (3 x 15 mL). Entonces se secó la solución de diclorometano combinada (Na_2SO_4), se filtró y se evaporó.

Una mezcla del mesilato crudo y $(n\text{-Bu})_4NCl$ (1.032 g, 3.7 mmol) en tolueno (3.5 mL) se agitó a 40 °C durante 22 horas. La mezcla se dejó enfriar a temperatura de la sala y luego se filtró a través de gel de sílice eluyendo con acetato de etilo. El disolvente se evaporó y el residuo se llevó al siguiente paso.

Éster metílico de ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-but-2-iniloxi)-acético (10-6). HF-piridina (1.7 mL) se agregó a una solución CH_3CN (10 mL) a 0 °C del cloruro crudo de más arriba (0.39 mmol). La reacción se agitó a 0 °C durante 21 horas y luego se agregó una solución de $NaHCO_3$ saturado (255 mL). La mezcla resultante se extrajo con diclorometano (3 x 100 mL) y la solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (40% acetato de etilo/hexanos → 45% → 50%) produjo el diol del título (152 mg, 0.34 mmol, 87% de **10-4**).

Ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-but-2-iniloxi)-acético (10-7). Una mezcla del éster (11 mg, 0.024 mmol) y esterasa de hígado de conejo (5 mg) en CH_3CN (0.2 mL)/pH 7.2 amortiguador de fosfato (2 mL) se agitó durante 24 horas. A continuación la mezcla se co-evaporó con CH_3CN (2 x 50 mL) y el residuo se tomó en 10% metanol/diclorometano y se filtró a través de lana de vidrio. La purificación mediante cromatografía preparativa de capa fina (20% metanol/diclorometano) produjo el ácido del título (6 mg, 0.014 mmol, 57%).

Éster metílico de ácido ((Z)-4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil)-but-2-eniloxi)-acético (11-1). Etanol (95%, 2 mL) se agregó a $NiCl_2$ (47 mg, 0.36 mmol) y $NaBH_4$, (5 mg, 0.13 mmol). La mezcla negra resultante se agitó durante 5 minutos y luego se agregó

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etilendiamina (35 µL, 0.52 mmol). Después de 15 minutos se agregó una solución de alquino **10-6** (29 mg, 0.065 mmol) en 0.5 mL 95% etanol, enjuagando con 0.5 mL etanol. El matraz se purgó con H_2 y se dejó agitar bajo 1 atmósfera de H_2 durante 24 horas. La mezcla se filtró entonces a través de celita, se evaporó y el residuo se purificó por cromatografía de destello en gel de sílice (45 → 50% acetato de etilo/hexanos) para producir 17 mg (0.038 mmol, 58%) de **11-1**.

Ácido ((Z)-4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-but-2-eniloxi)-acético (11-2). Se siguió el procedimiento representativo de esterasa de hígado de conejo , iniciando con el éster metílico correspondiente.

Éster metílico de ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-butoxi)-acético (11-3). Una mezcla de **10-6** (11 mg, 0.024 mmol) y 5% Pd/C (6 mg, 0.003 mmol) en acetato de etilo (1 mL) se agitó bajo 1 atmósfera de H_2 (balón) durante 18 horas. La mezcla se filtró y se evaporó. El residuo se purificó por TLC preparativa en gel de sílice (45% acetato de etilo/hexanos) para producir **11-3** (8 mg, 0.018 mmol, 75%).

Ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-butoxi)-acético (11-4). Se siguió el procedimiento representativo de esterasa de hígado de conejo, iniciando con el éster metílico correspondiente.

Éster metílico de ácido (3-hidroximetil-fenoxi)-acético (12-2). Una mezcla de **12-1** (5.031 g, 40.5 mmol) y K_2CO_3 (5.750 g, 41.6 mmol) en 10 mL metanol se trató con bromoacetato de metilo (3.9 mL, 42.4 mmol). La reacción se agitó en un baño de aceite a 50 °C durante 23 horas y luego se dejó enfriar a temperatura de la sala. A continuación se agregó HCl (100 mL, 1 M) y la mezcla se extrajo con diclorometano (3 x 75 mL). La solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó y el residuo se purificó por cromatografía de destello en gel de sílice (10% → 15% → 20% → 25% acetato de etilo/hexanos) para producir **12-2** (5.795 g, 29.5 mmol, 73%).

Éster metílico de ácido (3-yodometil-fenoxi)-acético (12-3). Diclorometano (85 mL) se agregó a Ph_3P (4.942 g, 18.8 mmol), imidazol (1.311 g, 19.3 mmol) y I_2 (4.735 g, 18.7 mmol). La mezcla se agitó durante 5 minutos y a continuación se agregó mediante cánula una solución de **12-2** (2.937 g, 15.0 mmol) en 15 mL diclorometano. La reacción se agitó durante 3 horas, se agregó gel de sílice y la mezcla se evaporó. El residuo se purificó por cromatografía de destello en gel de

sílice(10% → 20% → 30% acetato de etilo/hexanos) para producir **12-3** (4.246 g, 13.9 mmol, 93%).

Éster metílico de ácido [3-((1R,2S,3R)-3-(*terc*-butil-dimetil-silaniloxi)-2-{3-[(*terc*-butil-dimetil-silaniloxi)-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentilmetil)-fenoxi]-acético (13-2). Se utilizó el método representativo de acoplamiento de tres componentes, como se describe para **10-3**, el cual proporcionó **13-2** (278 mg, 43%).

Éster metílico de ácido [3-((1R,2S,3R)-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentilmetil)-fenoxi]-acético (13-3). Se utilizó el procedimiento representativo de desprotección de HF-piridina.

Ácido [3-((1R,2S,3R)-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentilmetil)-fenoxi]-acético (13-4). Se siguió el procedimiento representativo de esterasa de hígado de conejo, iniciando con **13-3**.

Éster metílico de ácido [3-((1R,2S,3R,5S)-3-(*terc*-butil-dimetil-silaniloxi)-2-{3-[(S)-(*terc*-butil-dimetil-silaniloxi)-(1-propil-ciclobutil)-metil]-fenil}-5-hidroxi-ciclopentilmetil)-fenoxi]-acético (14-1). Se utilizó el procedimiento representativo L-selectride.

Éster metílico de ácido [3-((1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-2-{3-[(S)-(*terc*-butil-dimetil-silaniloxi)-(1-propil-ciclobutil)-metil]-fenil}-5-cloro-ciclopentilmetil)-fenoxi]-acético (14-2). Se utilizó el método representativo para la conversión del alcohol C9 en el cloruro C9, como se describe para **6-2**.

Éster metílico de ácido [3-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentilmetil)-fenoxi]-acético (14-3). Se utilizó el procedimiento representativo de desprotección de HF-piridina.

Ácido [3-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentilmetil)-fenoxi]-acético (14-4). Se siguió el procedimiento representativo de esterasa de hígado de conejo.

5-Bromo-indan-1-ol (15-2). $NaBH_4$ (350 mg, 9.25 mmol) se agregó a una solución helada de cetona **15-1** (1.632 g, 7.73 mmol) en metanol (15 mL). La reacción se dejó calentar a temperatura de la sala y después de 45 minutos, se agregaron 50 mL 1 M HCl. La mezcla resultante se extrajo con acetato de etilo (3 x 60 mL) y la solución de acetato de etilo combinada se lavó con salmuera. Seguidamente la solución se secó (Na_2SO_4), se filtró y se evaporó. El residuo se purificó por cromatografía de destello en gel de sílice (25% acetato de etilo/hexanos) para producir **15-2** (1.607 g, 98%).

5-Bromo-1-(4-metoxi-benciloxi)-indan (15-3). Se utilizó un procedimiento similar al de **7-2**.

Éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-(*terc*-butil-dimetil-silaniloxi)-2-[1-(4-metoxi-benciloxi)-indan-5-il]-5-oxo-ciclopentil}-hept-5-enoico (15-4). Una solución a -78 °C de tiofeno (240 µL, 3.0 mmol) en éter (2.5 mL) se trató con *n*-BuLi (2.1 mL, 3.36 mmol, 1.6 M/hexanos). La reacción se agitó a 0 °C durante 1 hora y luego se volvió a enfriar a -78 °C. La mezcla resultante se transfirió entonces mediante cánula a una mezcla a -78 °C de CuCN (306 mg, 3.4 mmol) en 2.5 mL éter. La reacción se agitó a temperatura de la sala durante 30 minutos y luego se volvió a enfriar a - 78 °C.

En otro matraz, una solución a -78 °C de bromuro de arilo 15-3 (833 mg, 2.5 mmol) en 5 mL de éter se trató con *t*-BuLi (3.2 mL, 5.4 mmol, 1.7 M/pentano). La mezcla resultante se agitó durante 1 hora a -78 °C y luego se agregó a la mezcla de 2-tienilCuCNLi de más arriba, enjuagando con 1 mL de éter. La reacción se agitó durante 15 minutos a 0 °C y luego se volvió a enfriar a -78 °C, momento en el cual se agregó mediante cánula una solución de la enona **5-2** (893 mg, 2.5 mmol, obtenida de Nissan Chemical Industries, LTD, Chemicals Division 3-7-1 Kanda-Nishiki-cho, Chiyoda-ku, Tokio 101-0054, Japón) en 3 mL de éter. La reacción se agitó durante 15 minutos a -78 °C y luego se dejó calentar a temperatura de la sala.

Después de 1 hora, la reacción se extinguió por la adición de 65 mL 10% de una solución de NH_4OH (concentrado)/NH_4Cl saturado. La mezcla se extrajo con acetato de etilo (3 x 50 mL) y la solución de acetato de etilo combinada se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (15% acetato de etilo/hexanos) produjo el compuesto del título (792 mg, 1.3 mmol, 52%).

Éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-[1-(4-metoxi-benciloxi)-indan-5-il]-5-oxo-ciclopentil}-hept-5-enoico (15-5). Una mezcla de **15-4** (20 mg, 0.032 mmol) en ácido acético (0.3 mL)/agua (0.1 mL)/THF (0.1 mL) se agitó a temperatura de la sala. Luego de dos días, se agregó una solución de $NaHCO_3$ saturado y la mezcla resultante se extrajo con diclorometano (3 x 20 mL). La solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó. El residuo se purificó por cromatografía de destello en gel de sílice (20% acetato de etilo/hexanos → 30% → 40%), lo cual produjo el compuesto del título (11 mg, 67%).

Éster metílico de ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-hept-5-enoico (15-6). DDQ (41 mg, 0.18 mmol) se agregó a una mezcla de **15-5** (11 mg, 0.021 mmol) en diclorometano (3.5 mL)/agua (175 µL). Luego de 55 minutos, se agregó una solución de $NaHCO_3$ saturado y la mezcla resultante se extrajo con diclorometano (3 x 50 mL). La solución de diclorometano combinada se lavó con salmuera y a continuación se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (50% → 60% acetato de etilo/hexanos) produjo **15-6** (34 mg, 60%).

Ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-hept-5-enoico (15-7). Se siguió el procedimiento representativo de esterasa de hígado de conejo.

Éster metílico de ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-5-oxo-2-(1-oxo-indan-5-il)-ciclopentil]-hept-5-enoico (15-8). DDQ (10 mg, 0.041 mmol) se agregó a una mezcla de **15-5** (11 mg, 0.021 mmol) en diclorometano (0.5 mL)/agua (25 µL). Luego de 1 hora, se agregó dicloroetano (0.5 mL) y la reacción se agitó de un día para otro. Se agregó una solución de $NaHCO_3$ saturado y la mezcla resultante se extrajo con diclorometano (3 x 20 mL). La solución de diclorometano combinada se lavó con salmuera y luego se secó (Na_2SO_4), se filtró y se evaporó. La purificación del residuo por cromatografía de destello en gel de sílice (60% acetato de etilo/hexanos) produjo **15-8** (5 mg, 59%).

Ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-5-oxo-2-(1-oxo-indan-5-il)-ciclopentil]-hept-5-enoico (15-9). Se siguió el procedimiento representativo de esterasa de hígado de conejo.

Éster metílico de ácido 7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-heptanoico (15-10) y éster metílico de ácido 7-((1R,2S,3R)-3-hidroxi-2-indan-5-il-5-oxo-ciclopentil)-heptanoico (15-12). Se siguió el procedimiento de hidrogenación representativo, usando acetato de etilo como disolvente, y se produjo **15-10** (13 mg, 0.034 mmol, 63%) y **15-12** (3.9 mg, 0.011 mmol, 20%).

Ácido 7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-heptanoico (15-11). Se siguió el procedimiento representativo de esterasa de hígado de conejo.

Ácido 7-((1R,2S,3R)-3-hidroxi-2-indan-5-il-5-oxo-ciclopentil)-heptanoico (15-13). Se siguió el procedimiento representativo de esterasa de hígado de conejo.

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5S)-3-(*terc*-butil-dimetil-silaniloxi)-5-hidroxi-2-[1-(4-metoxi-benciloxi)-indan-5-il]-ciclopentil}-hept-5-enoico (16-1). Se utilizó el procedimiento representativo L-selectride.

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-5-cloro-2-[1-(4-metoxi-benciloxi)-indan-5-il]-ciclopentil}-hept-5-enoico (16-2). Se utilizó el procedimiento representativo.

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[1-(4-metoxi-benciloxi)-indan-5-il]-ciclopentil}-hept-5-enoico (16-3). Se utilizó un procedimiento análogo al utilizado para preparar **15-5**.

Éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico (16-4). Se utilizó un procedimiento análogo al utilizado para preparar **15-6**.

Ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico (16-5). Se utilizó la hidrólisis representativa con esterasa de hígado de conejo.

Procedimiento representativo para la preparación de ésteres isopropílicos:

Éster isopropílico de ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico (16-6). Yoduro de isopropilo (32 µL, 0.32 mmol) se agregó a una solución de **16-5** (12 mg, 0.032 mmol) en acetona (0.5 mL). Después de 3 días, se agregó HCl (10 mL, 1 M) y la mezcla resultante se extrajo con diclorometano (3 x 15 mL). La solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó. El residuo se purificó por cromatografía de destello en gel de sílice (50% acetato de etilo/hexanos → 53%) para producir **16-6** (9 mg, 0.021 mmol, 67%).

Éster metílico de ácido 7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico (16-7) y éster metílico de ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-indan-5-il-ciclopentil)-heptanoico (16-9). Una mezcla de **16-4** (22 mg, 0.056 mmol) y 5% Pd/C (13 mg, 0.006 mmol) en acetato de etilo (2.5 mL) se agitó bajo 1 atmósfera de H_2 (balón). Luego de 19 horas, la mezcla se filtró a través de celita y se evaporó. La purificación por cromatografía de destello en gel de sílice (40% → 45% acetato de etilo/hexanos) produjo 12 mg (0.030 mmol, 53%) de **16-7** y 10 mg (0.025 mmol, 45%) de **16-9**.

Ácido 7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico (16-8). Se utilizó el procedimiento representativo de esterasa de hígado de conejo.

Ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-indan-5-il-ciclopentil)-heptanoico (16-10). Se utilizó el procedimiento representativo de esterasa de hígado de conejo.

Éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-(*terc*-butil-dimetil-silaniloxi)-5-fluoro-2-[1-(4-metoxi-benciloxi)-indan-5-il]-ciclopentil}-hept-5-enoico y éster metílico de ácido (17-1) y éster metílico de ácido (Z)-7-{(4R,5R)-4-(*terc*-butil-dimetil-silaniloxi)-5-[1-(4-metoxi-benciloxi)-indan-5-il]-ciclopent-1-enil}-hept-5-enoico (17-2). Una solución de 16-1 (212 mg, 0.35 mmol) en 1 mL THF se agregó a una solución a -78 °C de de trifluoruro (dietilamino)sulfúrico (DAST, 50 µL, 0.38 mmol) en 1 mL THF, enjuagando con 0.5 mL THF. La reacción se agitó a temperatura de la sala durante 1.5 horas y se evaporaron los volátiles. El residuo se purificó por cromatografía de destello en gel de sílice (5% → 8% acetato de etilo/hexanos) para producir **17-1** (54 mg, 25%) y **17-2** (54 mg, 26%).

Éster metílico de ácido 7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico (17-3). Este compuesto se preparó por una secuencia análoga al derivado 9-cloro (**16-7**, figura 16).

Ácido 7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico (17-4). Se empleó el procedimiento representativo de hidrólisis mediada por LiOH.

Éster metílico de ácido (Z)-7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico (17-5). Este compuesto se preparó por una secuencia análoga al derivado 9-cloro (**16-4**, figura 16).

Ácido (Z)-7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico (17-6). Se empleó el procedimiento representativo de hidrólisis mediada por LiOH.

EXPERIMENTAL

(R)-4-(*terc*-butil-dimetil-silaniloxi)-2-iodo-ciclopent-2-enona (18-2). Se siguió un procedimiento similar al descrito en A.G. Myers y P. S. Dragovich *J. Am. Chem. Soc.* **1993**, *115*, 7021. Una solución a 0 °C de enona **10-1** (3.163 g, 14.9 mmol, Evotec OAI, 151 Milton Park, Abingtoń, Oxon, OX 14 4SD, Reino Unido) y piridina (5 mL) en diclorometano (5 mL) se trató con una solución de I_2 (6.511 g, 25.7 mmol) en piridina (12 mL)/diclorometano (12 mL). La reacción se dejó calentar a temperatura de la sala y luego de 2 horas, se agregó 1 M HCl (60 mL). La mezcla resultante se vertió en 100 mL 1 M HCl y luego se extrajo con diclorometano (3 x

60 mL). La solución de diclorometano combinada se lavó con solución de $NaHSO_3$ saturado y con salmuera y luego se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (5% acetato de etilo/hexanos) produjo el compuesto del título (4.600 g, 91 %).

1-(4-Bromo-fenil)-hexan-1-ol (18-4). *n*-PentilMgBr (29 mL, 58 mmol, 2 M/éter) se agregó a una solución a 0 °C de 4-bromobenzaldehído (9.953 g, 54 mmol) en THF (100 mL). Luego de 1 hora, la reacción se extinguió por la adición de 200 mL de solución de cloruro de amonio saturado. La mezcla resultante se extrajo con acetato de etilo (3 x 100 mL), y la solución de acetato de etilo combinada se secó (Na_2SO_4), se filtró y se evaporó. La purificación del residuo por cromatografía de destello en gel de sílice produjo **18-4** (10.501 g, 76%).

[1-(4-Bromo-fenil)-hexiloxi]-*terc*-butil-dimetil-silano (18-5). TBSOTf (2.9 mL, 12.6 mmol) se agregó a una solución helada de **18-4** (3.017 g, 11.7 mmol) y 2,6-lutidina (1.6 mL, 13.7 mmol) en diclorometano (30 mL). La reacción se agitó durante 2 horas a temperatura de la sala y luego se agregaron 100 mL de solución de bicarbonato de sodio saturado. La mezcla resultante se extrajo con diclorometano (30 mL) y la capa de diclorometano se lavó con 1 M HCl (2 x 50 mL) y salmuera (50 mL). A continuación la solución de diclorometano se secó ($MgSO_4$), se filtró y se evaporó. La purificación del residuo por cromatografía de destello en gel de sílice (hexanos) produjo **18-5** (3.843 g. 88%).

Éster etílico de ácido 3-alil-benzoico (18-7). Una solución a -45 °C de 3-yodobenzoato de etilo (2.434 g, 8.8 mmol) en 40 mL THF se trató con *i*-PrMgCl (4.8 mL, 9.6 mmol, 2 M/éter). Luego de 1 hora, se agregó bromuro de alilo (1.6 mL, 18.9 mmol) seguido por CuCN (79 mg, 0.88 mmol). La reacción se agitó durante 1 hora y luego se extinguió mediante la adición de 50 mL de una solución de NH_4Cl saturado. Se agregó agua (30 mL) y la mezcla resultante se extrajo con acetato de etilo (3 x 50 mL). La solución de acetato de etilo combinada se secó ($MgSO_4$), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (5% acetato de etilo/hexanos → 10%) produjo el compuesto del título (1.145 g, 68%).

Éster etílico de ácido 3-{3-[(R)-3-(*terc*-butil-dimetil-silaniloxi)-5-oxo-ciclopent-1-enil]-propil}-benzoico (1-8). Una solución de **18-7** (303 mg, 1.6 mmol) en 0.5 mL THF se agregó a una solución de dímero 9-BBN (393 mg, 1.6 mmol) en 6 mL THF. Luego de 4 horas, de agregó 0.1 mL H_2O. La solución se agitó durante 20 minutos y luego se transfirió mediante cánula a una mezcla de $PdCl_2$ (dppf) (78

mg, 0.11 mmol) y **18-2** (387 mg, 2.0 mmol) en DMF (3.2 mL). Se agregó K_3PO_4 (0.7 mL, 2.1 mmol, 3 M) y la solución oscura se agitó durante 1.25 horas. Seguidamente la solución se vertió en 50 mL de salmuera y la mezcla resultante se extrajo con acetato de etilo (2 x 30 mL). La solución de acetato de etilo combinada se secó ($MgSO_4$), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice produjo 292 mg (46%) de enona **1-8**.

Ácido 1-8→→3-{3-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-benzoico (18-13). Se completó la secuencia que condujo a **18-13**, como se muestra en el Esquema 18 y como se describe en figura 5,6.

Éster metílico de ácido 5-{3-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-tiofen-2)-carboxílico. Se preparó el compuesto del título usando un procedimiento análogo al descrito para **18-12**, iniciando con éster metílico de ácido 5-bromo-tiofen-2-carboxílico, el cual se preparó de ácido 5-bromo-tiofen-2-carboxílico en la siguiente forma: Cloruro de acetilo (6.87 mL, 96.6 mmol) se agregó a una solución de ácido 5-bromo-tiofen-2-carboxílico (4.0 g, 19.3 mmol) en metanol (30 mL). La reacción se dejó agitar de un día para otro y luego se calentó a reflujo durante 1.5 horas. La reacción se dejó enfriar a temperatura de la sala y luego se evaporó. El residuo se trató con 120 mL de solución de bicarbonato de sodio saturado y la mezcla resultante se extrajo con diclorometano (3 x 100 mL). La solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó para producir 3.57 g (84%) de éster metílico de ácido 5-bromo-tiofen-2-carboxílico.

Ácido 5-{3-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-tiofen-2-carboxílico (102). El compuesto del título se preparó por hidrólisis del éster metílico usando el procedimiento descrito de esterasa de hígado de conejo.

Éster isopropílico de ácido 5-{3-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-tiofen-2-carboxílico. Se preparó el compuesto del título a partir del ácido correspondiente utilizando el procedimiento estándar descrito.

Éster metílico de ácido (E)-3-(3-hidroximetil-fenil)-acrílico (19-3). Se siguió el procedimiento descrito en Reich, S.H. *et. al. J. Med. Chem.* **2000**, *43*, 1670. $Pd(OAc)_2$ (8.2 mg, 0.037 mmol) y trietilamina (0.360 mL, 2.58 mmol) se agregaron a una solución de alcohol 3-yodobencílico **19-1** (0.27 mL, 2.13 mmol) y acrilato de metilo **19-2** (0.220 mL, 2.44 mmol) en CH_3CN (4.5 mL). El recipiente de reacción

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se selló con una tapa roscada de teflón y se calentó a 100 °C durante 5 horas. En este momento, la reacción se dejó enfriar a temperatura de la sala y el tubo se cargó con 0.22 mL más de acrilato de metilo, 11.7 mg $Pd(OAc)_2$ y 0.360 mL trietilamina. La reacción se calentó a 100 °C de un día para otro y luego se agregaron 10 mL de solución de cloruro de amonio saturado. La mezcla resultante se extrajo con diclorometano (3 x 40 mL) y la solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (30 % acetato de etilo/hexanos) produjo 395 mg (97%) de **19-3**.

Éster metílico de ácido 3-(3-hidroximetil-fenil)-propiónico (19-4). $(Ph_3P)_3RhCl$ (11.5 mg, 0.012 mmol) se agregó a una solución de **19-3** (25 mg, 0.13 mmol) en 0.400 mL etanol. La reacción se agitó en un balón con 1 atmósfera de H_2 durante 20 horas y luego se filtró a través de celita. La evaporación a sequedad y la purificación por cromatografía de destello en gel de sílice (30% acetato de etilo/hexanos) produjo **192-4** (21 mg, 82%).

Éster metílico de ácido 3-(3-yodometil-fenil)-propiónico (19-5). Una mezcla de Ph_3P (36 mg, 0.14 mmol), I_2 (41 mg, 0.16 mmol) e imidazol (10.5 mg, 0.15 mmol) en 0.40 mL 1,2-dicloroetano se agitó durante 15 minutos, y luego se agregó mediante cánula una solución de **2-4** (20.5 mg, 0.11 mmol) en 0.1 mL 1,2-dicloroetano. La mezcla resultante se agitó durante 1 hora y luego se filtró a través de óxido de aluminio básico, lavando con acetato de etilo. Se evaporó el filtrado y el residuo se purificó por cromatografía de destello en gel de sílice para producir **19-5** (26 mg, 81%).

Éster metílico de ácido 3-[3-((1R,2S,3R)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[1-(*terc*-butil-dimetil-silaniloxi)-hexil]-fenil}-5-oxo-ciclopentilmetil)-fenil]-propiónico (20-1). Una solución a -78 °C de bromuro de arilo **18-5** (759 mg, 2.0 mmol) en THF (3 mL) se trató con *terc*-butil litio (2.6 mL, 4.4 mmol, 1.7 M/pentano). Luego de 30 minutos, se agregó Me_2Zn (1.1 mL, 2.2 mmol, 2 M/tolueno) y la solución resultante se agitó durante 15 minutos a 0 °C y luego se volvió a enfriar a -78 °C. Una solución de enona **10-1** (319 mg, 1.5 mmol, Evotec OAI, 151 Milton Park, Abington, Oxon, OX 14 4SD, Reino Unido) en 1.7 mL THF mediante bomba de jeringa durante 1 hora. La mezcla resultante se agitó a - 78 °C durante 2 horas, y luego se agregó HMPA (2.2 mL, 12.6 mmol) seguido por una solución de **19-5** (2.641 g, 8.7 mmol) en THF (1.6 mL). La reacción se agitó de un día para otro a -20 °C y luego se extinguió mediante la adición de 40 mL de

solución de cloruro de amonio saturado. Se agregó un poco de agua para disolver los sólidos y la mezcla resultante se extrajo con acetato de etilo (3 x 30 mL). La solución de acetato de etilo combinada se secó ($MgSO_4$), se filtró y se evaporó: La purificación por cromatografía de destello en gel de sílice (10 % acetato de etilo/hexanos) produjo la cetona del título contaminada con aproximadamente 35% de yoduro de bencilo **19-5** (438 mg).

Éster metílico de ácido 3-[3-((1R,2S,3R,5S)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[1-(*terc*-butil-dimetil-silaniloxi)-hexil]-fenil}-5-hidroxi-ciclopentilmetil)-fenil]-propiónico (20-2). Se utilizó el procedimiento estándar con L-selectride, descrito previamente, el cual produjo 224 mg (22% de la enona **1-1**) de **20-2** puro.

Ácido 3-2 → → 3-(3-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentilmetil}-fenil)-propiónico (20-5). Se completó la secuencia como se muestra en el Esquema 3 usando los procedimientos estándar en figura 6.

Éster metílico de ácido 3-[3-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentilmetil)-fenil]-propiónico y éster metílico de ácido 3-[3-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentilmetil)-fenil]-propiónico (104). Los compuestos del título se prepararon análogamente a **20-4/20-5** iniciando con bromuro de arilo **20-6** (preparado como se describe en figura 1,4).

(2R,3S,4R)-2-Alil-4-(*terc*-butil-dimetil-silaniloxi)-3-{4-[1-(*terc*-butil-dimetil-silaniloxi)-hexil]-fenil}-ciclopentanona (21-1). El compuesto **21-1** se preparó usando un procedimiento análogo al descrito para **16-1**.

4-1→(1S,2R,3S,4R)-2-Alil-4-(*terc*-butil-dimetil-silaniloxi)-3-{4-[1-(*terc*-butil-dimetil-silaniloxi)-hexil]-fenil}-ciclopentanol (21-2) → 1-[(1S,2R,3R,5R)-2-Alil-5-(*terc*-butil-dimetil-silaniloxi)-3-cloro-ciclopentil]-4-[1-(*terc*-butil-dimetil-silaniloxi)-hexil]-benceno (21-3). Esta secuencia se realizó como se describe en figura 6.

Éster etílico de ácido 2-[3-((1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[1-(*terc*-butil-dimetil-silaniloxi)-hexil]-fenil}-5-cloro-ciclopentil)-propil]-tiazol-5-carboxílico (21-5). Una solución de **21-3** (39 mg, 0.069 mmol) en 0.2 mL THF se transfirió mediante cánula a una mezcla de dímero 9-BBN (17 mg, 0.07 mmol) en 0.2 mL THF, enjuagando con 0.2 mL THF. La reacción se puso en un baño de aceite a 50 °C durante 2.5 horas, se dejó enfriar a temperatura de la sala y se agregó H_2O (10 µL). Luego de 30 minutos, la solución se transfirió mediante cánula a una solución de 2-bromotiazol-5-carboxilato de etilo **21-4** (15 mg, 0.063

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mmol) y se agregó $PdCl_2$ (dppf) (5 mg, 0.007 mmol) en DMF (0.2 mL). Se agregó K_3PO_4 (31 µL, 0.09 mmol, 3 M) y la solución se puso en un baño de aceite a 50 °C. La reacción se agitó de un día para otro y luego se repartió en porciones entre 15 mL acetato de etilo/15 mL agua (se agregó un poco de salmuera). Posteriormente la capa acuosa se extrajo con 15 mL acetato de etilo y la solución de acetato de etilo combinada se secó ($MgSO_4$), se filtró y se evaporó. La purificación por TLC preparativa en gel de sílice (10% acetato de etilo/hexanos) produjo el compuesto del título (4 mg, 0.0057 mmol, 8%).

Éster etílico de ácido 4-5 → 2-{3-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-tiazol-5-carboxílico (21-6) → ácido 2-(3-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-propil)-tiazol-5-carboxílico (21-7). Esta secuencia se realizó como se describe en la solicitud 17693, figura 6.

Éster metílico de ácido (Z)-7-((1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[1-(*terc*-butil-dimetil-silaniloxi)-hexil]-fenil}-5-fluoro-ciclopentil)-hept-5-enoico (22-1). Una solución de 22-0 (109 mg, 0.17 mmol) en 0.5 mL diclorometano se transfirió mediante cánula a una solución a -78 °C de trifluoruro deoxofluor[bis(2-etoxietil)aminosulfúrico, 34 µL, 0.18 mmol) en 0.75 mL diclorometano, enjuagando con 0.25 mL diclorometano. La reacción se agitó durante 2 horas a -78 °C y luego se extinguió mediante la adición de 10 mL de $NaHCO_3$ saturado. La mezcla se extrajo con diclorometano (3 x 15 mL) y la solución de diclorometano combinada se secó ($MgSO_4$), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (1% acetato de etilo/hexanos → 2%) produjo 53 mg de **22-1** sin purificar.

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-fluoro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (22-2). Se siguió el procedimiento HF-piridina descrito en la solicitud 17693, el cual produjo 30 mg de **22-2** sin purificar luego de cromatografía de destello en gel de sílice (40% acetato de etilo/hexanos). La posterior purificación por TLC preparativa (35% acetato de etilo/hexanos) produjo 7 mg de **22-2** puro.

Ácido (Z)-7-{(1R,2S,3R,5R)-5-fluoro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (22- 3). Se utilizó el procedimiento LiOH descrito previamente.

Éster metílico de ácido (Z)-7-((1R,2S,3R,5S)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4[1-(*terc*-butil-dimetil-silaniloxi)-hexil]-fenil}-5-hidroxi-ciclopentil)-hept-5-

enoico (18-0) y éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[1-(*terc*-butil-dimetil-silaniloxi)-hexil]-fenil}-5-hidroxi-ciclopentil)-hept-5-enoico (23-2). $NaBH_4$ (9 mg, 0.24 mmol) se agregó a una solución de éster metílico de ácido (Z)-7-((1R,2S,3R)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[1-(*terc*-butil-dimetil-silaniloxi)-hexil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico (**23-1**) (55 mg, 0.087 mmol, preparado como se describe en figura 5) en metanol (0.5 mL). Luego de 20 minutos, se agregó 1 M HCl (10 mL) y la mezcla resultante se extrajo con diclorometano (3 x 10 mL). La solución de diclorometano combinada se secó ($MgSO_4$), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (10% acetato de etilo/hexanos → 15%) produjo 27 mg (49%) de **23-2** y 16 mg (29%) de **22-0** junto con una fracción mixta de 8 mg.

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5S)-3-(*terc*-butil-dimetil-silaniloxi)-2-{4-[1-(*terc*-butil-dimetil-silaniloxi)-hexil]-fenil}-5-cloro-ciclopentil)-hept-5-enoico (23-3). Cloruro de metanosulfonilo (15 µL, 0.19 mmol) y trietilamina (30 µL, 0.21 mmol) se agregaron a una solución de **23-2** (50 mg, 0.08 mmol) en diclorometano (0.3 mL). Luego de 1.5 horas, se agregó una solución de bicarbonato de sodio saturado (15 mL) y la mezcla resultante se extrajo con diclorometano (3 x 15 mL). La solución de diclorometano combinada se evaporó para producir el mesilato crudo.

El mesilato crudo se tomó en 0.7 mL de tolueno y se agregó $(n\text{-Bu})_4NCl$ (246 mg, 0.90 mmol). La mezcla se agitó a 80 °C durante 1 hora y luego se filtró a través de gel de sílice (20% acetato de etilo/hexanos) para producir **22-3** (40 mg, 77%).

7-3 → Éster metílico de ácido (Z)-7-{(1R,2S,3R,5S)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (23-4) → ácido (Z)-7-{(1R,2S,3R,5S)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (23-5). Esta secuencia se completó como se muestra en figura 23, siguiendo los procedimientos descritos previamente.

Ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (24-4). Se preparó el compuesto del título, como se muestra en figura 24, en una manera similar a la descrita en figura 9.

Éster isopropílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (24-5). Se preparó el compuesto del título usando el procedimiento estándar descrito previamente.

Preparación de diastereómeros individuales de 20-4. Los diastereómeros individuales se separaron por HPLC preparativa en la fase de **24-2**: aproximadamente una muestra de 5 mg/ciclo; columna semipreparativa OD Chiralcel (1 x 25 cm), flujo 2.4 mL/minuto, 10% alcohol isopropílico/hexanos; tiempos de retención = 17.6 minutos y 23.8 minutos. Los diastereómeros individuales se tomaron separadamente como se muestra en el Esquema 8 y como se describe previamente.

Compuestos 115-130. Estos compuestos se prepararon en una forma análoga a **24-4** (figura 24).

Ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-heptil)-fenil]-ciclopentil}-hept-5-enoico (131) y ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-hexil)-fenil]-ciclopentil}-hept-5-enoico (132). Los compuestos del título se prepararon como se muestra en figura 25, usando procedimientos análogos a los descritos en figura 7-9.

Éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-2-(4-hexil-fenil)-3-hidroxi-ciclopentil]-hept-5-enoico (26-1). Et_3SiH (30 µL, 0.19 mmol) seguido por TFA (90 µL, 1.17 mmol) se agregaron a una solución de **24-3** (23 mg, 0.046 mmol) en dicloroetano (0.10 mL). Luego de 15 minutos, la reacción se extinguió mediante la adición de 4 mL de solución de bicarbonato de sodio saturado. La mezcla resultante se extrajo con diclorometano (3 x 30 mL) y la solución de diclorometano combinada se secó (Na_2SO_4), se filtró y se evaporó. La purificación por cromatografía de destello en gel de sílice (10% acetato de etilo/hexanos → 15% → 20%) produjo 21 mg (110%) de **26-1**.

Ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-2-(4-hexil-fenil)-3-hidroxi-ciclopentil]-hept-5-enoico (26-2). Se preparó el compuesto del título usando el procedimiento LiOH estándar descrito previamente.

Éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-2-[4-(1-acetoxi-hexil)-fenil]-3-(*terc*-butil-dimetil-silaniloxi)-5-cloro-ciclopentil]-hept-5-enoico (27-1). *n*-PentilMgBr (130 µL, 0.26 mmol) se agregó a una solución a 0 °C de **24-1** (114 mg, 0.24 mmol) en THF (0.9 mL). Luego de 2.5 horas, se agregó 1 mL acetato de etilo y la reacción se dejó calentar a temperatura de la sala. Luego de 30 minutos a temperatura de la sala, se agregaron 10 mL de solución de cloruro de amonio saturado y la mezcla resultante se extrajo con acetato de etilo (3 x 30 mL). La solución de acetato de etilo combinada se secó (Na_2SO_4), se filtró y se evaporó.

La purificación por cromatografía de destello en gel de sílice (10% acetato de etilo/hexanos) produjo 113 mg (80%) de **27-1**.

Éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-2-[4-(1-acetoxi-hexil)-fenil]-5-cloro-3-hidroxi-ciclopentil}-hept-5-enoico (27-2). Se utilizó la desprotección de HF piridina estándar descrita previamente.

(1S,2S,3R,4R)-2-[4-(1-acetoxi-hexil)-fenil]-4-cloro-3-((Z)-6-metoxicarbonil-hex-2-enil)-ciclopentil éster de ácido 4-nitro-benzoico (27-3). Azodicarboxilato de diisopropilo (11 µL, 0.057 mmol) se agregó a una mezcla de Ph_3P (15.6 mg, 0.059 mmol), ácido 4-nitrobenzoico (8.3 mg, 0.050 mmol), y **27-2** (17 mg, 0.036 mmol) en THF (0.600 mL). La reacción se agitó de un día para otro y luego se evaporaron los volátiles *in vacuo*. La purificación del residuo por cromatografía de destello en gel de sílice (30% acetato de etilo/hexanos) produjo 10 mg (45%) de **27-3**.

Ácido (Z)-7-{(1R,2S,3S,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-hexil)-fenil]-ciclopentil}-hept-5-enoico (27-4). Se utilizó el procedimiento estándar de hidrólisis con LiOH, descrito previamente.

Ejemplo 2

Datos de Unión

Ki

Se llevaron a cabo experimentos de unión por competición en un medio que contenía solución salina de Hank, Hepes 20 mM, pH 7.3, membranas (~60 µg proteína) ó $2x10^5$ células HEK 293 que expresan establemente los receptores EP2 humanos, [^{3}H]PGE2 (10 nM) y varias concentraciones de compuestos de prueba en un volumen total de 300 µl. Las mezclas de reacción se incubaron a 23 °C durante 60 minutos, y se filtraron sobre filtros Whatman GF/B bajo vacío. Los filtros se lavaron tres veces con 5 ml de amortiguador helado que contenía 50 mM Tris/HCl (pH 7.3). La unión no específica se calculó en la presencia de PGE2 en exceso no marcada (10 µM). Los datos de unión se ajustaron al modelo de unión para una sola clase de sitios de unión, usando análisis de regresión no lineal. Los valores IC_{50} así obtenidos se convirtieron en Ki usando la ecuación de Ki = (IC_{50}/(1+[L]/K_D) donde [L] representa la concentración de PGE2 (10 nM) y K_D la constante de disociación para [^{3}H]PGE2 en receptores EP2 humanos (40 nM).

Unión de Radioligando

Células que expresan establemente los Receptores EP_1, EP_2, EP_4 y FP

Células HEK-293 que expresan establemente el receptor FP humano o felino, o los receptores EP_1, EP_2, o EP_4 se lavaron con amortiguador TME, se rasparon del fondo de los matraces, y se homogeneizaron durante 30 segundos utilizando Brinkman PT 10/35 polytron. Se agregó amortiguador TME para lograr un volumen final de 40 ml en los tubos de la centrífuga (la composición de TME es 100 mM base TRIS, 20 mM $MgCl_2$, 2M EDTA; se agrega 10N HCl para obtener un pH de 7.4).

El homogenado de células se centrifugó a 19.000 r.p.m. durante 20 minutos a 4° C usando un rotor Beckman Ti-60. El sedimento celular resultante se re-suspendió en amortiguador TME para producir una concentración final de proteína de 1 mg/ml, como se determinó mediante análisis Biorad. Análisis competición de unión de radioligando vs. [^{3}H-]17-fenilPGF$_{2\alpha}$ (5 nM) se llevaron a cabo en un volumen de 100µl durante 60 minutos. Las reacciones de unión se iniciaron agregando una fracción de membrana plasmática. La reacción se terminó por la adición de 4 ml de amortiguador TRIS-HCl helado y filtración rápida a través de un filtro de vidrio GF/B usando un cosechador de células Brandel. Los filtros se lavaron 3 veces con amortiguador helado y se secaron en un horno durante una hora.

Se utilizó [^{3}H-] PGE_2 (actividad específica 180 Ci mmol) como el radioligando para los receptores EP. Se empleó [^{3}H]1 7-fenilPGF$_{2\alpha}$ para los estudios de unión de receptor FP. Se realizaron estudios de unión usando receptores EP_1, EP_2, EP_4 y FP en duplicado en por lo menos tres experimentos separados. Se utilizó un volumen de análisis de 200µl. Las incubaciones se realizaron durante 60 minutos a 25°C y se terminaron por la adición de 4 ml de 50 mM TRIS-HCl helado, seguido por la rápida filtración a través de filtros Whatman GF/B y tres lavados adicionales de 4 ml en un cosechador de células (Brandel). Se realizaron estudios de competición usando una concentración final de 5 nM [^{3}H]-PGE_2, o 5 nM [^{3}H] 17-fenil PGF$_{2\alpha}$ y la unión no específica se determinó con 10^{-5}M de PGE_2 no marcada, o 17-fenil PGF$_{2\alpha}$, de acuerdo con el subtipo de receptor estudiado.

MÉTODOS DE ESTUDIOS FLIPR™

(a) CULTIVO CELULAR

Células HEK-293 (EBNA), que expresan establemente un tipo o subtipo de receptores de prostaglandina humana recombinante (receptores de prostaglandina expresados: hDP/Gqs5; hEP_1; hEP_2/Gqs_5; hEP_{3A}/Gqi5; hEP_4/Gqs5; hFP; hIP; hTP), se cultivaron en placas de cultivo de 100 mm en medio DMEM con alto contenido de glucosa que incluía suero fetal bovino al 10%, 2 mM 1-glutamina, 250 µg/ml geneticina (G418) y 200 µg/ml higromicina B como marcadores de selección, y 100 unidades/ml penicilina G, 100 µg/ml estreptomicina y 0.25 µg/ml anfotericina B.

(b) ESTUDIOS DE SEÑALES DE CALCIO EN EL FLIPR™

Las células se sembraron con una densidad de $5x10^4$ células por pocillo en placas de 96 pocillos, de fondo transparente, de paredes negras, recubiertas con Biocoat® Poli-D-lisina (Becton-Dickinson) y se dejaron unir de un día para otro en un incubador a 37 °C. A continuación las células se lavaron dos veces con amortiguador HBSS-HEPES (Solución Salina Balanceada de Hank sin bicarbonato y fenol rojo, 20 mM HEPES, pH 7.4) usando un lavador de placas Denley Cellwash (Labsystems). Luego de 45 minutos de carga de colorante en la oscuridad, usando el colorante sensible a calcio Fluo-4 AM con una concentración final de 2 µM, las placas se lavaron cuatro veces con amortiguador HBSS-HEPES para retirar el colorante en exceso dejando 100 µl en cada pocillo. Las placas se volvieron a equilibrar a 37 °C durante unos cuantos minutos.

Las células de excitaron con láser de argón a 488 nm, y se midió la emisión a través de un filtro de emisión de 510-570 nm de ancho de banda (FLIPR™, Molecular Devices, Sunnyvale, CA). Se agregó una solución del medicamento en un volumen de 50 µl a cada pocillo para producir la concentración final deseada. Se registró el aumento del pico en la intensidad de fluorescencia para cada pocillo. En cada placa, cada cuatro pocillos sirvieron como controles negativos (amortiguador HBSS-HEPES) y positivos (agonistas estándar: BW245C (hDP); PGE_2 (hEP_1; hEP_2/Gqs5; hEP_{3A}/Gqi5; hEP_4/Gqs5); $PGF_{2\alpha}$ (hFP); carbaciclina (hIP); U-46619 (hTP), dependiendo del receptor). La variación del pico de fluorescencia en cada pocillo que contenía medicamento se expresó entonces en relación con los controles.

Los compuestos se probaron en un formato de alto rendimiento (HTS) o de respuesta a la concentración (CoRe). En el formato HTS, se examinaron cuarenta

y cuatro compuestos por placa en duplicados, con una concentración de 10^{-5} M. Para generar curvas de respuesta a la concentración, se analizaron cuatro compuestos por placa en duplicados en un rango de concentración entre 10^{-5} y 10^{-11} M. Los valores de los duplicados se promediaron. En cualquiera de los dos formatos, HTS o CoRe cada compuesto se probó en por lo menos 3 placas separadas usando células de diferentes pasadas para producir una $n \geq 3$.

Los resultados de los estudios de unión y actividad, presentados en la siguiente Tabla 1, demuestran que los compuestos divulgados en esta solicitud son agonistas selectivos de prostaglandina EP_2 y, en consecuencia, son útiles para el tratamiento de glaucoma, hipertensión ocular y las demás enfermedades o afecciones divulgadas en esta solicitud.

Tabla 1

NÚMERO	ESTRUCTURA	IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
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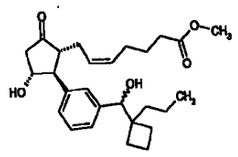
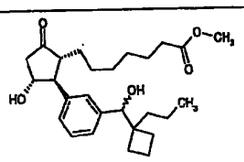
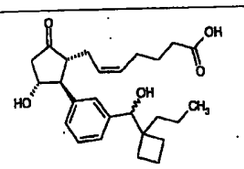
					NA	NA	>10K	>10K	>10K	NA	NA	NA
					NA	NA	>10K	>10K	>10K	NA	>10K	>10K
					NA	NA	5294	1698	NA	NA	NA	NA

Tabla 1

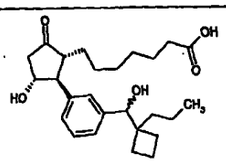
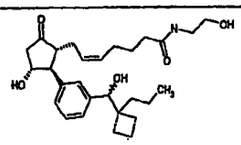
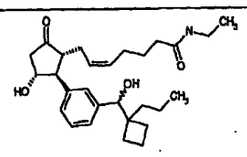
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
					NA	NA	5259		NA	NA	NA	NA
e2-2					NA	NA	NA	NA	NA	NA	NA	NA
e2-2					NA	NA	>10K	NA	>10K	NA	NA	NA

Tabla 1

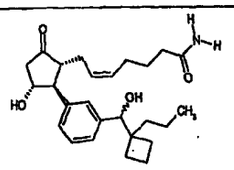
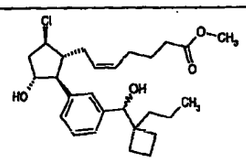
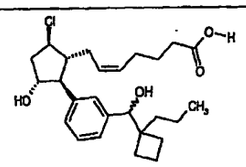
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
e2-2					NA	NA	NA	NA	NA	NA	NA	NA
					NA	NA	>10K	>10K	NA	>10K	NA	NA
					NA	NA	322	455	NA	>10K	NA	>10K

Tabla 1

		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
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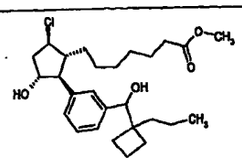
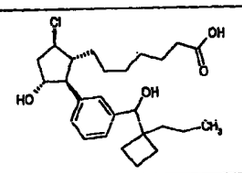
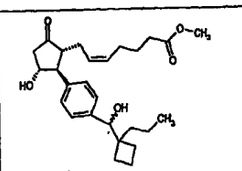
					NA	NA	NA	NA	NA	NA	NA	NA
					NA	NA	1479	3118	NA	NA	NA	NA
					NA	NA	NA	NA	NA	>10K	NA	NA

Tabla 1

		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
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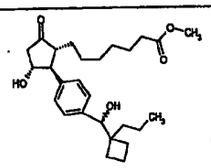
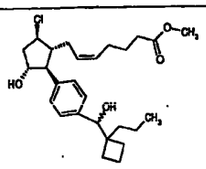
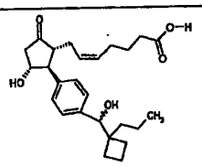
					NA	NA	>10K	NA	NA	NA	NA	NA
					NA	NA	>10K	NA	NA	NA	NA	NA
					NA	NA	3723	NA	NA	NA	NA	NA

Tabla 1

		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
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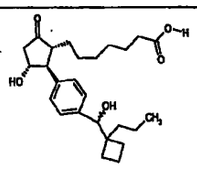
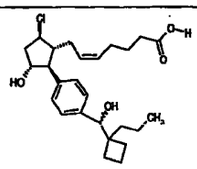
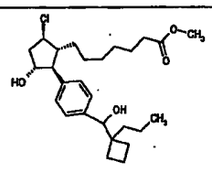
					NA	NA	635	NA	NA	NA	NA	NA
					NA	NA	2270	NA	NA	NA	NA	NA
					NA	NA	NA	NA	NA	NA	NA	NA

Tabla 1

		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
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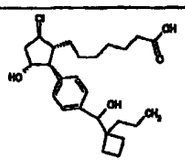
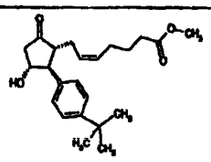
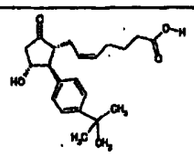
					NA	NA	546	NA	NA	NA	NA	NA
					NA	NA	>10K	NA	NA	>10K	NA	NA
					NA	>10K	1709	NA	NA	NA	NA	NA

Tabla 1

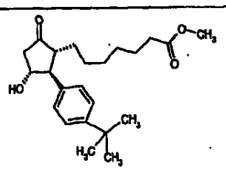
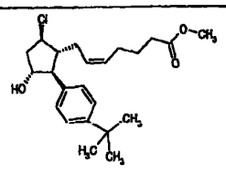
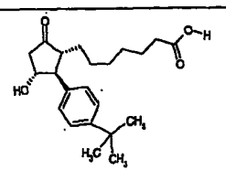
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
					NA	NA	936	>10K	>10K	>10K	NA	NA
					NA	NA	>10K	>10K	NA	NA	NA	NA
					NA	>10K	102	3390	NA	4273	>10K	NA

Tabla 1

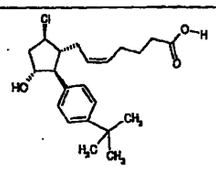
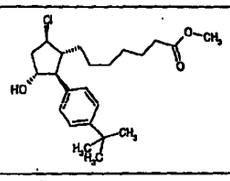
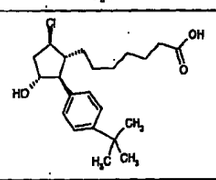
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
					NA	>10K	118	2053	>10K	1269	NA	>10K
					NA	NA	>10K	NA	NA	NA	NA	NA
					NA	>10K	264	>10K	NA	>10K	NA	>10K

Tabla 1

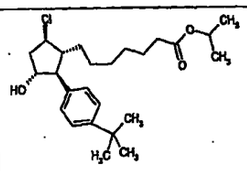
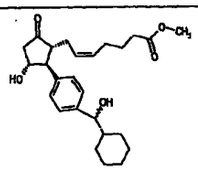
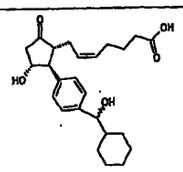
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
					NA	NA	NA	NA		NA	NA	NA
5-4					NA	NA	>10K	NA	>10K	NA	NA	NA
5-5					NA	NA	>10K	NA	NA	NA	NA	NA

Tabla 1

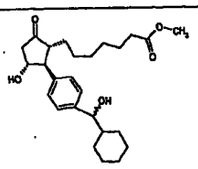
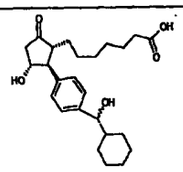
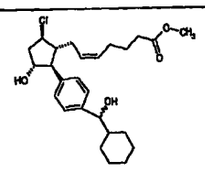
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
5-7					NA	NA	>10K	NA	NA	NA	NA	NA
5-8					NA	NA	450	NA	NA	NA	NA	NA
6-3					NA	NA	>10K	NA	NA	NA	NA	NA

Tabla 1

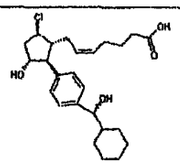
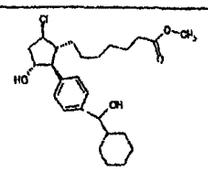
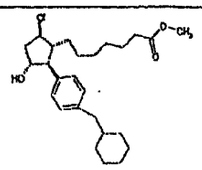
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
6-4					NA	NA	392	NA	NA	NA	NA	NA
6-6					NA	NA	NA	NA	NA	NA	NA	NA
6-8					NA	NA	NA	NA	NA	NA	NA	NA

Tabla 1

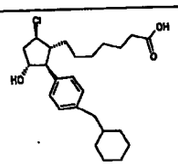
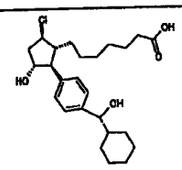
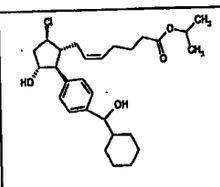
NÚMERO	ESTRUCTURA	IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
6-9					NA	NA	3445	NA	NA	NA	NA	>10K
6-7					NA	NA	2813	NA	NA	NA	NA	NA
6-5					NA	NA	NA	NA	NA	NA	NA	NA

Tabla 1

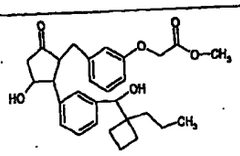
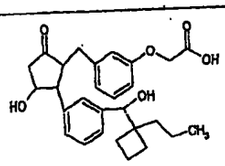
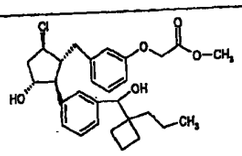
NÚMERO	ESTRUCTURA	IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
13-3					NA	NA	NA	NA	NA	NA	NA	NA
13-4					NA	NA	NA	NA	NA	NA	NA	>10K
14-3					NA	NA	NA	NA	NA	NA	NA	NA

Tabla 1

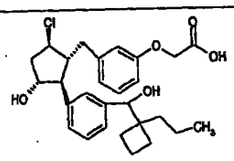
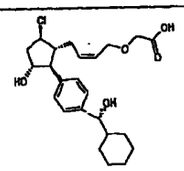
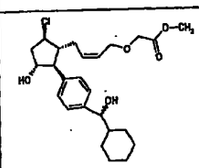
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
14-4		5200	NA	NA	NA	NA	266	NA	NA	NA	NA	
11-2					NA	NA	3844	NA	NA	NA	NA	NA
11-1					NA	NA	NA	NA	NA	NA	NA	NA

Tabla 1

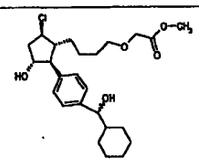
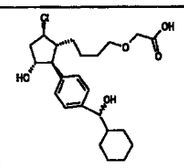
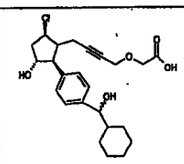
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
11-3					NA	NA	NA	NA	NA	NA	NA	NA
11-4					NA	NA	20773	NA	NA	NA	NA	NA
10-7					NA	NA	1550	NA	NA	NA	NA	NA

Tabla 1

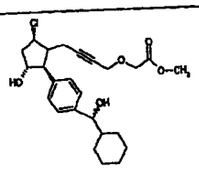
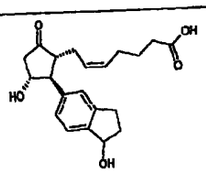
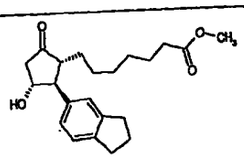
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
10-6					NA	NA	NA	NA	NA	NA	NA	NA
15-7					NA	NA		NA	NA	NA	NA	NA
15-12					NA	NA	>10K	>10K	>10K	>10K	NA	NA

Tabla 1

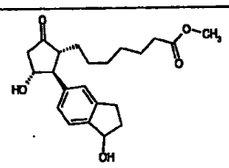
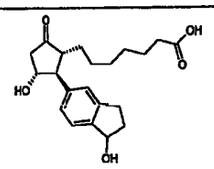
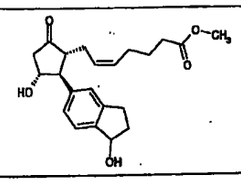
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HiP	HDP
15-10					NA	NA	NA	NA	NA	NA	NA	NA
15-11					NA	NA		NA	NA	>10K	NA	NA
15-6					NA	NA	NA	NA	NA	NA	NA	NA

Tabla 1

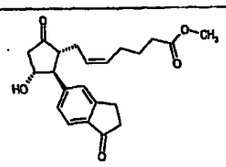
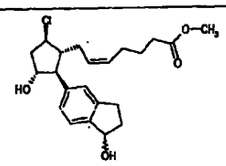
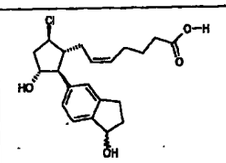
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
15-8					NA	NA	NA	NA	NA	NA	NA	NA
16-4							NA		NA			
16-5		2281			NA	NA	405	NA	NA	NA	NA	NA

Tabla 1

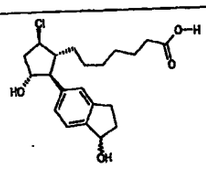
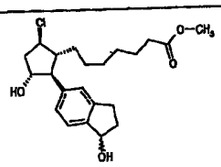
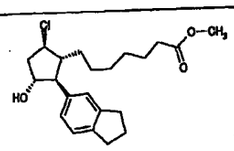
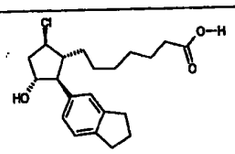
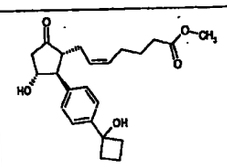
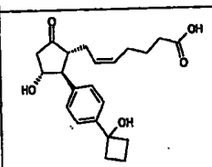
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
16-8		13139			NA	NA	529	NA	NA	2993	NA	NA
16-7					NA	NA	NA	NA	22457	17525	NA	NA
16-9				13100	NA	NA	NA	NA	NA	506	NA	NA

Tabla 1

		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
16-10		6251			NA	221	818	NA	NA	200	NA	
e1-2					NA	NA	NA	NA	NA	NA	NA	NA
					NA	NA	>10K	NA	NA	NA	NA	NA

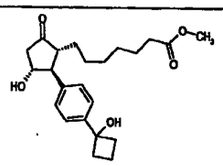
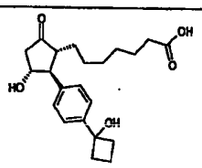
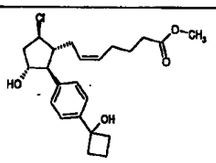
ESTRUCTURA	IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
				NA	NA	NA	NA	NA	NA	NA	NA
				NA	NA	>10K	NA	NA	NA	>10K	NA
				NA	NA	>10K	NA	NA	NA	NA	NA

Tabla 1

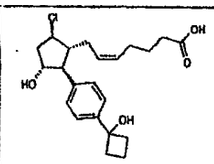
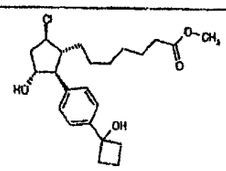
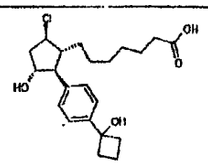
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
					NA	NA	513	NA	NA	>10K	NA	NA
					NA	NA	>10K	NA	NA	>10K	NA	NA
					NA	NA	743	NA	NA	>10K	NA	NA

Tabla 1

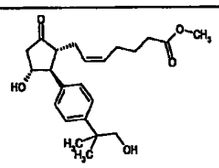
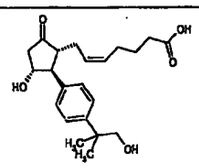
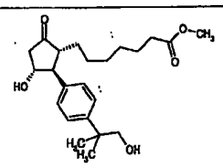
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
							NA		>10K			
					NA	NA	>10K	NA		NA	NA	NA
					NA	NA	>10K	NA	26289	NA	NA	NA

Tabla 1

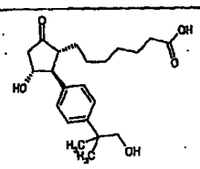
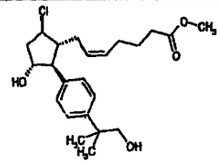
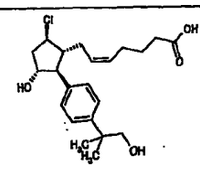
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
		18735			NA	NA	526	NA		NA	NA	NA
		48765					>10K		>10K			
		4185			NA	NA	173	NA		NA	NA	NA

Tabla 1

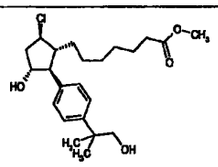
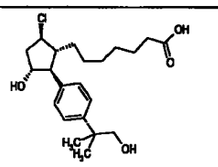
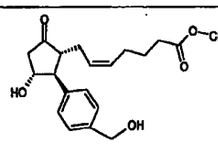
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
							>10K		>10K			
		8950			NA	NA	708	NA	>10K	NA	NA	NA
7-5							NA		NA			

Tabla 1

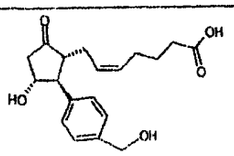
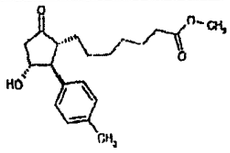
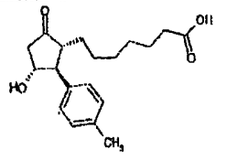
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
7-6							NA		NA			
7-9					NA	NA	>10K	NA	NA	NA	NA	NA
7-10					NA	1873	3120	NA	NA	94	NA	NA

Tabla 1

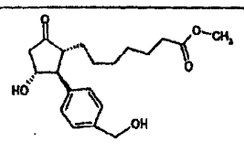
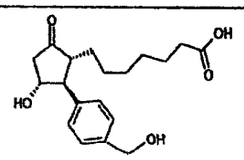
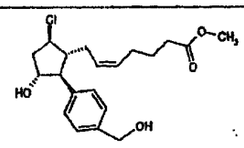
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
7-7							NA		NA			
7-8							NA		NA			
8-4							>10K		NA			

Tabla 1

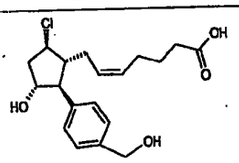
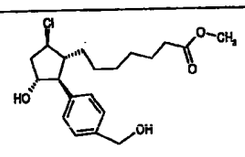
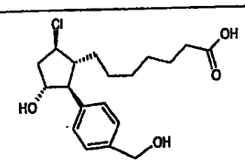
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
8-5		13150			NA	NA		NA	NA	NA	NA	NA
8-6							NA		>10K			
8-7							>10K		NA			

Tabla 1

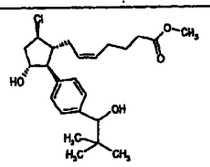
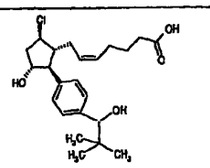
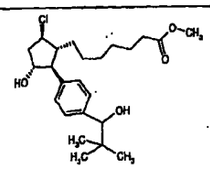
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
9-6					NA	NA	4995	NA	>10K	NA	NA	NA
9-8		1537			NA	NA	779	NA	>10K	NA	NA	NA
					NA	NA	6575	NA	>10K	NA	NA	NA

Tabla 1

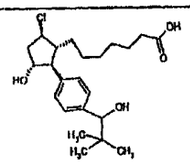
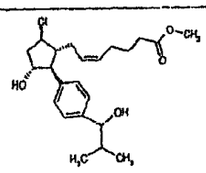
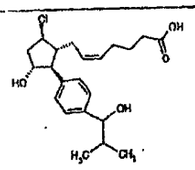
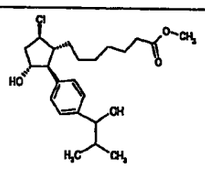
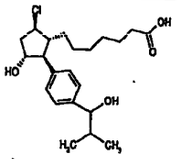
		IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
NÚMERO	ESTRUCTURA	HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
		3630			NA	NA	1265	NA	>10K	NA	NA	NA
9-5							>10K		>10K			
9-7			KI 1340		NA	NA	497	NA	NA	NA	NA	NA

Tabla 1

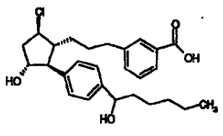
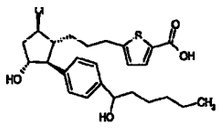
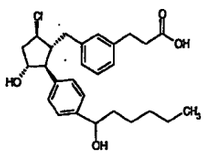
NÚMERO	ESTRUCTURA	IC_{50} DE UNIÓN (nm)			EC_{50} FUNCIONAL (nm)							
		HEP2	HEP3	HEP4	HFP	HEP1	HEP2	HEP3A	HEP4	HTP	HIP	HDP
							>10K		>10K			
			Ki 3022				>10K		NA			

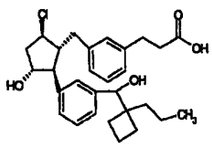
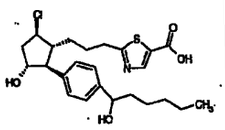
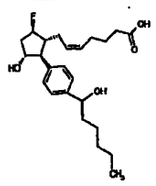
"NA significa No Activo"

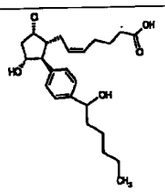
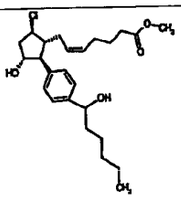
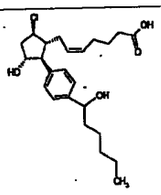
Análisis cAMP

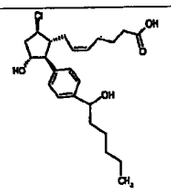
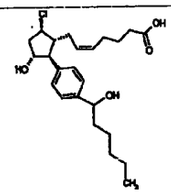
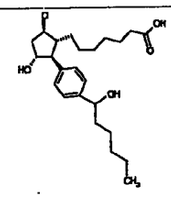
Se preparó una placa de medicamento de 384 pocillos para que contuviera 6 compuestos de prueba, PGE2 y cAMP en 16 diluciones seriales en triplicado, usando una estación Biomek. Células HEK-EBNA que expresan un subtipo de receptor PG diana (EP2 ó EP4) se suspendieron en un amortiguador de estimulación (HBSS, 0.1 % BSA, 0.5 mM IBMX y 5 mM HEPES, pH 7.4) con una densidad de 10^4 células/5µl. La reacción se inició mezclando diluciones de medicamento de 5 µL con 5 µl de células HEK-EBNA en un pocillo, se llevó a cabo durante 30 minutos a temperatura de la sala y se continuó por la adición de 5 µl de microcápsulas aceptoras anti-cAMP en el amortiguador de control con Tween-20 (25 mM NaCl, 0.03 % Tween-20, 5 mM HEPES, pH7.4). Luego de 30 minutos en la oscuridad a temperatura de la sala, las mezclas se incubaron con 15 µl de microcápsulas donadoras cAMP biotiniladas/estrepavidina en amortiguador de lisis/detección (0.1 % BSA, 0.3 % Tween-20 y 5 mM HEPES, pH 7.4) durante 45 minutos a la temperatura de la sala. Los cambios de fluorescencia se leyeron usando un lector de microplacas Fusion-alpha HT.

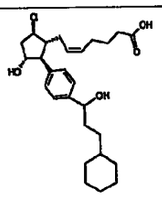
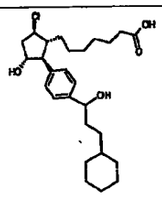
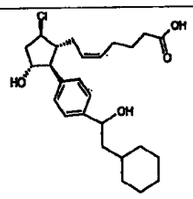
Tabla 2 proporciona datos de compuestos adicionales, los cuales se ensayaron con el análisis de cAMP, así como los descritos anteriormente.

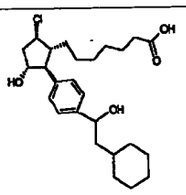
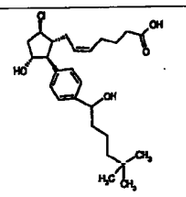
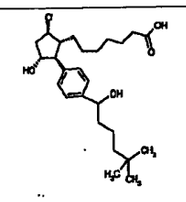
COMPUESTO	ESTRUCTURA[a]	Ki DE UNIÓN (nM)		Ca^{2+} EC_{50} de Señal (nM)[b]							
		EP2	EP4	FP	EP1	EP2	EP3	EP4	TP	IP	DP
18-13				no activo	917	2446	4152	no activo	no activo	no activo	no activo
102		24	3018	no activo	664	4 (2)	348	no activo	no activo	no activo	no activo
20-5		2779	3950	no activo	no activo	158 (56)	4674		no activo	no activo	no activo

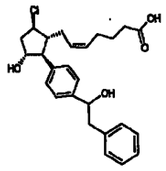
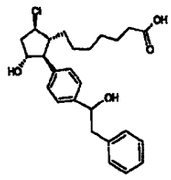
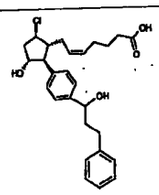
104		>10K	>10K	no activo	no activo	4111 (69)	no activo	>10K	no activo	no activo	no activo
21-7		6175		no activo	no activo	619 (1065)	no activo	>10K	no activo	no activo	no activo
22-3		804	>10K	no activo	no activo	53 (8)	1451	no activo	no activo	10061	no activo

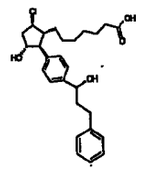
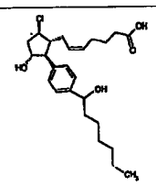
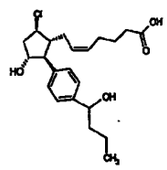
23-5		3951	4586	no activo	no activo	242 (324)	7235	947	no activo	6882	no activo
110				no activo	no activo	3956	no activo	no activo	no activo	no activo	no activo
24-4		209	>10K	no activo	no activo	7 (3)	456	>10K	no activo	no activo	no activo

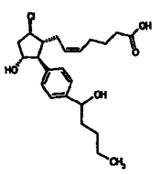
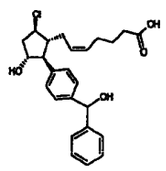
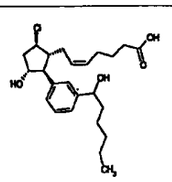
24-4[c]		209	>10K	no activo	no activo	36 (38)	no activo	>10K	no activo	6882	no activo
24-4[d]		73	>10K	no activo	no activo	11 (3)	2999	>10K	no activo	no activo	no activo
114		287	8612	no activo	no activo	28 (76)	477	>10K	no activo	no activo	no activo

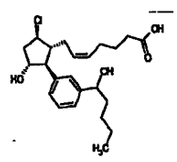
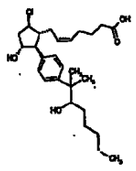
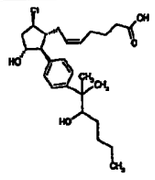
115		260	3812	no activo	no activo	495 (176)	2224	no activo	no activo	no activo	no activo
116		1289	5581	no activo	no activo	2334 (5259)	1708	no activo	no activo	no activo	no activo
117		483	15922	no activo	no activo	953 (495)	no activo	no activo	no activo	no activo	no activo

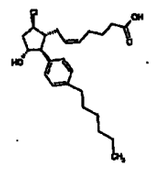
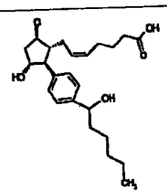
118		2287	3812	no activo	no activo	2254 (2660)	no activo	>10K	no activo	no activo	no activo
119		1053	5581			>10K (815)		>10K			
120		3849	3805	no activo	no activo	5394 (>10K))	4449	10725	no activo	no activo	no activo

121		77	>10K	no activo	no activo	9 (14)	no activo	>10K	no activo	no activo	no activo
122		148	>10K	no activo	no activo	51 (59)	no activo	15806	no activo	no activo	no activo
123		1128	>10K	no activo	no activo	548 (125)	13712	>10K	no activo	no activo	no activo

124		2162	>10K	no activo	4523	735 (628)	8826	>10K	no activo	no activo	no activo
125		278	2263	no activo	no activo	58 (12)	5932	no activo	no activo	no activo	no activo
126		1657	>10K	no activo	no activo	154 (7)	no activo	no activo	no activo	no activo	no activo

127		589		no activo	no activo	10	no activo	no activo	no activo	no activo	no activo
128		564	no activo	no activo	no activo	142 (9)	no activo	no activo	no activo	1647	
129		1388	>10K	no activo	no activo	119 (38)	37	no activo	no activo	8489	no activo

130		1255	>10K	no activo	no activo	68 (10)	23	no activo	3747	2059	no activo
131		182	5406	no activo	no activo	544 (19)	1301	no activo	no activo	no activo	no activo
132		225	9636	no activo	no activo	164 (9)	2811	no activo	no activo	no activo	no activo

26-2		83	>10K	no activo	no activo	26 (27)	no activo	>10K	no activo	no activo	no activo
27-4		12		no activo	no activo	16 (5)	25	no activo	6931	3283	no activo

a) Todos los compuestos son mezclas de diastereómeros excepto donde se indica
b) Datos en paréntesis se refieren a la medición de cAMP (véase la Sección Experimental para más detalles)
c) Diastereómero de elución más rápida (HPLC); estereoquímica no determinada
d) Diastereómero de elución más lenta (HPLC); estereoquímica no determinada

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Experimentos In Vivo

Presión Intraocular (IOP)

Estudios de presión intraocular en perros incluyeron neumatonometría realizada en perros de raza Beagle, conscientes, de ambos sexos (10-15 kg). Los animales permanecieron conscientes de principio a fin del estudio y se reprimieron delicadamente con la mano. Los medicamentos se administraron tópicamente en un ojo en forma de gotas con un volumen de 25 µL, el otro ojo recibió 25 µL de vehículo (0.1 % polisorbato 80:10 mM TRIS) como control. Para anestesia corneal durante la tonometría se utilizó proparacaína (0.1%). Se determinó la presión intraocular justo antes de la administración del medicamento y a las 2, 4 y 6 horas después cada día del estudio de 5 días. El medicamento se administró inmediatamente después de la primera lectura de IOP.

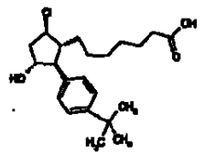
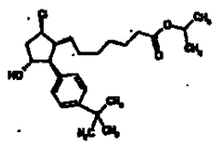
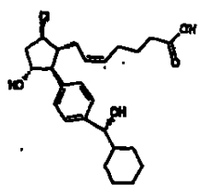
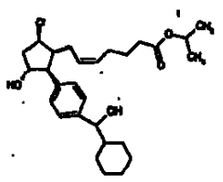
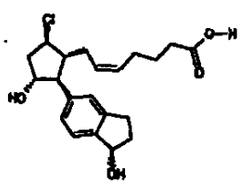
Hiperemia de la Superficie Ocular

La hiperemia de la superficie ocular se evaluó visualmente y se calificó de acuerdo con un sistema empleado típicamente en tratamiento clínico.

Calificación de Hiperemia	Valor Asignado
<1 traza	0.5
1 leve	1
moderada	2
grave	3

La hiperemia de superficie ocular se evaluó en los mismos puntos de tiempo que la medición de la presión intraocular. Debe anotarse que los ojos de los perros no tratados tienen frecuentemente un color rosado/rojo. En consecuencia, los valores de traza, o incluso leves, no están necesariamente fuera del rango normal. Pruebas similares se utilizaron para determinar la hiperemia de la superficie ocular en monos y conejos.

Las siguientes Tablas 3 y 4 presentan los resultados de los experimentos *in vivo*.

NÚMERO	ESTRUCTURA		PERRO		MONO	CONEJO
		Conc. (g/100 mL)	ΔIOP máx. (mm Hg)	Hiperemia máx.	ΔIOP máx. (mm Hg)	Hiperemia máx.
		0.10%	-4	0.9		0
		0.01%			8	0.1
6-4		0.10%	-4	1		0
6-5		0.01%	-4	0.6		
16-5		0.30%	-7	1		

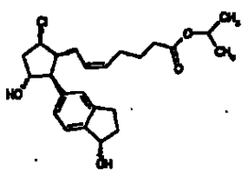
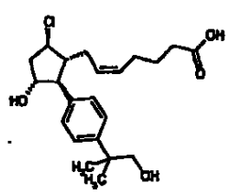
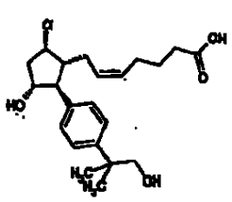
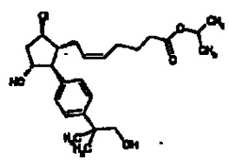
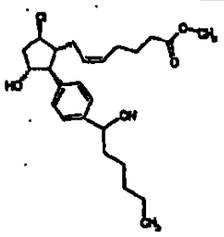
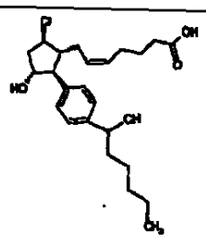
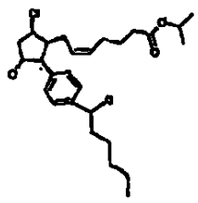
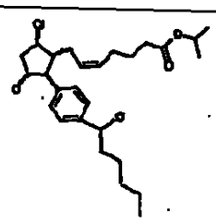
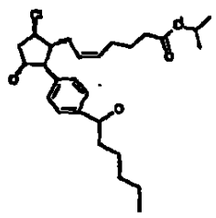
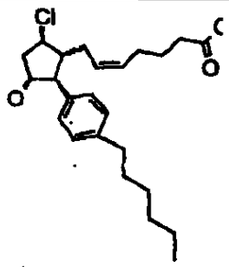
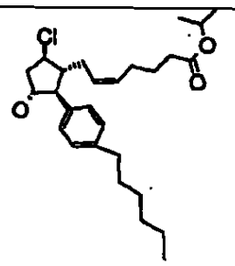
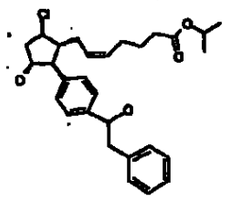
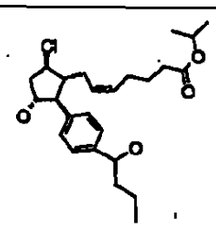
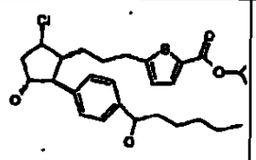
NÚMERO	ESTRUCTURA		PERRO		MONO	CONEJO
		Conc. (g/100 mL)	ΔIOP máx. (mm Hg)	Hiperemia máx.	ΔIOP máx. (mm Hg)	Hiperemia máx.
16-6		0.10%	-12			0.25
		0.30%	-8	0.9		
						
		0.10%	-5	0.7	6	0.1

Tabla 4

ENTRADA	ESTRUCTURA		PERRO		MONO	CONEJO
		Conc. (g/100 mL)	ΔIOP máx. (%)	Hiperemia máx.	ΔIOP máx. (%)	Hiperemia máx.
24-3[a]		0.1%	-50	1.5		
24-4[a]		0.03%	-21	1	21	0
24-5[a]		0.03%	-33	1	16	0.2
24-5[b]		0.1%	-13	0.5	24	
24-5[c]		0.1%	-47	1.5	26	1.5

ENTRADA	ESTRUCTURA		PERRO		MONO	CONEJO
		Conc. (g/100 mL)	ΔIOP máx. (%)	Hiperemia máx.	ΔIOP máx. (%)	Hiperemia máx.
26-2		0.1%	-43	0.6	32	0.25
207		0.1	20	0.5	21	
208		0.1%	-40	0.8	39	0
209		0.1%	-36	0.5	35	
210		0.1	-50	1.8		1

(a) mezcla de diastereómeros

(b) diastereómero de elución más rápida (HPLC)

(c) diastereómero de elución más lenta (HPLC)

La anterior descripción detalla métodos específicos y composiciones que pueden emplearse para poner en práctica la presente invención, y representa el mejor modo contemplado. Sin embargo, es evidente para una persona de

habilidad ordinaria en el arte que, de manera análoga, pueden prepararse otros compuestos con las propiedades farmacológicas deseadas, y que los compuestos divulgados pueden obtenerse igualmente, a partir de compuestos iniciales diferentes mediante reacciones químicas distintas. Análogamente, pueden prepararse y usarse diferentes composiciones farmacéuticas con sustancialmente el mismo resultado. En consecuencia, por detallada que la anterior descripción pueda aparecer en el texto, no debe interpretarse como limitante del alcance general de la misma; más bien, el ámbito de la presente invención tiene que regirse únicamente por la interpretación legal de las reivindicaciones anexas.

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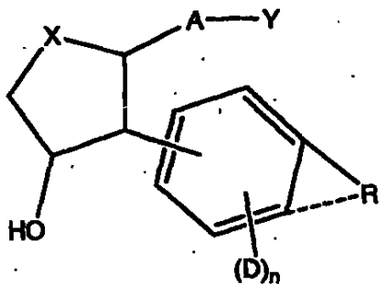
REIVINDICACIONES

Lo que se reivindica es:

1. Un compuesto que comprende



o su sal farmacéuticamente aceptable o profármaco,

en donde una línea discontinua representa la presencia o ausencia de un enlace covalente;

Y es un ácido carboxílico, ácido sulfónico, o ácido fosfónico; o una amida o éster de los mismos, que comprende de 0 a 12 átomos de carbono; o Y es un grupo funcional hidroximetilo, o tetrazolilo;

A es $-(CH_2)_6$, *cis*-$CH_2CH{=}CH-(CH_2)_3-$, o $-CH_2C{\equiv}C-(CH_2)_3-$, en donde 1 ó 2 átomos de carbono pueden sustituirse con S u O; o A es $-(CH_2)_m-Ar-(CH_2)_o-$ en donde Ar es fenilo sustituido o no sustituido o heteroarilo monocíclico, la sumatoria de **m** y **o** va de 1 a 4, y en donde un CH_2 puede sustituirse con S u O;

X es C=O, CHF, CF_2, CHCl, o CHOH; en donde si X es CHOH, entonces OH está en la configuración β;

R es una fracción hidrocarbilo o hidroxihidrocarbilo que comprende de 1 a 12 átomos de carbono;

D es independientemente una fracción que comprende de 1 a 6 átomos diferentes de hidrógeno; y

n es un entero de 0 a 4.

2. El compuesto de la reivindicación 1 en donde n es 0.

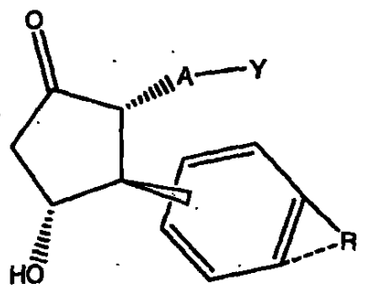
3. El compuesto de la reivindicación 1 en donde R comprende de 6 a 9 átomos de carbono y una estructura cíclica.

4. El compuesto de la reivindicación 3 en donde R es un fracción 1-hidroxihidrocarbilo.

5. El compuesto de la reivindicación 1 en donde R comprende de 1 a 5 átomos de carbono.

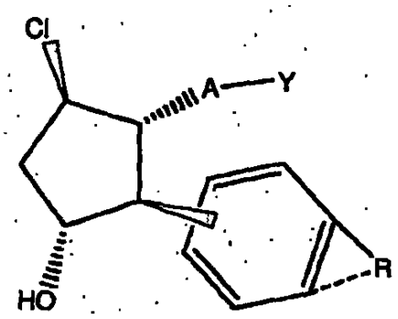
6. El compuesto de la reivindicación 5 en donde R está conformado por *t*-butilo.

7. El compuesto de la reivindicación 1 que comprende



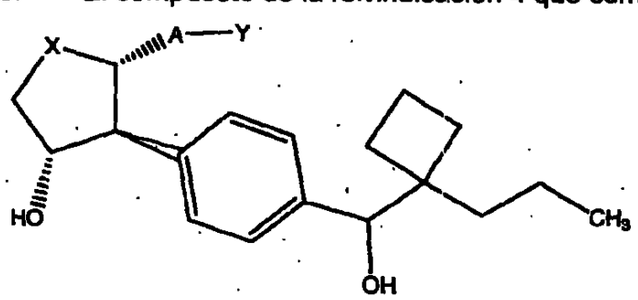
o su sal farmacéuticamente aceptable o profármaco.

8. El compuesto de la reivindicación 1 que comprende



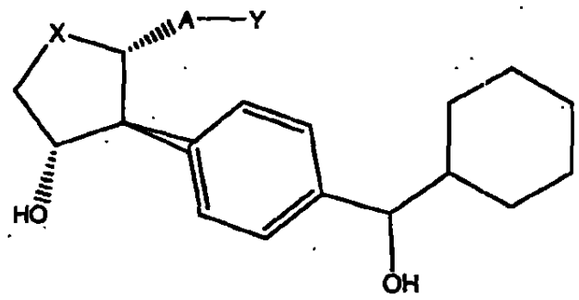
o su sal farmacéuticamente aceptable o profármaco.

9. El compuesto de la reivindicación 4 que comprende



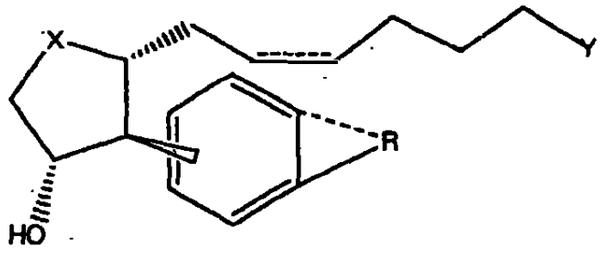
o su sal farmacéuticamente aceptable o profármaco.

10. El compuesto de la reivindicación 4 que comprende



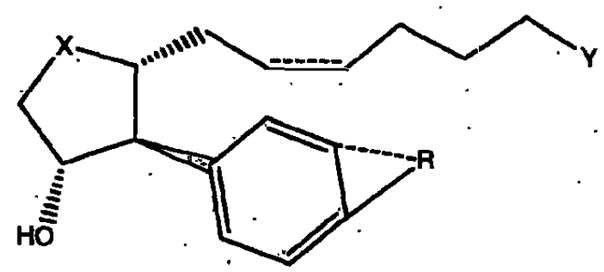
o su sal farmacéuticamente aceptable o profármaco.

11. El compuesto de la reivindicación 1 que comprende



o su sal farmacéuticamente aceptable o profármaco.

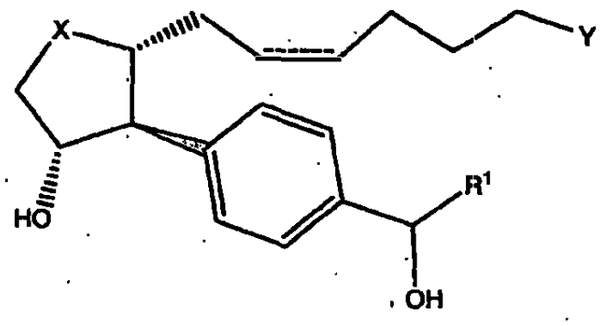
12. El compuesto de la reivindicación 11 que comprende



en donde X es C=O ó CHCl; y

R es alquilo con 3 a 6 átomos de carbono.

13. El compuesto de la reivindicación 11 que comprende

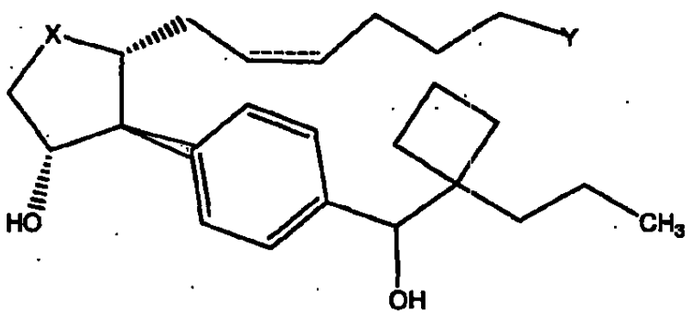


o su sal farmacéuticamente aceptable o profármaco,

en donde R^1 es cicloalquilo que comprende de 3 a 10 átomos de carbono; y

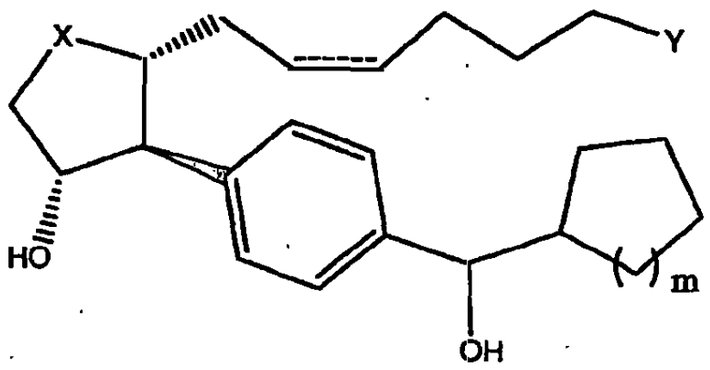
X es C=O ó CHCl.

14. El compuesto de la reivindicación 13 que comprende



o su sal farmacéuticamente aceptable o profármaco.

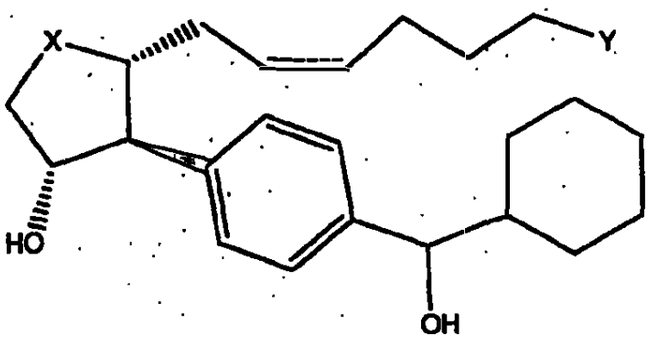
15. El compuesto de la reivindicación 13 que comprende



o su sal farmacéuticamente aceptable o profármaco

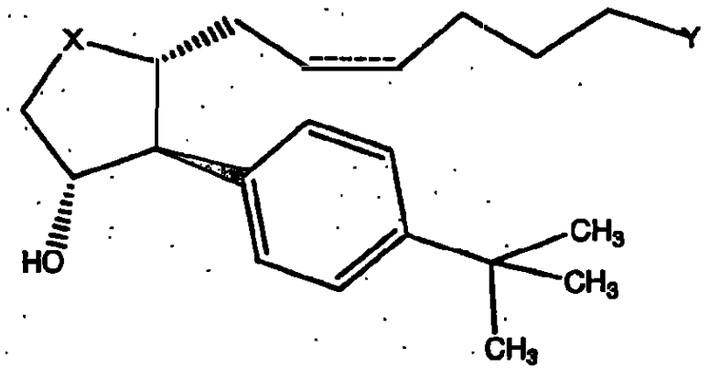
en donde **m** es un entero con un valor de desde 0 a 3.

16. El compuesto de la reivindicación 15 que comprende



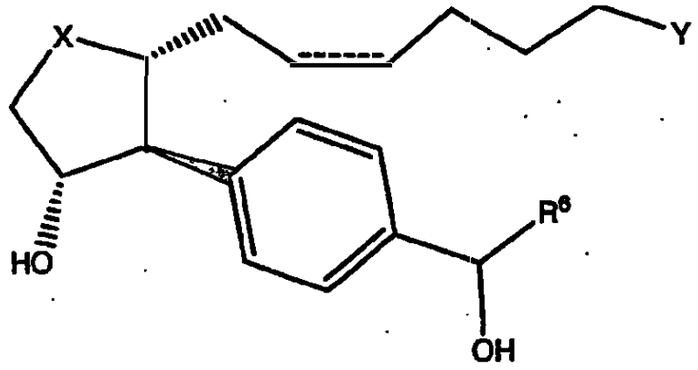
o su sal farmacéuticamente aceptable o profármaco.

17. El compuesto de la reivindicación 12 que comprende



o su sal farmacéuticamente aceptable o profármaco.

18. El compuesto de la reivindicación 11 que comprende



o su sal farmacéuticamente aceptable o profármaco,
en donde R^6 es alquilo ramificado que comprende de 3 a 10 átomos de carbono; y
X es C=O ó CHCl.

19. El compuesto de la reivindicación 11 que comprende
éster metílico de ácido (Z)-7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil)-hept-5-enoico;
ácido (Z)-7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil}-hept-5-enoico;
éster metílico de ácido 7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil}-heptanoico;
ácido 7-{(1R,2S,3R)-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-5-oxo-ciclopentil}-heptanoico;
éster metílico de ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico;

ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico;
éster metílico de ácido 7-((1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico;
ácido 7-((1R,2S,3R)-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico;
éster metílico de ácido (Z)-7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-hept-5-enoico;
ácido (Z)-7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-hept-5-enoico;
éster metílico de ácido 7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-heptanoico;
ácido 7-[(1R,2S,3R)-2-(4-*terc*-butil-fenil)-3-hidroxi-5-oxo-ciclopentil]-heptanoico;
éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-hept-5-enoico;
ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-hept-5-enoico;
éster metílico de ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-heptanoico;
ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-5-oxo-ciclopentil}-heptanoico;
éster metílico de ácido (Z)-7-{(1R,2S,3R)-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-5-oxo-ciclopentil}-hept-5-enoico;
éster metílico de ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-5-oxo-ciclopentil}-heptanoico;
ácido 7-{(1R,2S,3R)-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-5-oxo-ciclopentil}-heptanoico;
éster metílico de ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico;
ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico;
éster metílico de ácido 7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico;
ácido 7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-heptanoico;

(2-hidroxi-etil)-amida de ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico;
etil amida de ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico;
etil amida de ácido (Z)-7-((1R,2S,3R)-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentil)-hept-5-enoico;
éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-hept-5-enoico;
ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-hept-5-enoico;
éster isopropílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-hept-5-enoico;
éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-heptanoico;
éster metílico de ácido 7-[(1R,2S,3R,5R)-5-cloro-2-(4-ciclohexilmetil-fenil)-3-hidroxi-ciclopentil]-heptanoico;
ácido 7-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-heptanoico;
ácido 7-[(1R,2S,3R,5R)-5-cloro-2-(4-ciclohexilmetil-fenil)-3-hidroxi-ciclopentil]-heptanoico;
éster metílico de ácido (Z)-7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-hept-5-enoico;
ácido (Z)-7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil-metil]-fenil}-ciclopentil)-hept-5-enoico;
éster metílico de ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico;
ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico;
éster metílico de ácido (Z)-7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-hept-5-enoico;
ácido (Z)-7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-hept-5-enoico;
éster metílico de ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico;

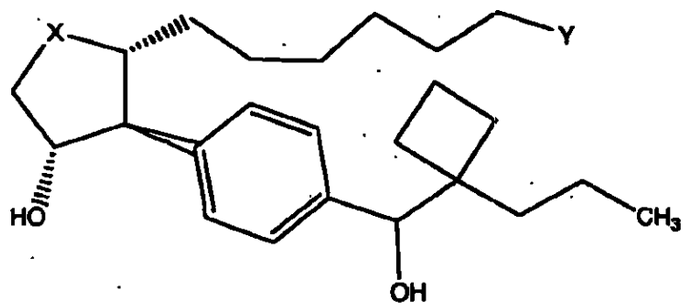
ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{4-[hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentil)-heptanoico;
éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-hept-5-enoico;
ácido (Z)-7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-hept-5-enoico;
éster metílico de ácido 7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-heptanoico;
ácido 7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-heptanoico;
éster isopropílico de ácido (Z)-7-[(1R,2S,3R,5R)-2-(4-*terc*-butil-fenil)-5-cloro-3-hidroxi-ciclopentil]-hept-5-enoico;
éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-hept-5-enoico;
ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-hept-5-enoico;
éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-heptanoico;
ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-ciclobutil)-fenil]-ciclopentil}-heptanoico;
éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-hept-5-enoico;
ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-hept-5-enoico;
éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-heptanoico;
ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-heptanoico;
éster isopropílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(2-hidroxi-1,1-dimetil-etil)-fenil]-ciclopentil}-heptanoico;
éster metílico de ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-hept-5-enoico;
ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-hept-5-enoico;

éster metílico de ácido 7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-heptanoico;
éster metílico de ácido 7-((1R,2S,3R)-3-hidroxi-5-oxo-2-*p*-tolil-ciclopentil)-heptanoico;
ácido 7-[(1R,2S,3R)-3-hidroxi-2-(4-hidroximetil-fenil)-5-oxo-ciclopentil]-heptanoico;
éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-hept-5-enoico;
ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-hept-5-enoico;
éster metílico de ácido 7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-heptanoico;
ácido 7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(4-hidroximetil-fenil)-ciclopentil]-heptanoico;
éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-hept-5-enoico;
éster metílico de ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-hept-5-enoico;
ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-hept-5-enoico;
ácido (Z)-7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-hept-5-enoico;
éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-heptanoico;
éster metílico de ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-heptanoico;
ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2-metil-propil)-fenil]-ciclopentil}-heptanoico;
ácido 7-{(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-[4-(1-hidroxi-2,2-dimetil-propil)-fenil]-ciclopentil}-heptanoico;
éster metílico de ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-but-2-iniloxi)-acético;
ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-but-2-iniloxi)-acético;
éster metílico de ácido ((Z)-4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-but-2-eniloxi)-acético;

ácido ((Z)-4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-but-2-eniloxi)-acético;
éster metílico de ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-butoxi)-acético;
ácido (4-{(1R,2S,3R,5R)-5-cloro-2-[4-(ciclohexil-hidroxi-metil)-fenil]-3-hidroxi-ciclopentil}-butoxi)-acético;
éster metílico de ácido [3-((1R,2S,3R)-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentilmetil)-fenoxi]-acético;
ácido [3-((1R,2S,3R)-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-5-oxo-ciclopentilmetil)-fenoxi]-acético;
éster metílico de ácido [3-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentilmetil)-fenoxi]-acético;
ácido [3-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-{3-[(S)-hidroxi-(1-propil-ciclobutil)-metil]-fenil}-ciclopentilmetil)-fenoxi]-acético;
éster metílico de ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-hept-5-enoico;
ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-hept-5-enoico;
éster metílico de ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-5-oxo-2-(1-oxo-indan-5-il)-ciclopentil]-hept-5-enoico;
ácido (Z)-7-[(1R,2S,3R)-3-hidroxi-5-oxo-2-(1-oxo-indan-5-il)-ciclopentil]-hept-5-enoico;
éster metílico de ácido 7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-heptanoico;
éster metílico de ácido 7-((1R,2S,3R)-3-hidroxi-2-indan-5-il-5-oxo-ciclopentil)-heptanoico;
ácido 7-[(1R,2S,3R)-3-hidroxi-2-(1-hidroxi-indan-5-il)-5-oxo-ciclopentil]-heptanoico;
ácido 7-((1R,2S,3R)-3-hidroxi-2-indan-5-il-5-oxo-ciclopentil)-heptanoico;
éster metílico de ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico;
ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico;
éster isopropílico de ácido (Z)-7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico;

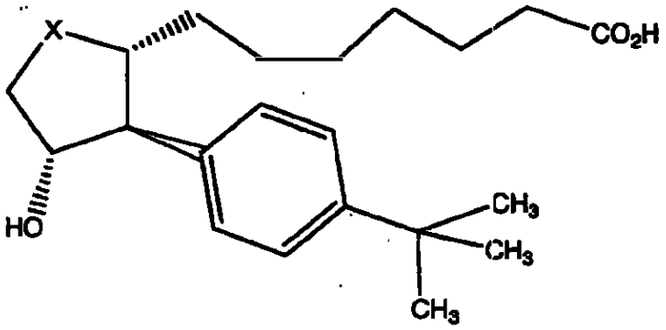
éster metílico de ácido 7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico;
éster metílico de ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-indan-5-il-ciclopentil)-heptanoico;
ácido 7-[(1R,2S,3R,5R)-5-cloro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico;
ácido 7-((1R,2S,3R,5R)-5-cloro-3-hidroxi-2-indan-5-il-ciclopentil)-heptanoico;
éster metílico de ácido 7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico;
ácido 7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-heptanoico;
éster metílico de ácido (Z)-7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico; o
ácido (Z)-7-[(1R,2S,3R)-5-fluoro-3-hidroxi-2-(1-hidroxi-indan-5-il)-ciclopentil]-hept-5-enoico;

20. El compuesto de la reivindicación 14 que comprende



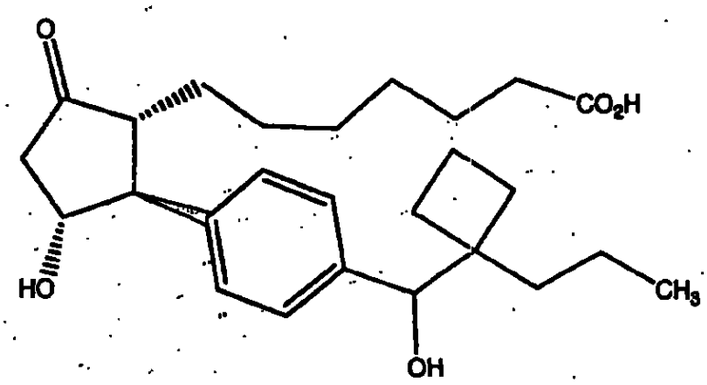
o su sal farmacéuticamente aceptable o profármaco.

21. El compuesto de la reivindicación 12 que comprende



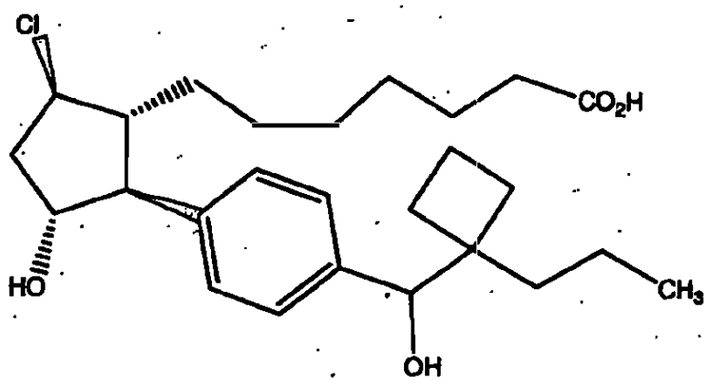
o su sal farmacéuticamente aceptable o profármaco.

22. El compuesto de la reivindicación 20 que comprende



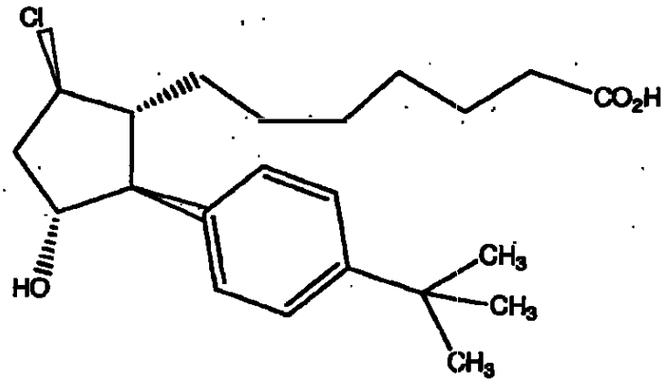
o su sal farmacéuticamente aceptable o profármaco.

23. El compuesto de la reivindicación 20 que comprende



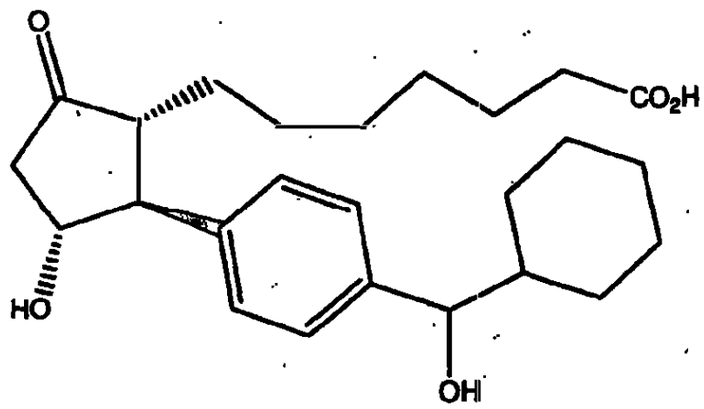
o su sal farmacéuticamente aceptable o profármaco.

24. El compuesto de la reivindicación 21 que comprende



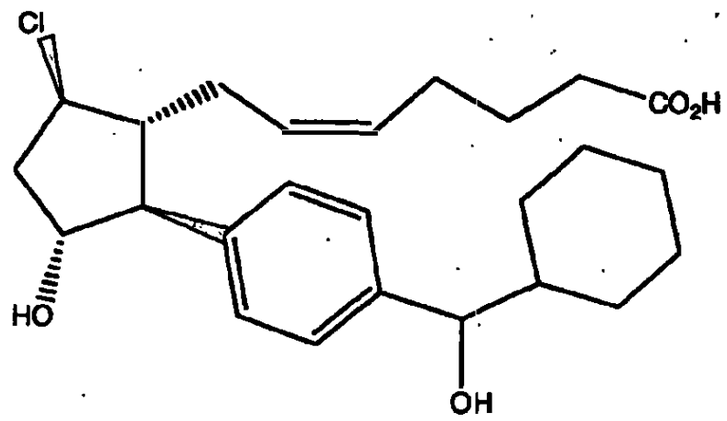
o su sal farmacéuticamente aceptable o profármaco.

25. El compuesto de la reivindicación 16 que comprende



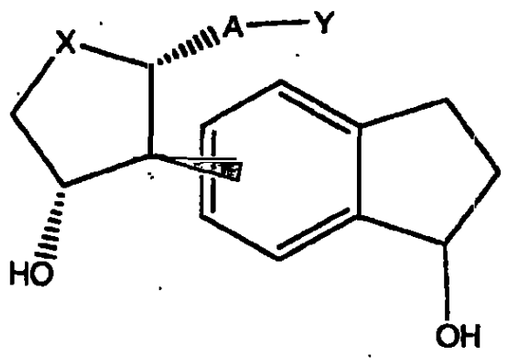
o su sal farmacéuticamente aceptable o profármaco.

26. El compuesto de la reivindicación 16 que comprende



o su sal farmacéuticamente aceptable o profármaco.

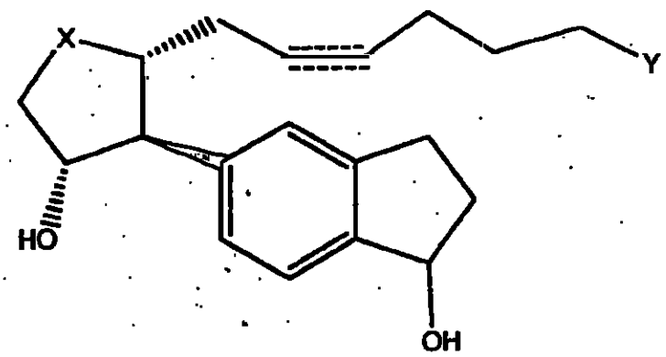
27. El compuesto de la reivindicación 1 que comprende



o su sal farmacéuticamente aceptable o profármaco.

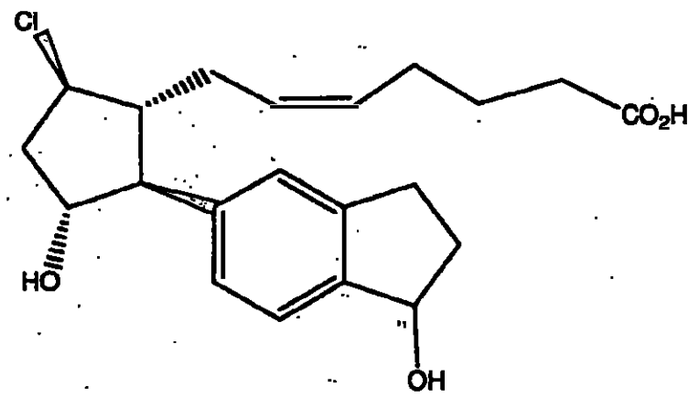
28. El compuesto de la reivindicación 27 en donde A es $-(CH_2)_6$, *cis*-$CH_2CH=CH-(CH_2)_3-$, ó $-CH_2C\equiv C-(CH_2)_3$.

29. El compuesto de la reivindicación 28 que comprende



o su sal farmacéuticamente aceptable o profármaco.

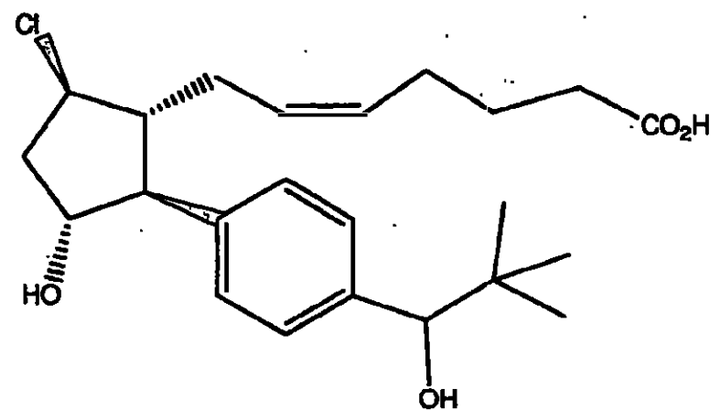
30. El compuesto de la reivindicación 29 que comprende



o su sal farmacéuticamente aceptable o profármaco.

31. El compuesto de la reivindicación 5 en donde R es 1-hidroxialquilo que tiene de 1 a 5 átomos de carbono.

32. El compuesto de la reivindicación 31 que comprende

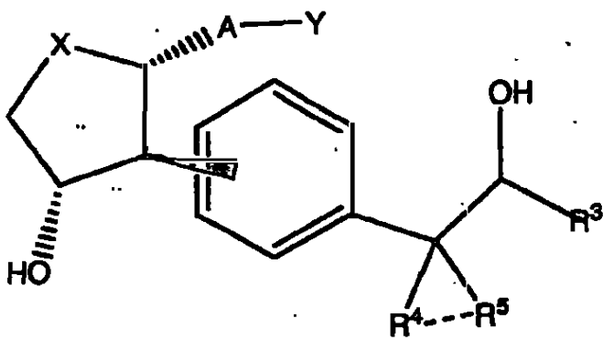


o su sal farmacéuticamente aceptable o profármaco.

33. El compuesto de la reivindicación 1 en donde Y se selecciona del grupo conformado por $CO_2(R^3)$, $CON(R^3)_2$, $CON(OR^3)R^3$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH, $P(O)(OH)_2$, $CONHSO_2R^3$, $SO_2N(R^3)_2$, SO_2NHR^3, y tetrazolil-R^3; en donde R^3 es independientemente H, C_1-C_6 alquilo, fenilo, o bifenilo.

34. El compuesto de la reivindicación 1 en donde R es 2-hidroxihidrocarbilo.

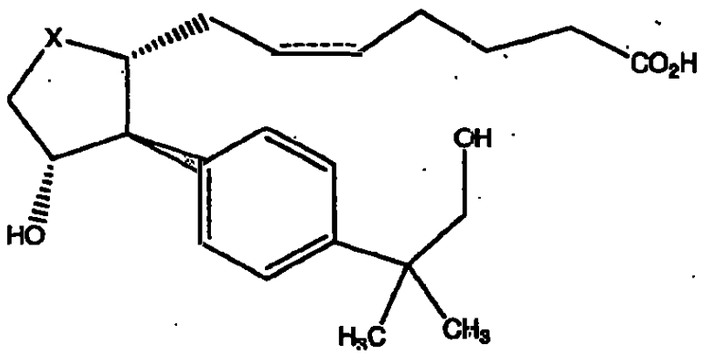
35. El compuesto de la reivindicación 34 que comprende



o su sal farmacéuticamente aceptable o profármaco;
en donde R^3, R^4, y R^5 son independientemente H o C_{1-6} alquilo.

36. El compuesto de la reivindicación 35 en donde R^4 y R^5 son metilo.

37. El compuesto de la reivindicación 36 que comprende

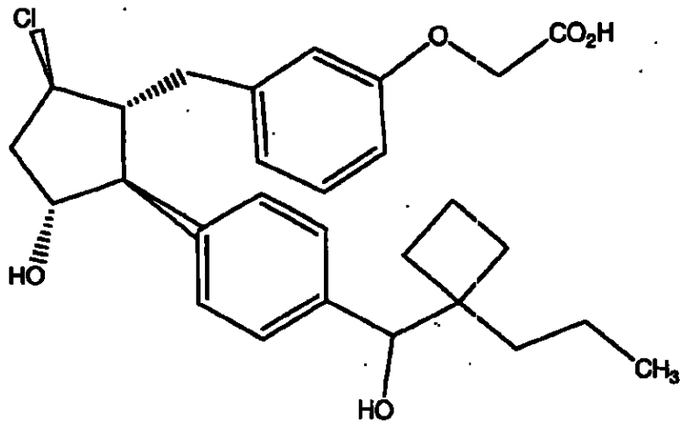


o su sal farmacéuticamente aceptable o profármaco,
en donde X es C=O ó CHCl.

38. El compuesto de la reivindicación 1 en donde **A** es $-(CH_2)_m-Ar-(CH_2)_o-$ en donde **Ar** es fenilo, la sumatoria de **m** y **o** va de 1 a 4, y en donde un CH_2 puede sustituirse con S u O.

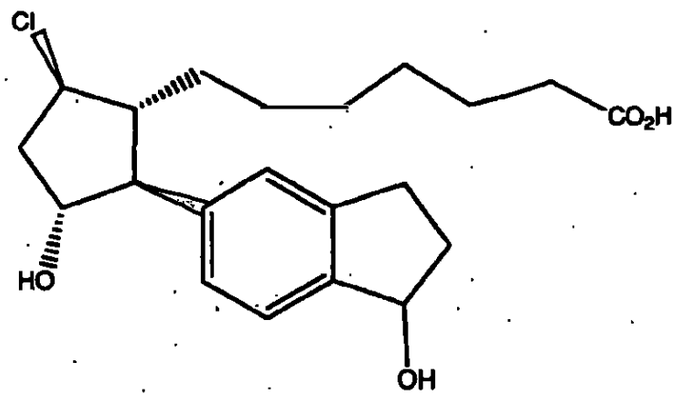
39. El compuesto de la reivindicación 38 en donde **A** es $-CH_2-Ar-O-CH_2-$.

40. El compuesto de la reivindicación 39 que comprende



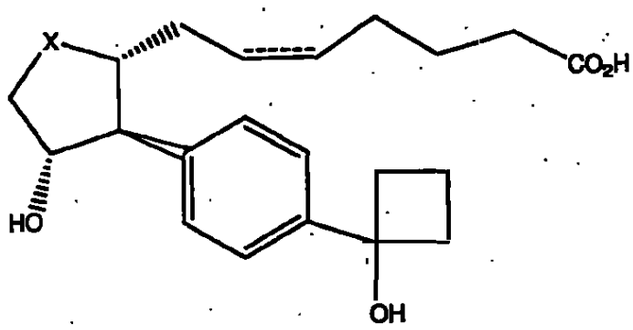
o su sal farmacéuticamente aceptable o profármaco.

41. El compuesto de la reivindicación 29 que comprende



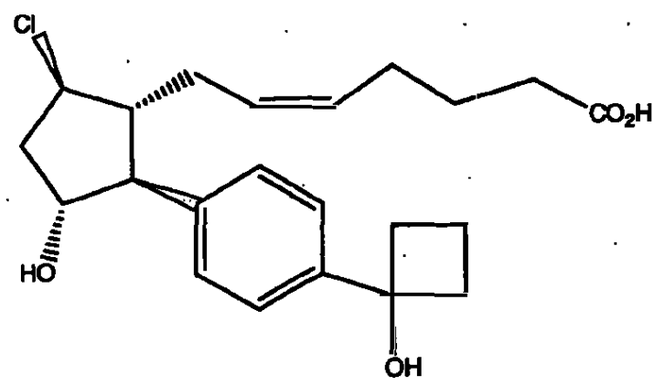
o su sal farmacéuticamente aceptable o profármaco.

42. El compuesto de la reivindicación 31 que comprende



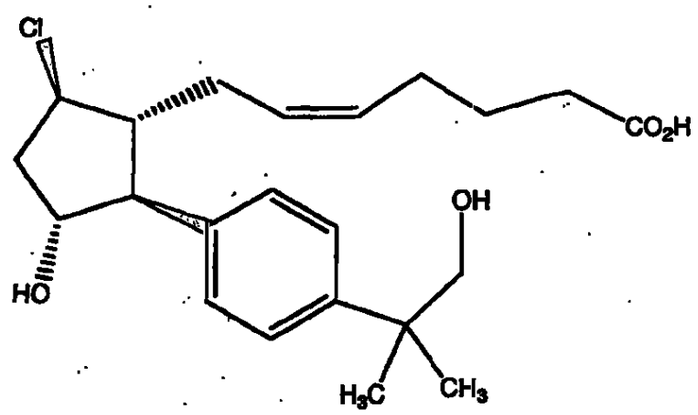
o su sal farmacéuticamente aceptable o profármaco
en donde X es C=O ó CHCl.

43. El compuesto de la reivindicación 42 que comprende



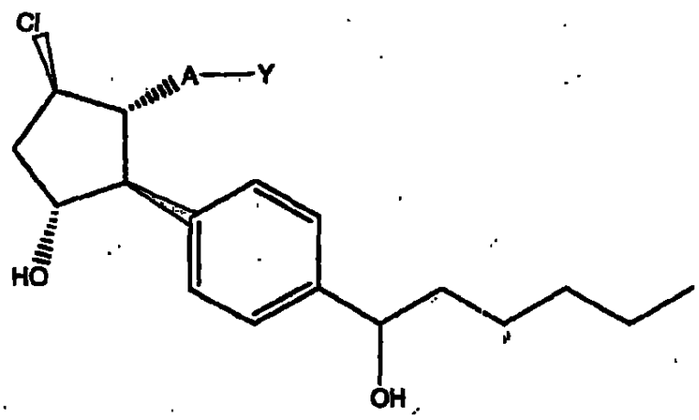
o su sal farmacéuticamente aceptable o profármaco.

44. El compuesto de la reivindicación 37 que comprende



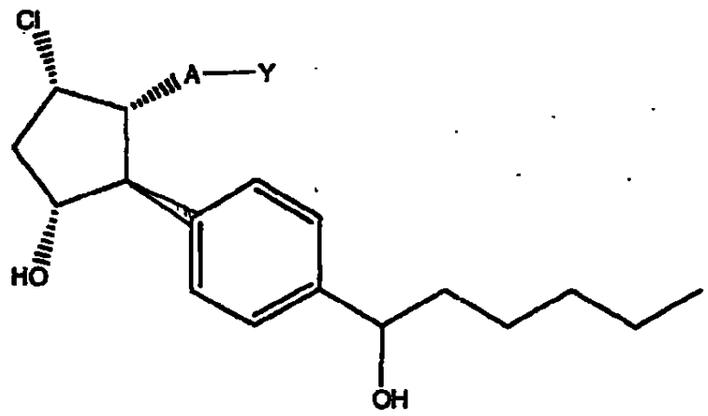
o su sal farmacéuticamente aceptable o profármaco.

45. El compuesto de la reivindicación 2 que comprende



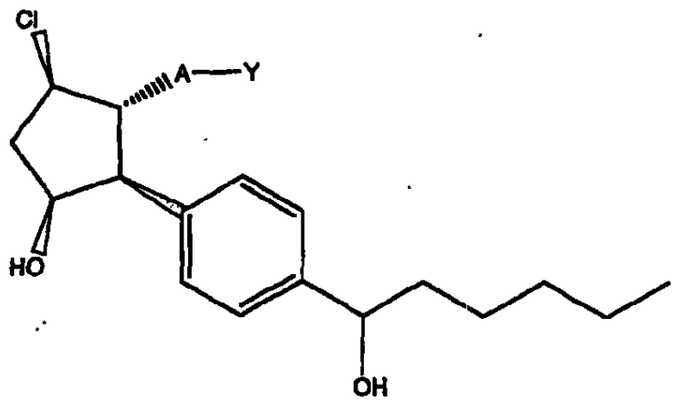
o su sal farmacéuticamente aceptable o profármaco.

46. El compuesto de la reivindicación 2 que comprende



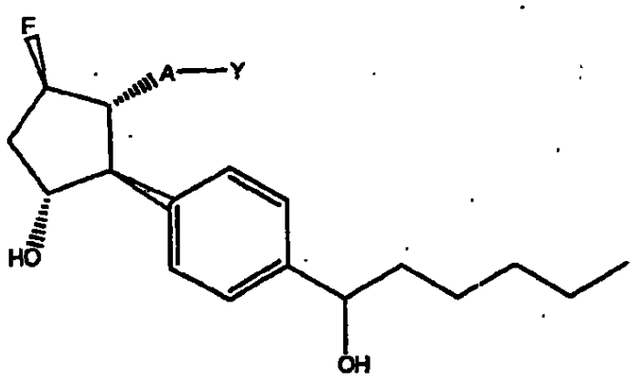
o su sal farmacéuticamente aceptable o profármaco.

47. El compuesto de la reivindicación 2 que comprende



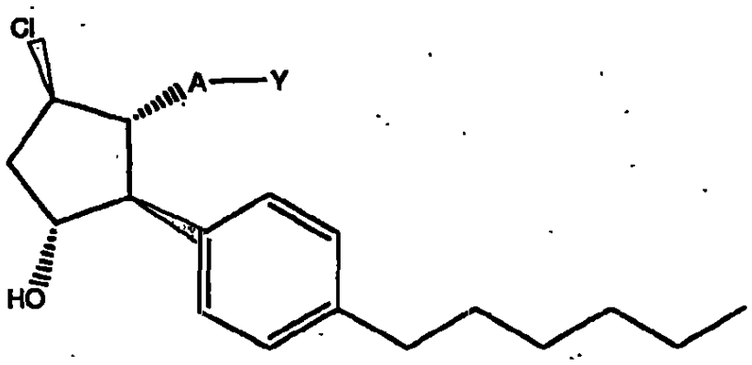
o su sal farmacéuticamente aceptable o profármaco.

48. El compuesto de la reivindicación 2 que comprende



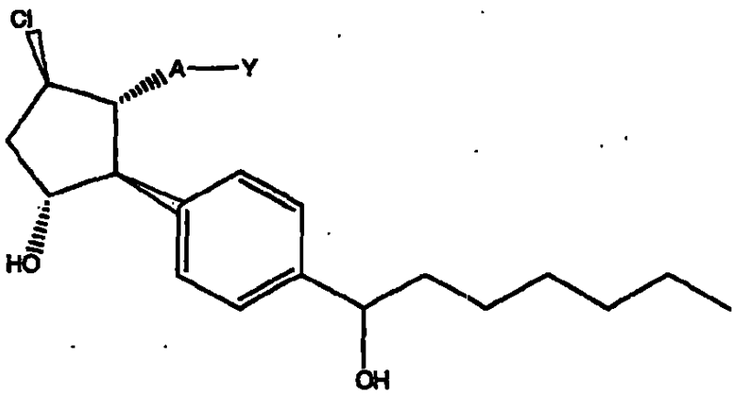
o su sal farmacéuticamente aceptable o profármaco.

49. El compuesto de la reivindicación 2 que comprende



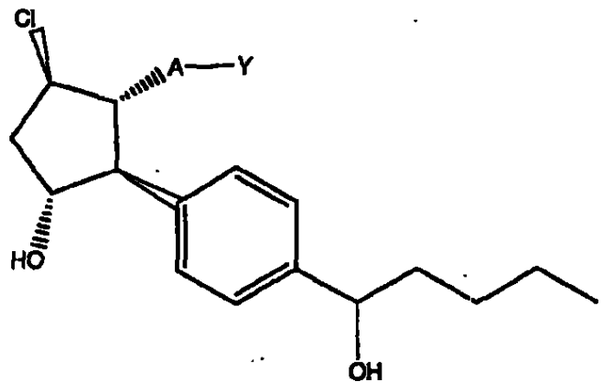
o su sal farmacéuticamente aceptable o profármaco.

50. El compuesto de la reivindicación 2 que comprende



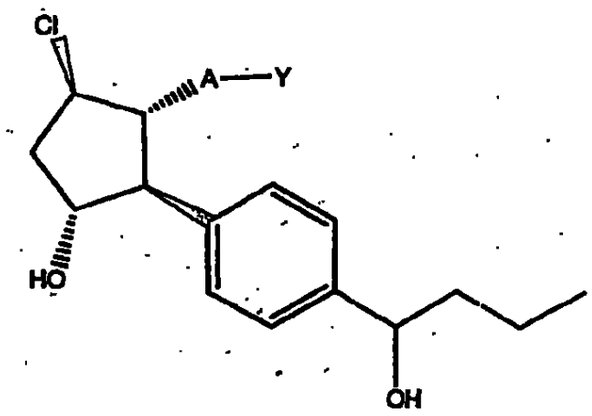
o su sal farmacéuticamente aceptable o profármaco.

51. El compuesto de la reivindicación 2 que comprende



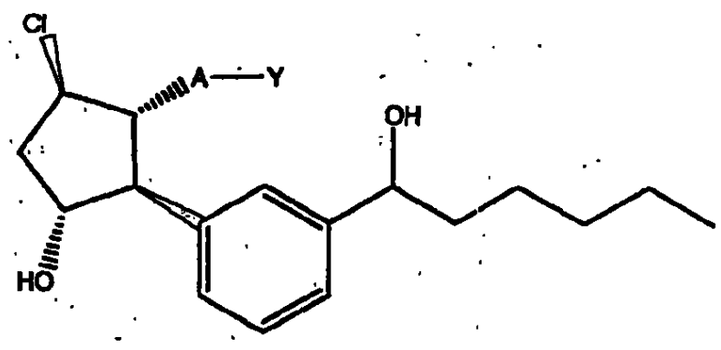
o su sal farmacéuticamente aceptable o profármaco.

52. El compuesto de la reivindicación 2 que comprende



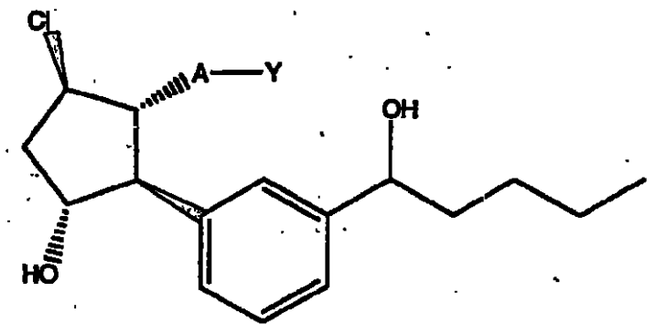
o su sal farmacéuticamente aceptable o profármaco.

53. El compuesto de la reivindicación 2 que comprende



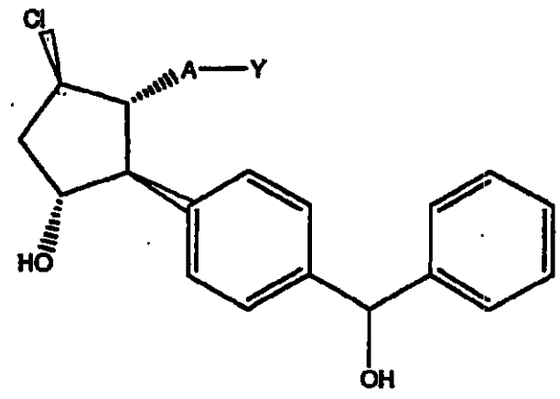
o su sal farmacéuticamente aceptable o profármaco.

54. El compuesto de la reivindicación 2 que comprende



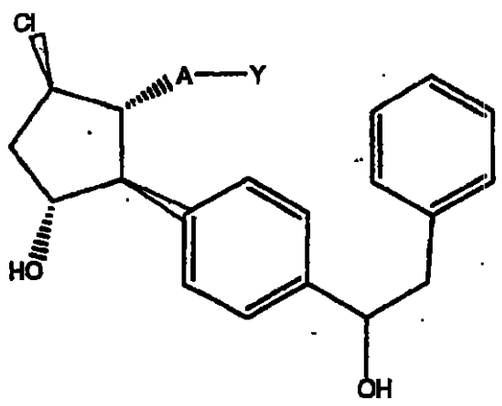
o su sal farmacéuticamente aceptable o profármaco.

55. El compuesto de la reivindicación 2 que comprende



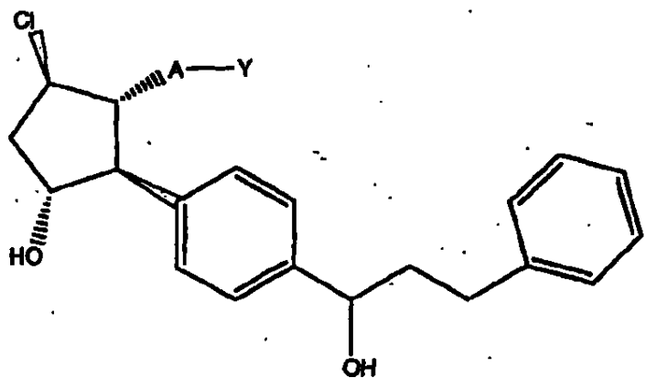
o su sal farmacéuticamente aceptable o profármaco.

56. El compuesto de la reivindicación 2 que comprende



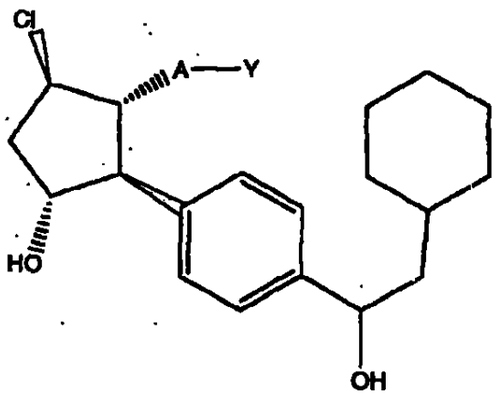
o su sal farmacéuticamente aceptable o profármaco.

57. El compuesto de la reivindicación 2 que comprende



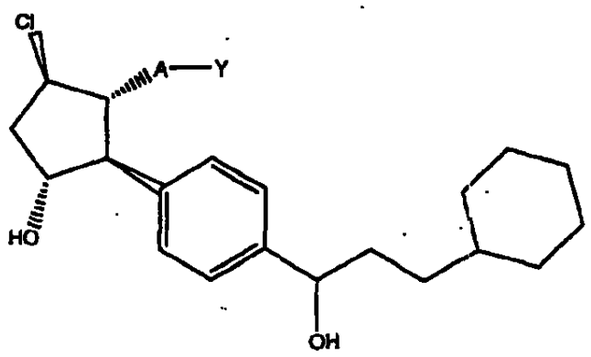
o su sal farmacéuticamente aceptable o profármaco.

58. El compuesto de la reivindicación 2 que comprende



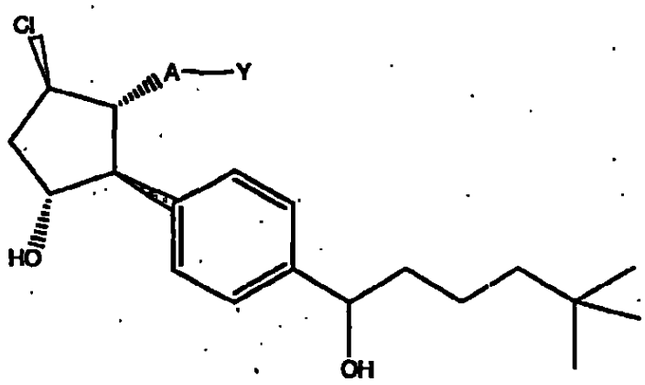
o su sal farmacéuticamente aceptable o profármaco.

59. El compuesto de la reivindicación 2 que comprende



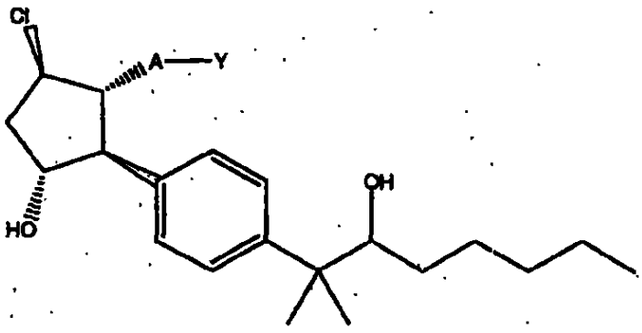
o su sal farmacéuticamente aceptable o profármaco.

60. El compuesto de la reivindicación 2 que comprende



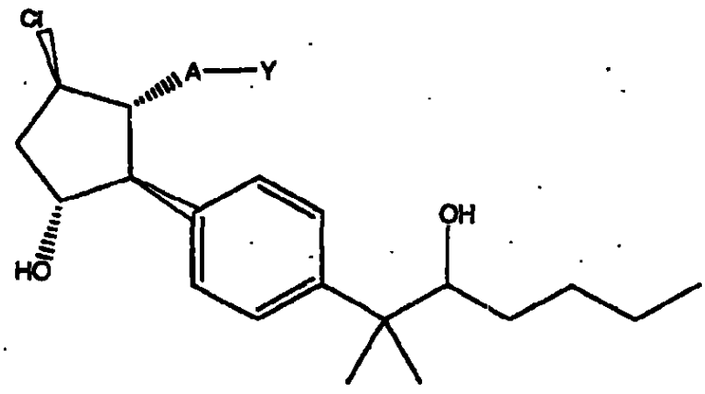
o su sal farmacéuticamente aceptable o profármaco.

61. El compuesto de la reivindicación 2 que comprende



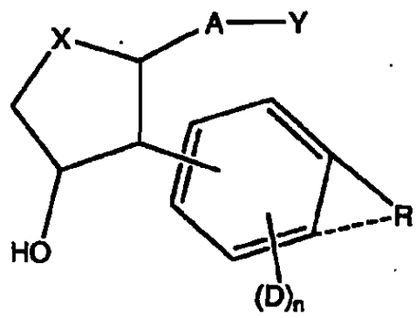
o su sal farmacéuticamente aceptable o profármaco.

62. El compuesto de la reivindicación 2 que comprende



o su sal farmacéuticamente aceptable o profármaco.

63. Uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-62 para la fabricación de un medicamento para el tratamiento de glaucoma o la reducción de la presión intraocular, comprendiendo dicho compuesto



o su sal farmacéuticamente aceptable o profármaco,

en donde una línea discontinua representa la presencia o ausencia de un enlace covalente;

Y es un ácido carboxílico, ácido sulfónico, o ácido fosfónico; o una amida o éster de los mismos, que comprende de 0 a 12 átomos de carbono; o Y es un grupo funcional hidroximetilo, o tetrazolilo;

A es $-(CH_2)_6-$, *cis*-$CH_2CH{=}CH-(CH_2)_3-$, o $-CH_2C{\equiv}C-(CH_2)_3-$, en donde 1 ó 2 átomos de carbono pueden sustituirse con S u O; o A es $-(CH_2)_m-Ar-(CH_2)_o-$ en donde **Ar** es fenilo sustituido o no sustituido o heteroarilo monocíclico, la sumatoria de **m** y **o** va de 1 a 4, en donde un CH_2 puede sustituirse con S u O;

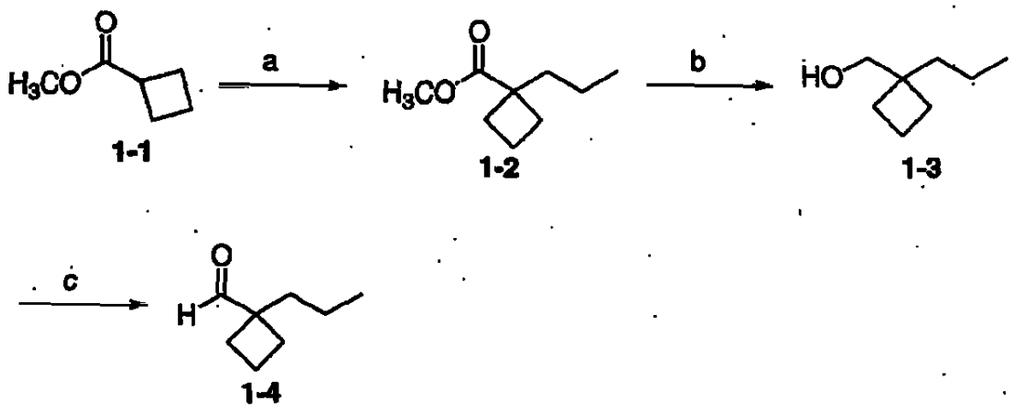
X es C=O, CHF, CF_2, CHCl, o CHOH; en donde si X es CHOH, entonces OH está en la configuración β;

R es una fracción hidrocarbilo o hidroxihidrocarbilo que comprende de 1 a 12 átomos de carbono;

D es independientemente una fracción que comprende de 1 a 6 átomos diferentes de hidrógeno; y

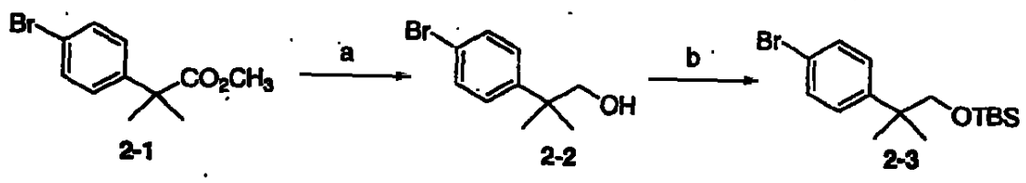
n es un entero de 0 a 4.

64. Un líquido que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-62 en donde dicho líquido es oftálmicamente aceptable. Un compuesto que comprende un agonista selectivo de prostaglandina EP2 en donde la cadena ω comprende un fenilo sustituido, en donde por lo menos un sustituyente está conformado por hidrocarbilo o hidroxihidrocarbilo no lineal, en donde dicho compuesto es efectivo en reducir IOP en un mono en por lo menos 20%.



a) LDA; yoduro de propilo; b) $LiBH_4$; c) TPAP, NMO, mallas moleculares de 4Å

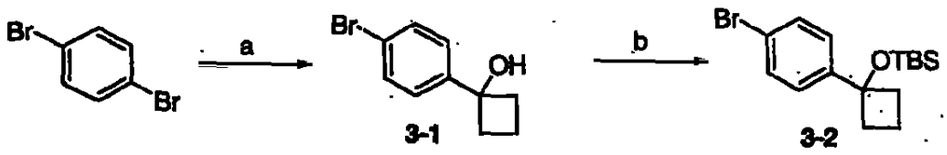
Fig. 2



2-1 2-2 2-3

a) $LiBH_4$; b)TBSOTf, 2,6-lutidina

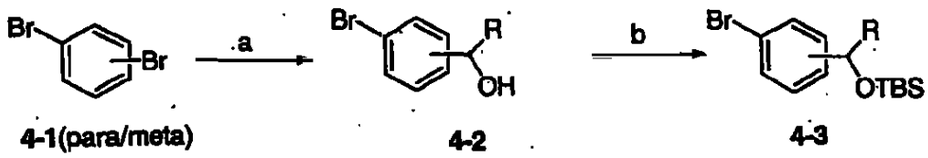
Fig. 3



a) *n*-Buli; ciclobutanona; (b) TBSOTf, 2,6-lutidina

339

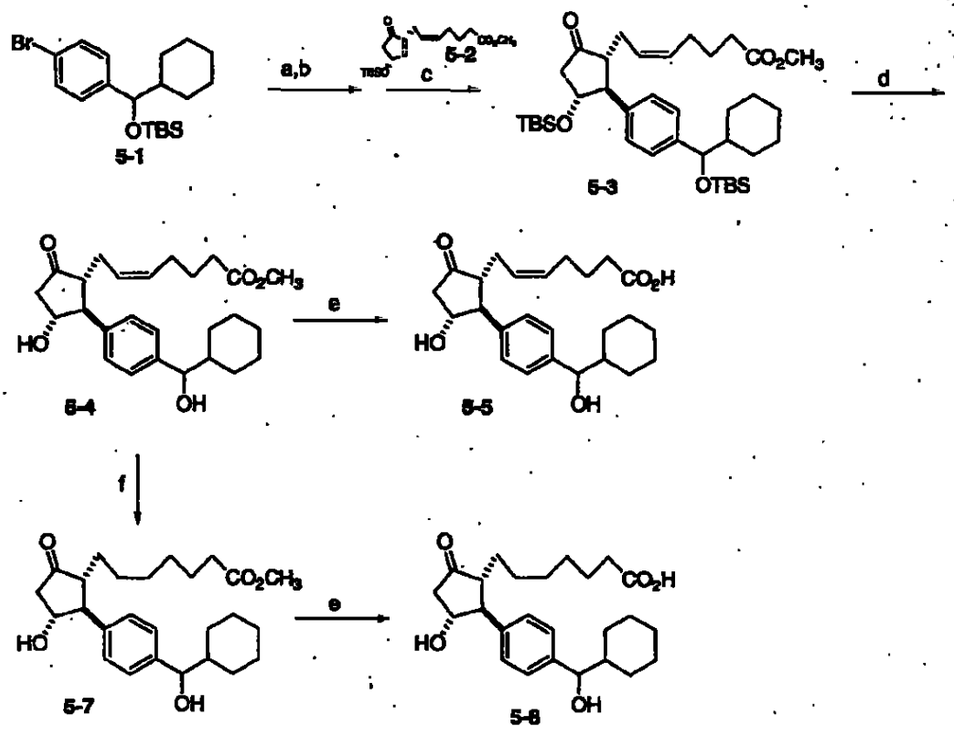
Fig. 4



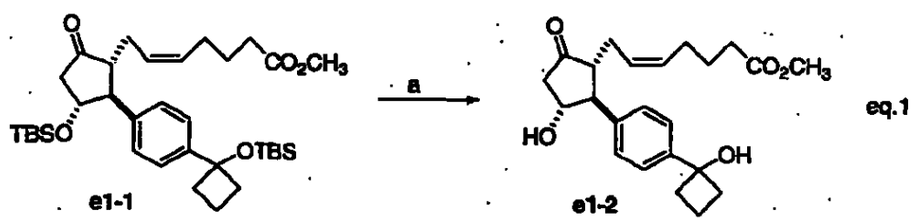
4-1(para/meta) 4-2 4-3

(a) *n*-Buli; RCHO; (b) TBSOTf, 2,6-lutidina

Fig. 5

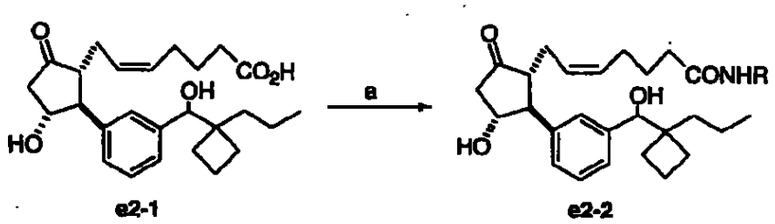


a) *t*-BuLi; (b) 2-tienilcuprato de litio; (c) **5-2**, THF -78 °C; (d) HF-piridina, 0 °C; (e) esterasa de hígado de conejo; (f) H_2, Pd/C



eq.1

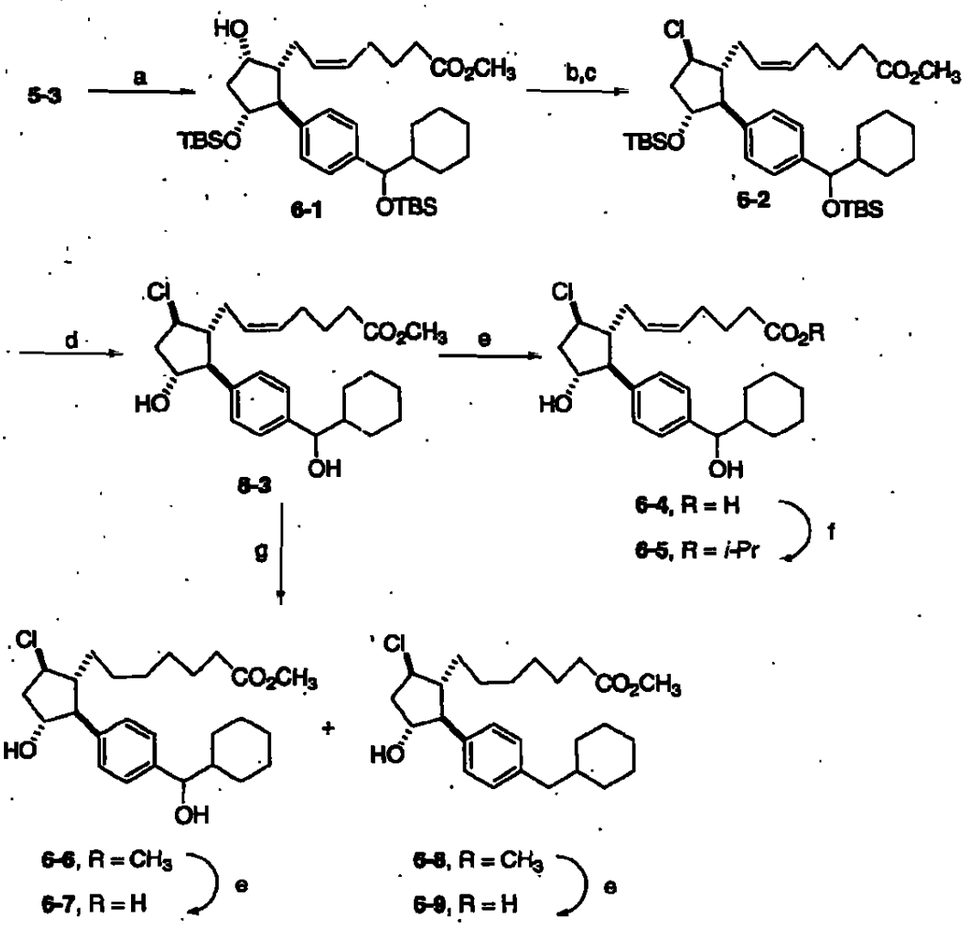
(a) HOAc/H_2O/THF.



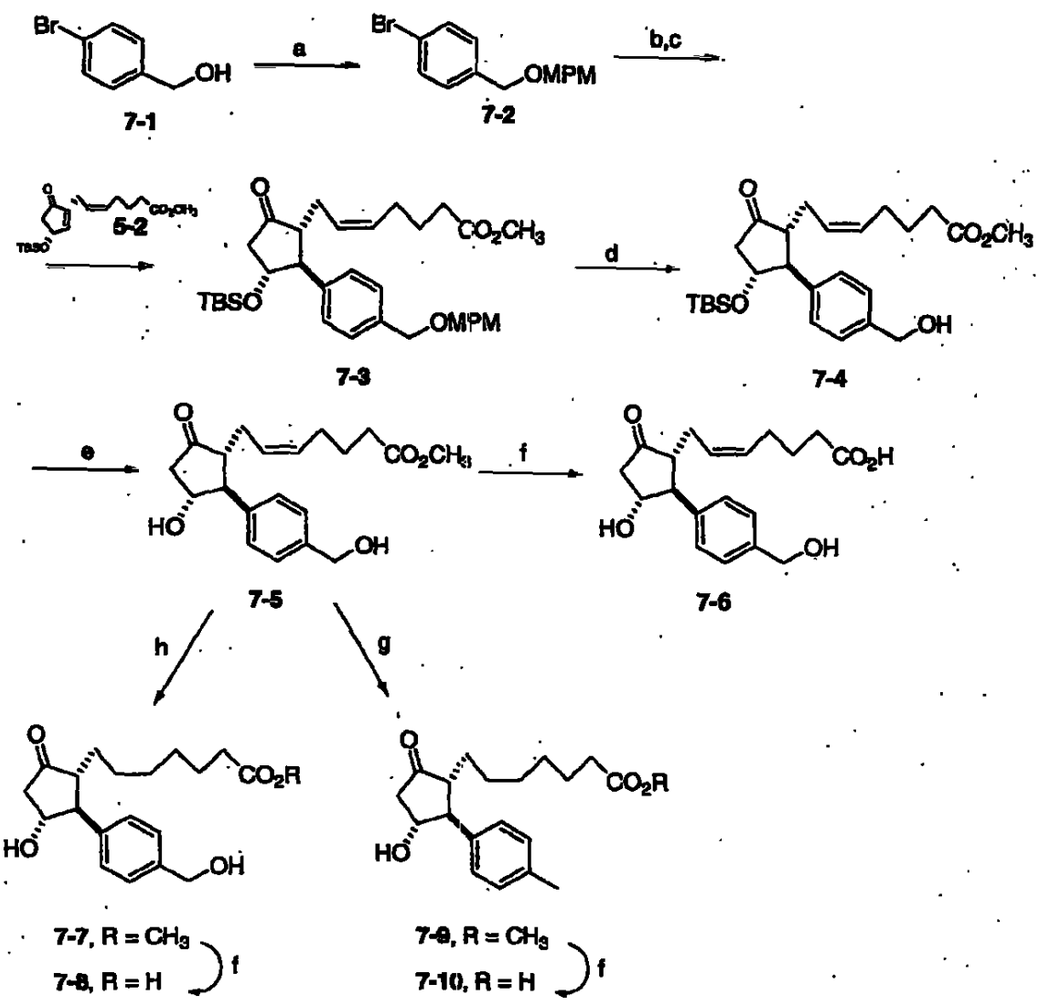
eq. 2

(a) EtOCOCl, TEA;RNH2 ó N-hidroxisuccinimida, EDCI, RNH_2, DMF

Fig. 6

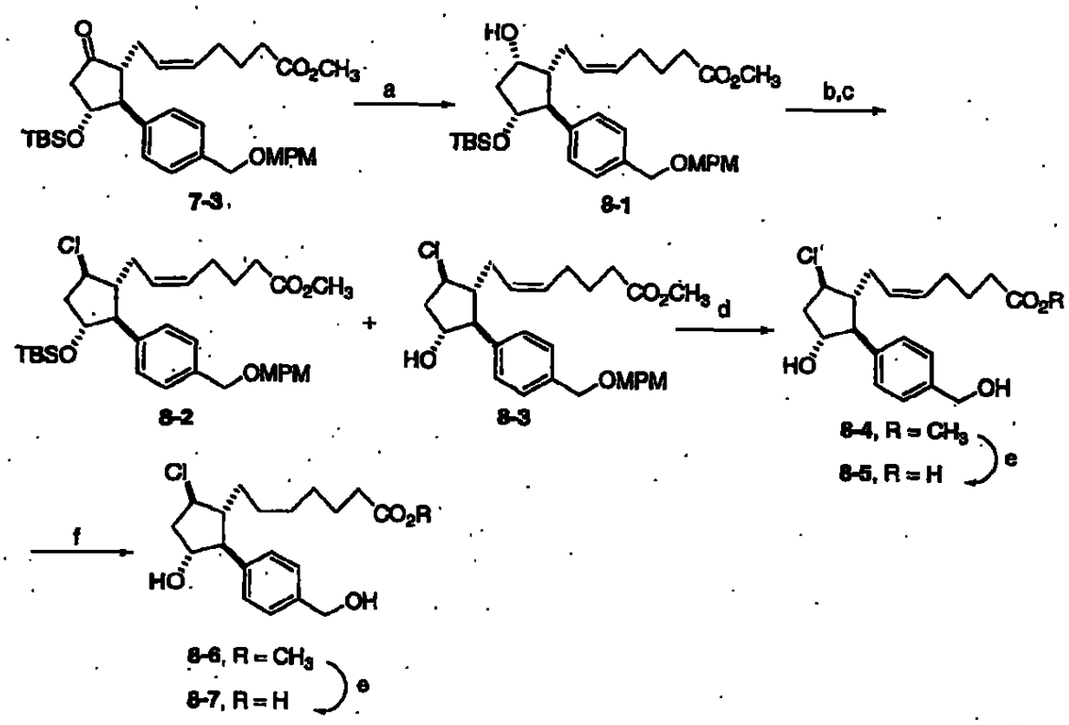


(a) L-Selectride; (b) MsCl, TEA; (c) $(n\text{-Bu})_4NCl$ 40 °C; (d) HF-piridina, 0 °C; (e) LiOH, H_2O, THF (f) *i*-PrI, DBU; (g) H_2, Pd/C



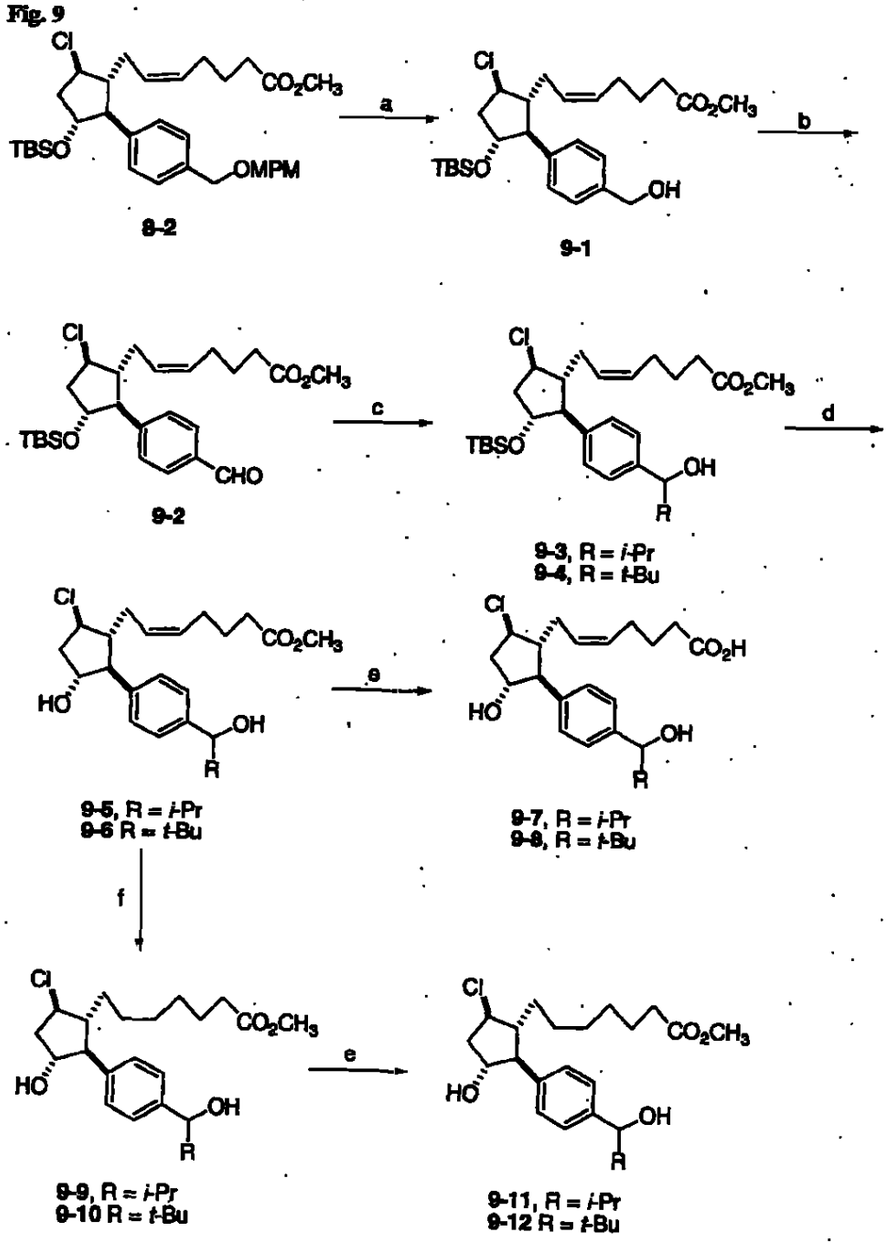
(a) NaH; MPMCl; (b) *t*-Buli; (c) 2-tienilcuprato de litio; (d) DDQ; (e) HF-piridina 0 °C;
(f) Esterasa de Hígado de Conejo; (g) H_2, Pd/C, EtOAC; (h) catalizador de Wilkinson, H_2, THF

Fig. 8



a) L-selectride; H_2O_2; (b) MsCl, Et_3N; (c) $(n\text{-}Bu)_4NCl$ 40 °C; (d) DDQ; (e) 1 M LiOH; (f) H_2, Pd/C, acetato de etilo

Fig. 9



(a) DDQ; (b) TPAP, NMO; (c) i-PrMgCl ó T-BuMgBr; (d) HF-piridina 0 °C; (e) 1 M LiOH
(f) H_2, Pd/C, acetato de etilo

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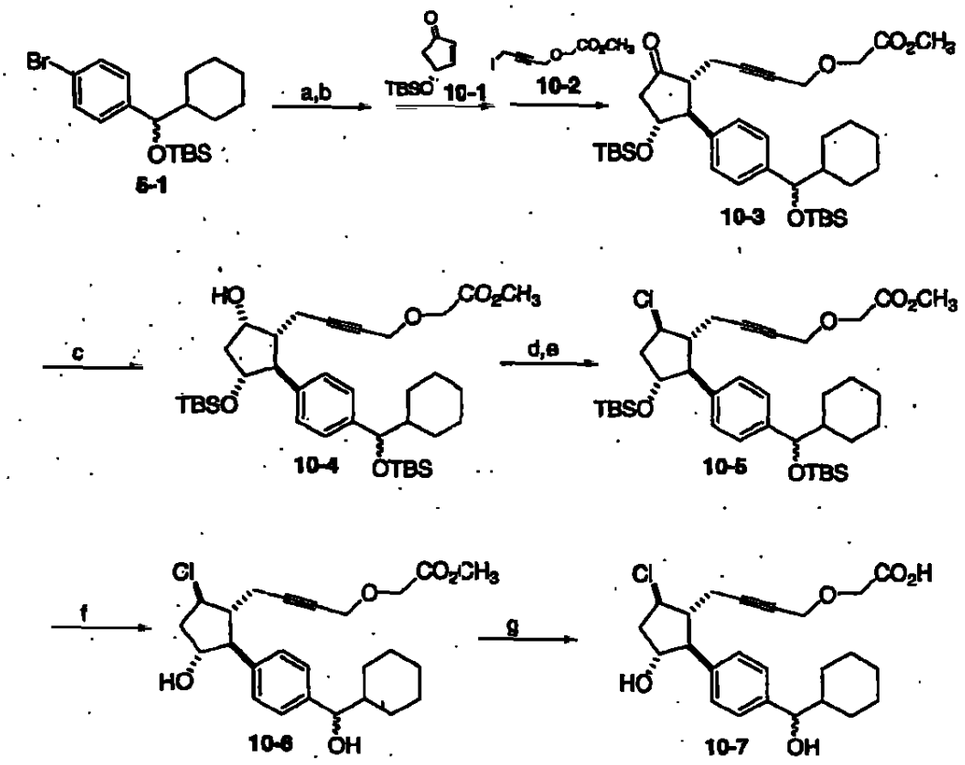
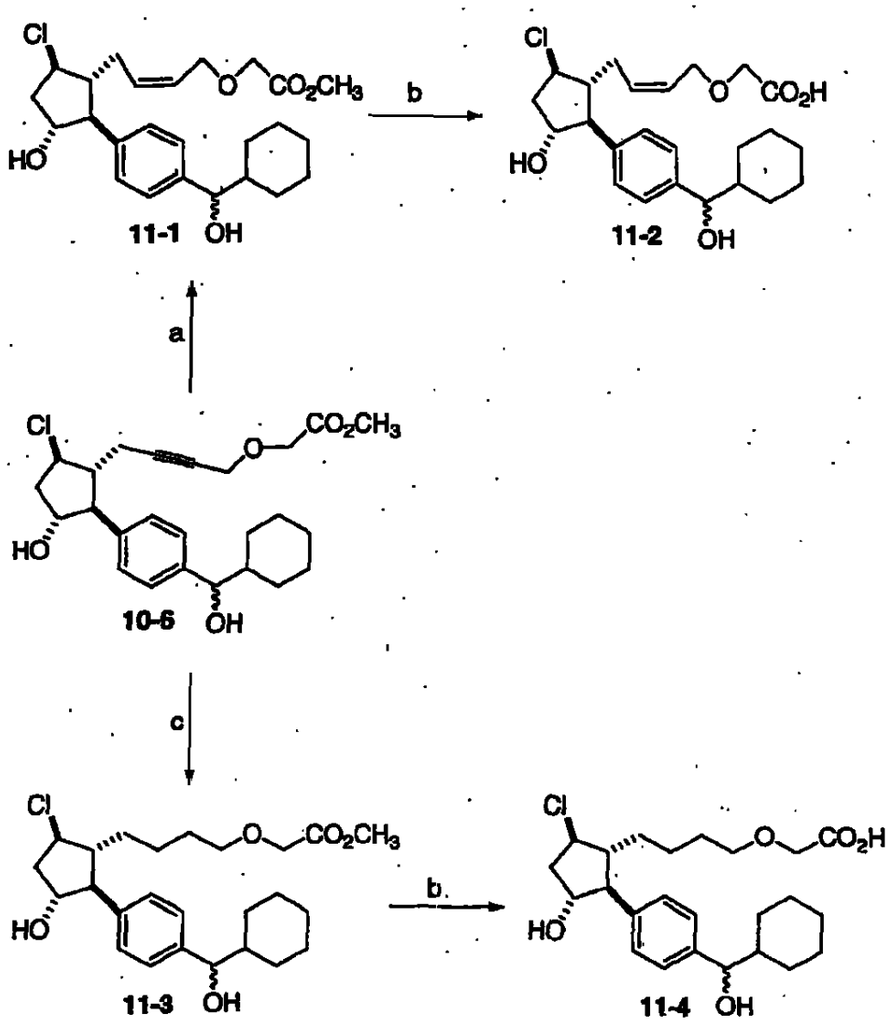
Fig. 10



(a) *t*-Buli ; (b)Me_2Zn ; (c) L-selectride ; H_2O_2; (d) MsCl, TEA ; (e) n-Bu4NCl (f) HF-piridina, 0 °C
(g) Esterasa de Hígado de Conejo

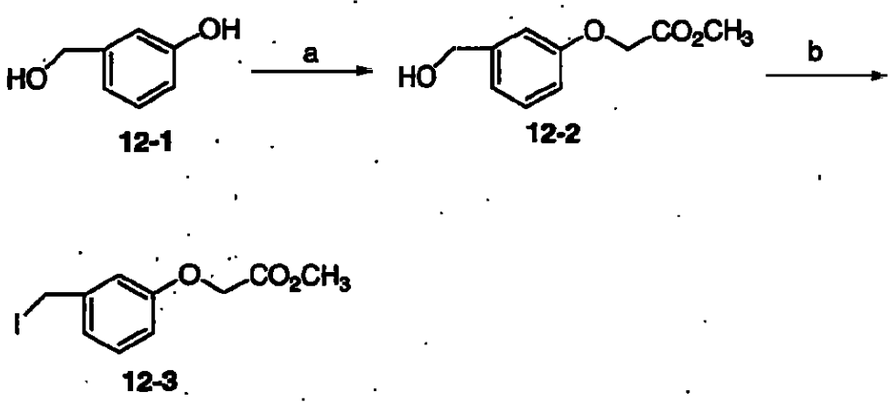
Fig. 11



(a) H_2, $NiCl_2$, $NaBH_4$, $H_2NCH_2CH_2NH_2$; (b) esterasa de hígado de conejo, (c) H_2, Pd/C

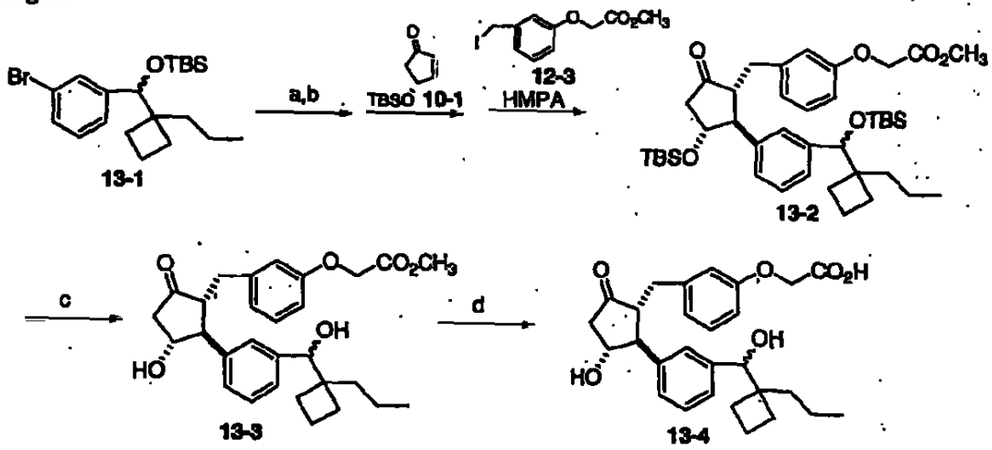
345

Fig. 12



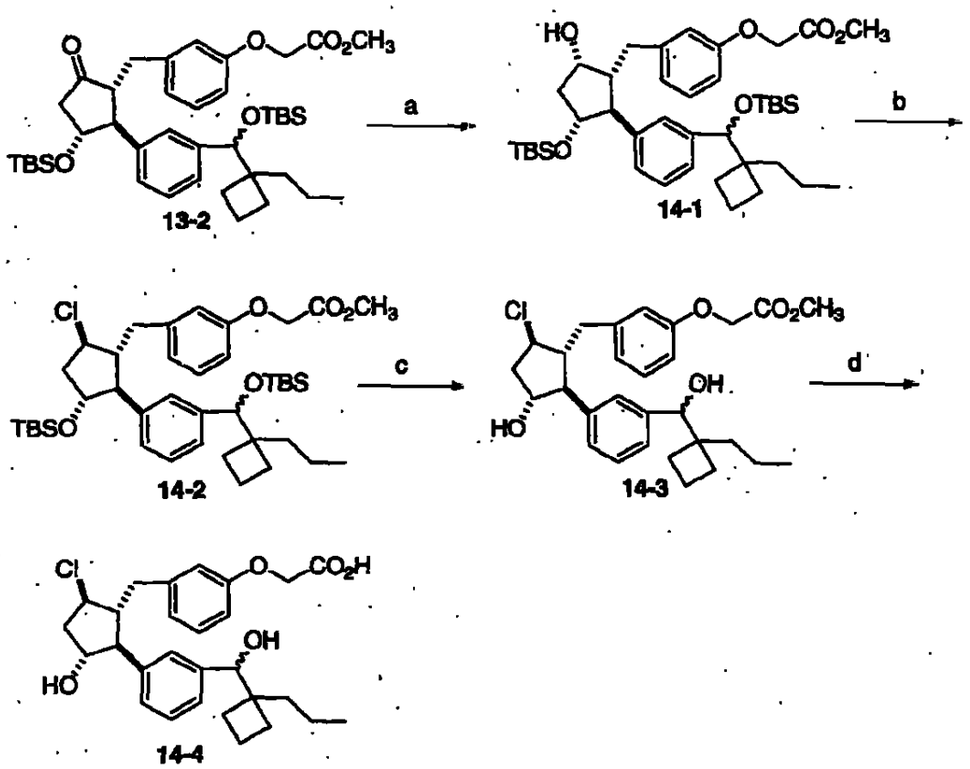
a) K_2CO_3, bromoacetato de metilo; (b)PPh_3P, I_2, imidazol, CH_2Cl_2

Fig. 13



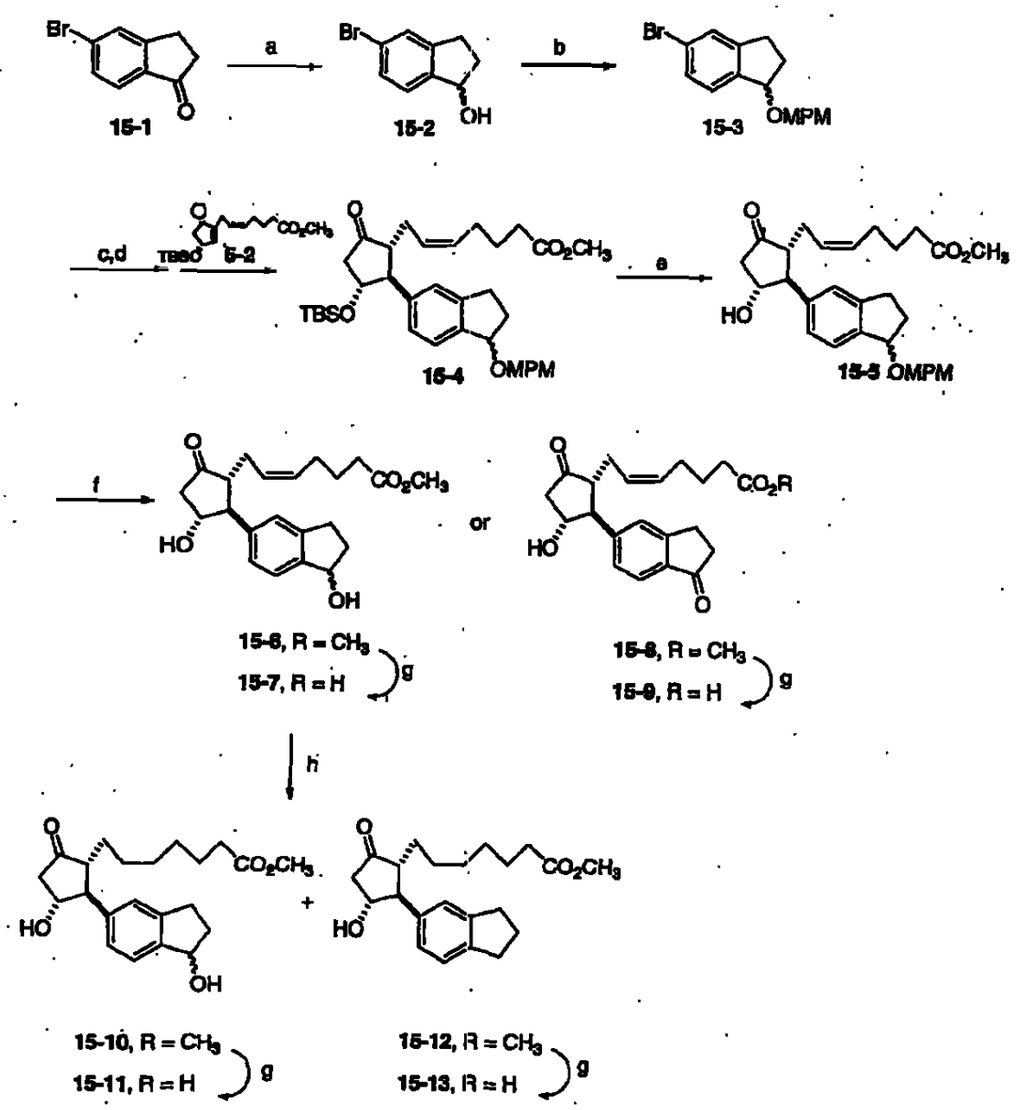
a) *t*-BuLi; (b)Me_2Zn; (c) HF-piridina, 0 °C; (d) esterasa de hígado de conejo

Fig. 14



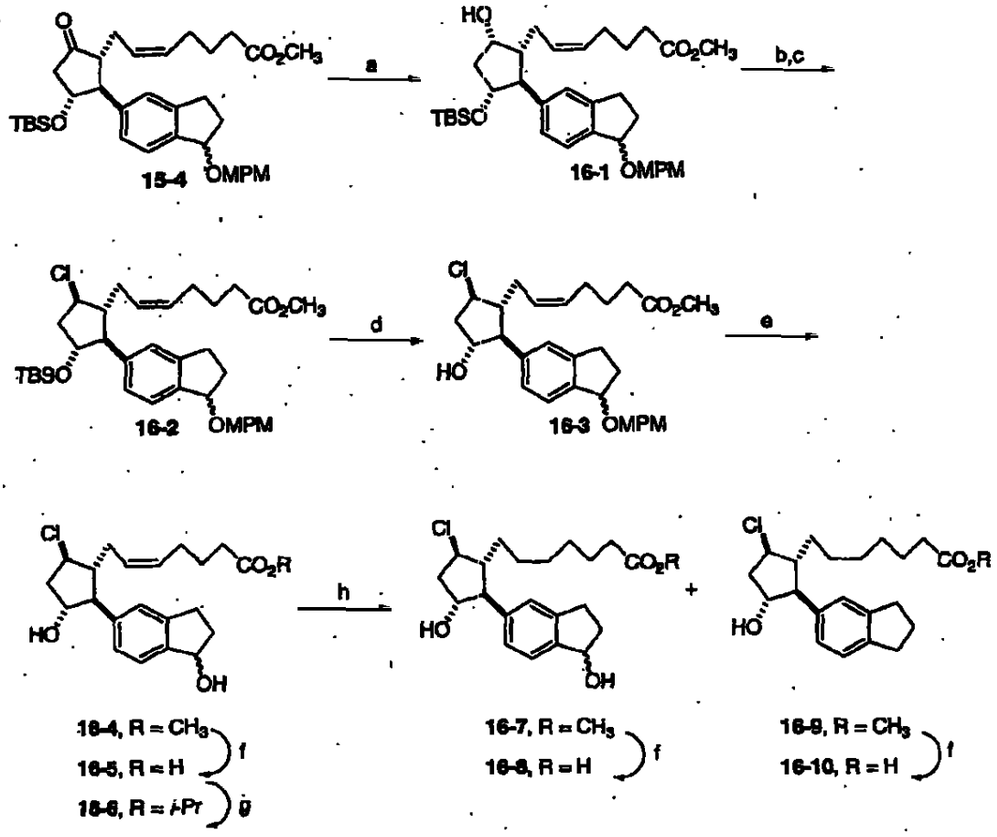
(a) L-selectride; (b) MsCl, TEA; $(n\text{-Bu})_4NCl$; (c) HF-piridina, 0 °C; (d) LiOH, H_2O, THF

Fig. 15



(a) $NaBH_4$; (b) MPMCl, NaH; (c) *t*-BuLi; (d) 2-tienilCuCNLi; (e) HOAc/H_2O/THF; (f) DDQ; (g) esterasa de hígado de conejo; (h) H_2, Pd/C

Fig. 16



(a) L-selectride; H_2O_2; (b) MsCl, TEA; (c)TBAC 40 °C; (d) HOAc/H_2O/THF; (e) DDQ; (f) esterasa de hígado de conejo; (g) *i*-PrI, DBU (h) H_2, Pd/C

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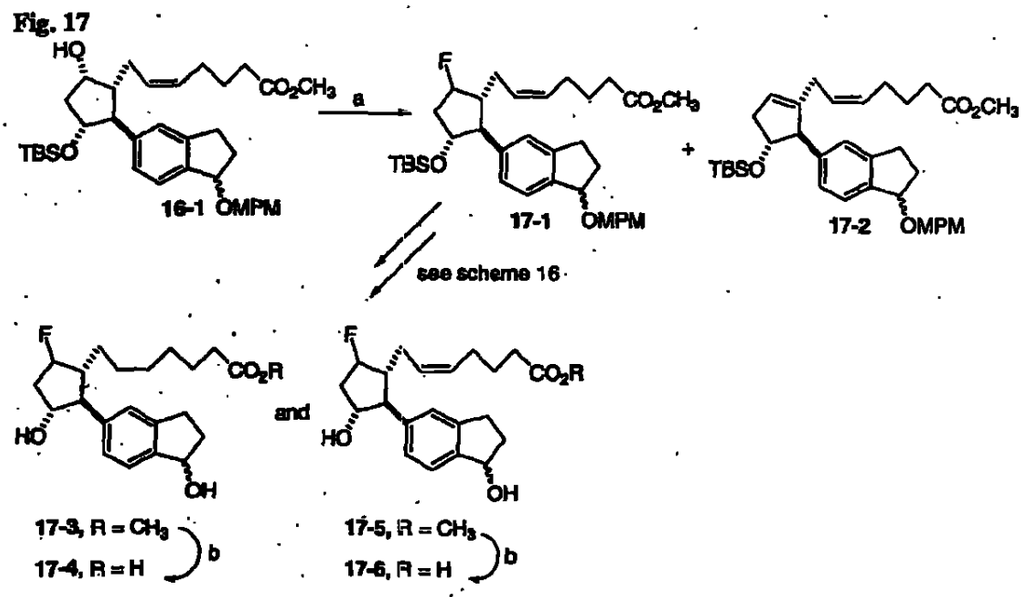
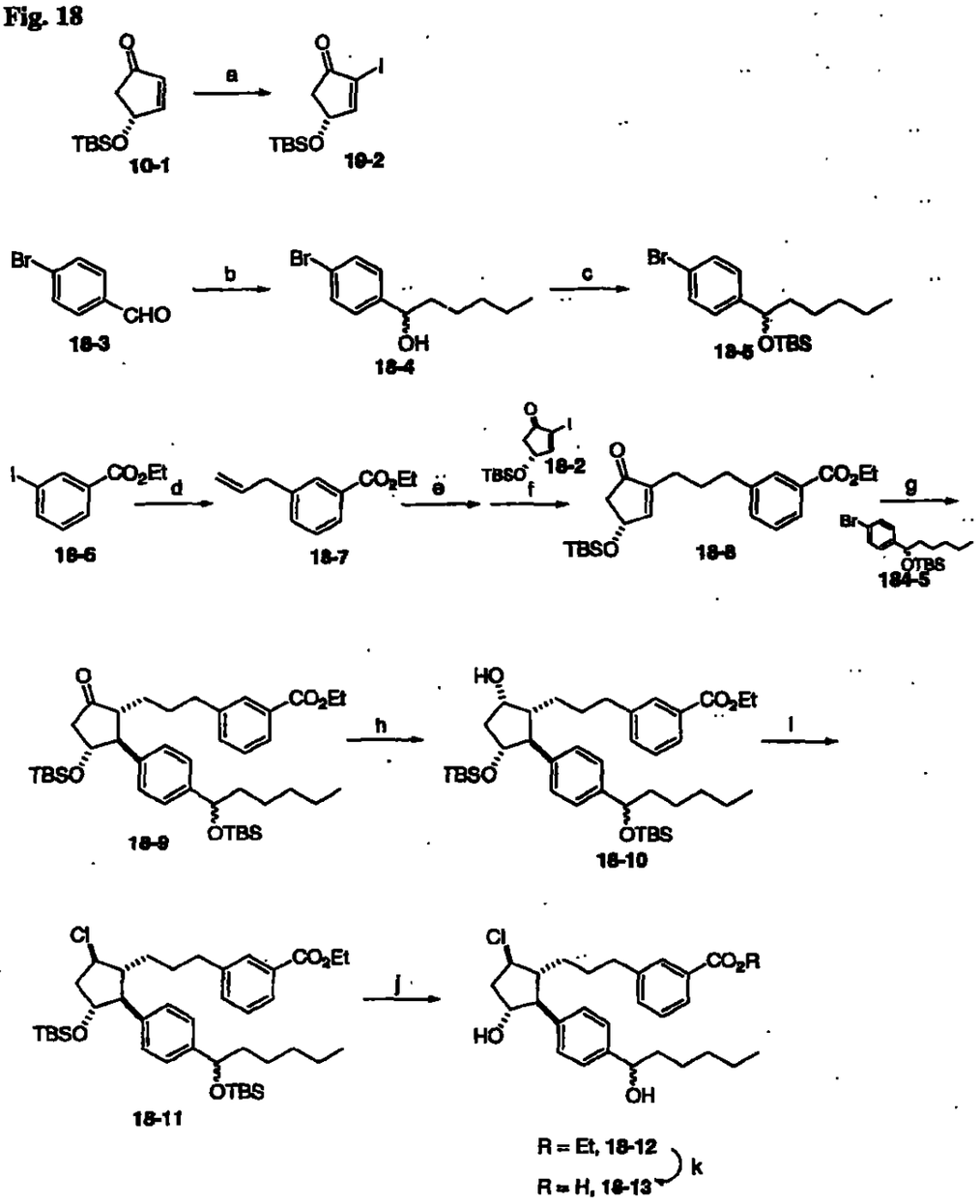
Fig. 17



(a) DAST, CH_2Cl_2 -78 °C; (b) 1 M LIOH, THF.

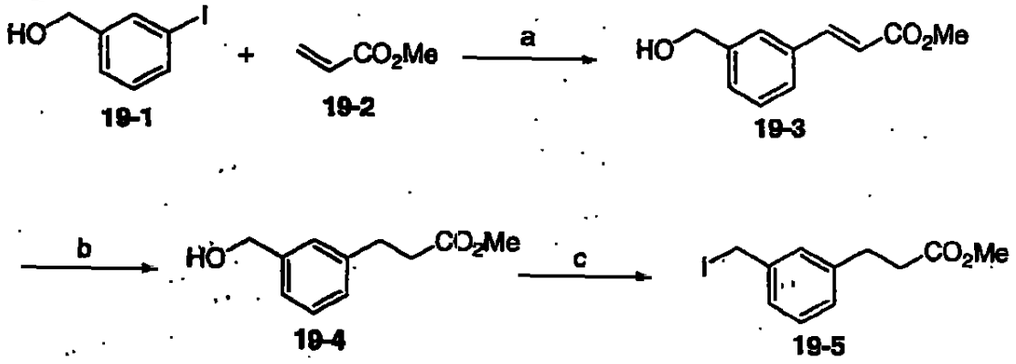
(b)

Fig. 18



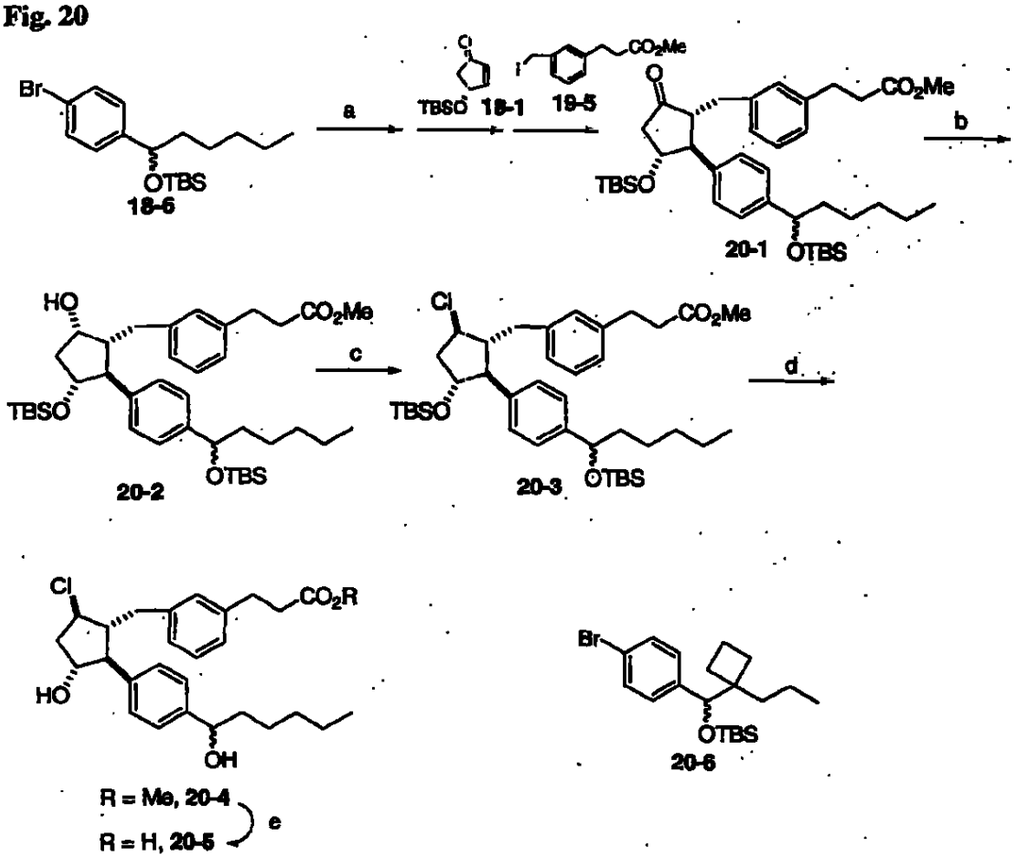
(a) I_2, piridina, CH_2Cl_2; (b) *n*-pentilMgBr; (c) TBSOTf, 2,6-lutidina, CH_2Cl_2; (d) *i*-PrMgCl; Cat. CuCN, bromuro de alilo; (e) 9-BBN; (f) $PdCl_2$ (dppf), K_3PO_4, DMF; (g) *t*-Buli; 2-tienilCuCNLi; (h) L-selectride; (i) MsCl, TEA; TBAC 40 °C (j) HF-piridina 0 °C; (k) 1 M LiOH, THF

Fig. 19



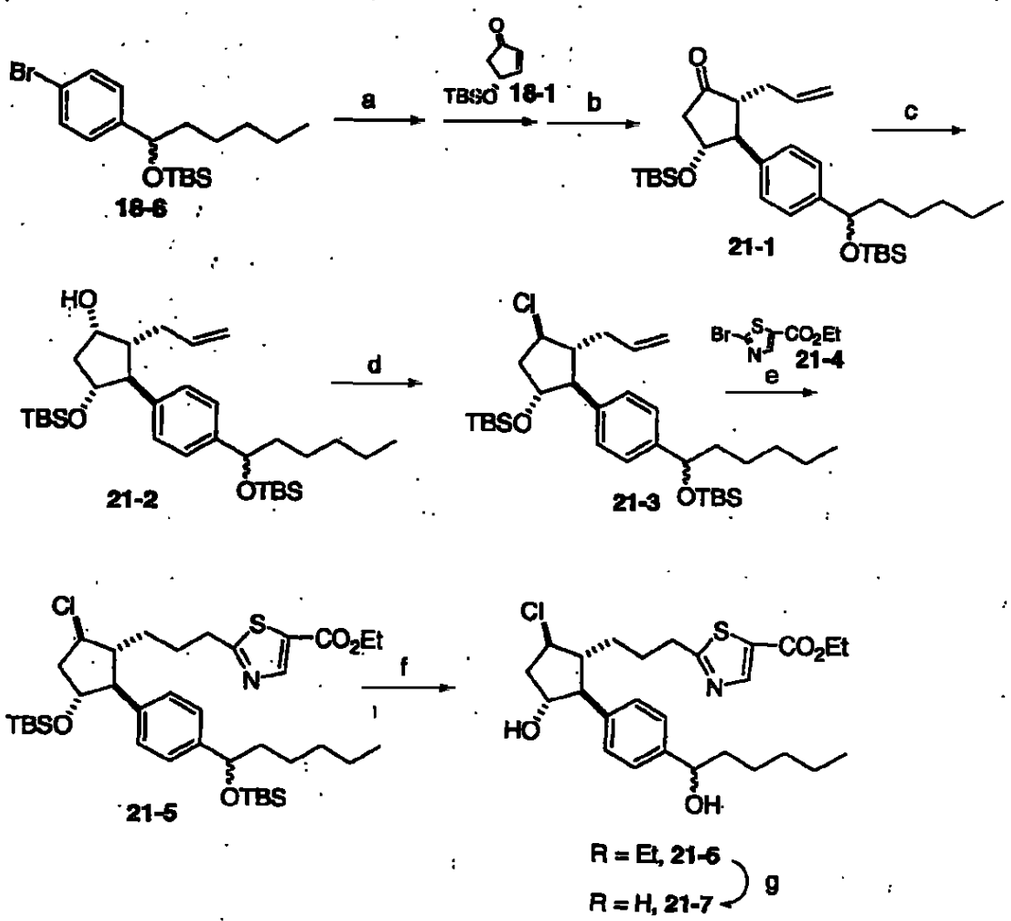
(a) $Pd(OAc)_2$, Et_3N CH_3CN 100 °C; (b) H_2, $(Ph_3P)_3RhCl$, EtOH ; (c) Ph_3P, I_2, imidazol, $ClCH_2CH_2Cl$

Fig. 20



(a) *t*-BuLi; Me_2Zn; (b) L-selectride; (c) MsCl, TEA; TBAC 40 °C;
(d) HF-piridina; (e) LiOH acuoso

Fig. 21



(a) t-BuLi; Me_2Zn; (b) bromuro de alilo, HMPA; (c) L-selectride; (d) MsCl, TEA; TBAC 40 °C;
(e) 9-BBN; $PdCl_2$(dppf), K_3PO_4, DMF 50 °C; (f) HF-piridina 0 °C; (g) LiOH acuoso, THF

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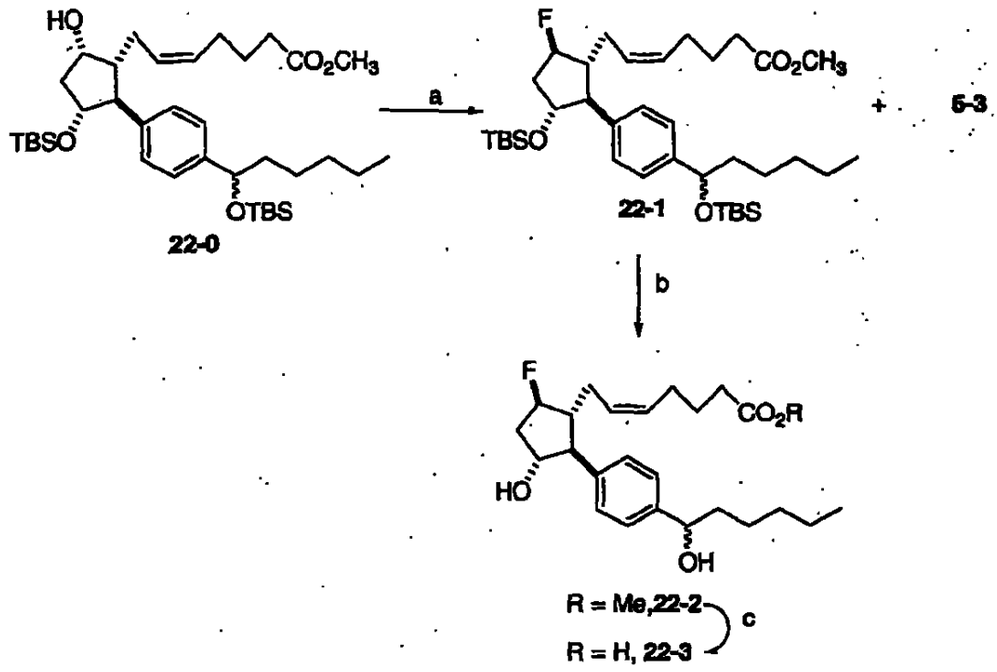
Fig. 22



(a) MsCl, TEA; NaCN, DMSO 80 °; (b) HF-piridina, 0 °C; (c) LiOH acuoso, THF

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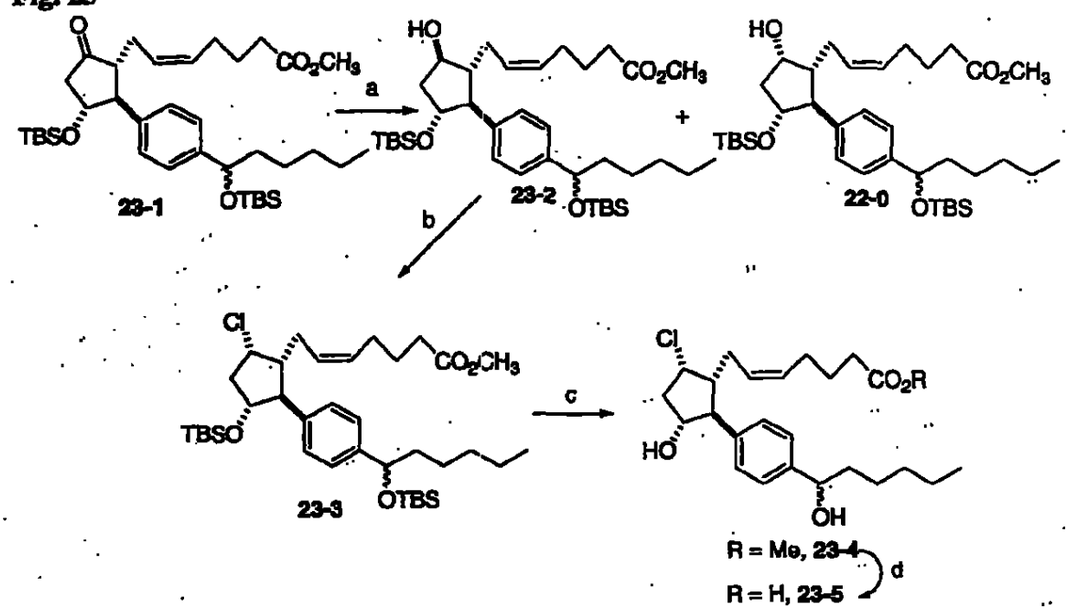
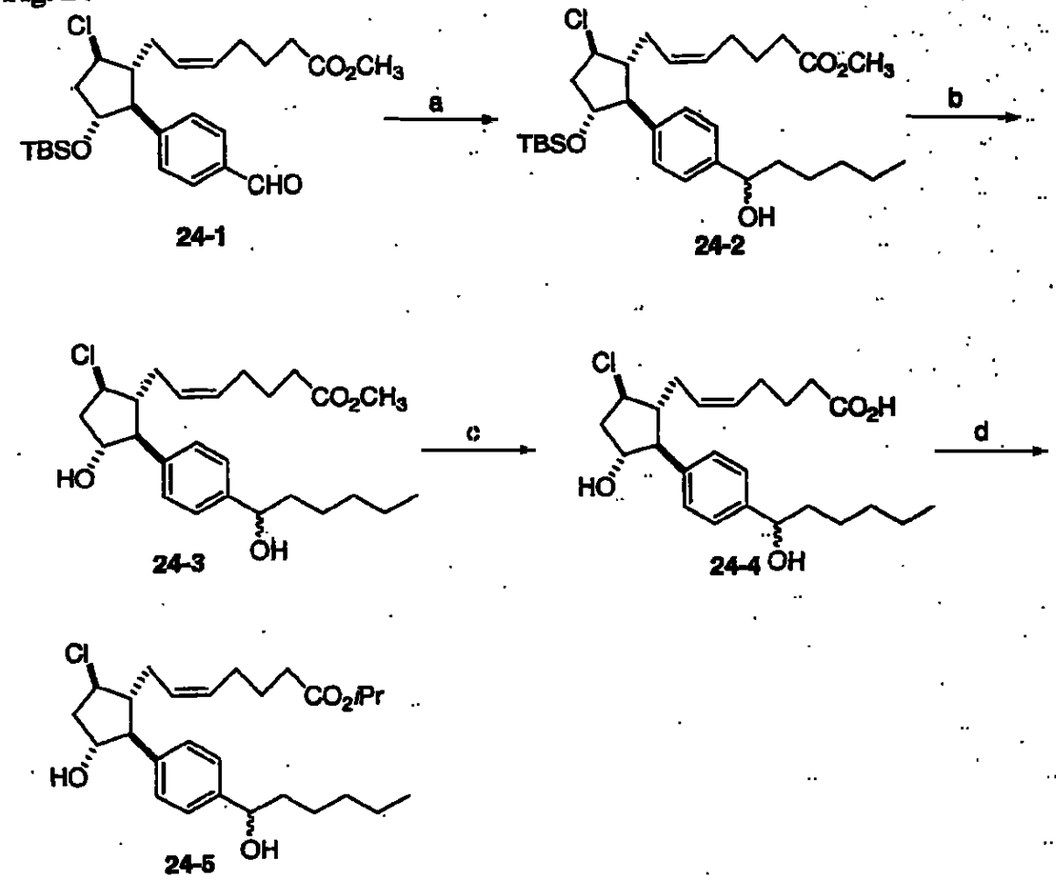
Fig. 23



(a) $NaBH_4$; (b) MsCl, TEA; TBAC 80 °C; (c) HF-piridina, 0 °C; (d) esterasa de hígado de conejo

Fig. 24



(a) *n*-pentilMgBr; (b) HF-piridina 0 °C; (c) 1 M LiOH, THF; (d) 2-yodopropano, DBU, acetona

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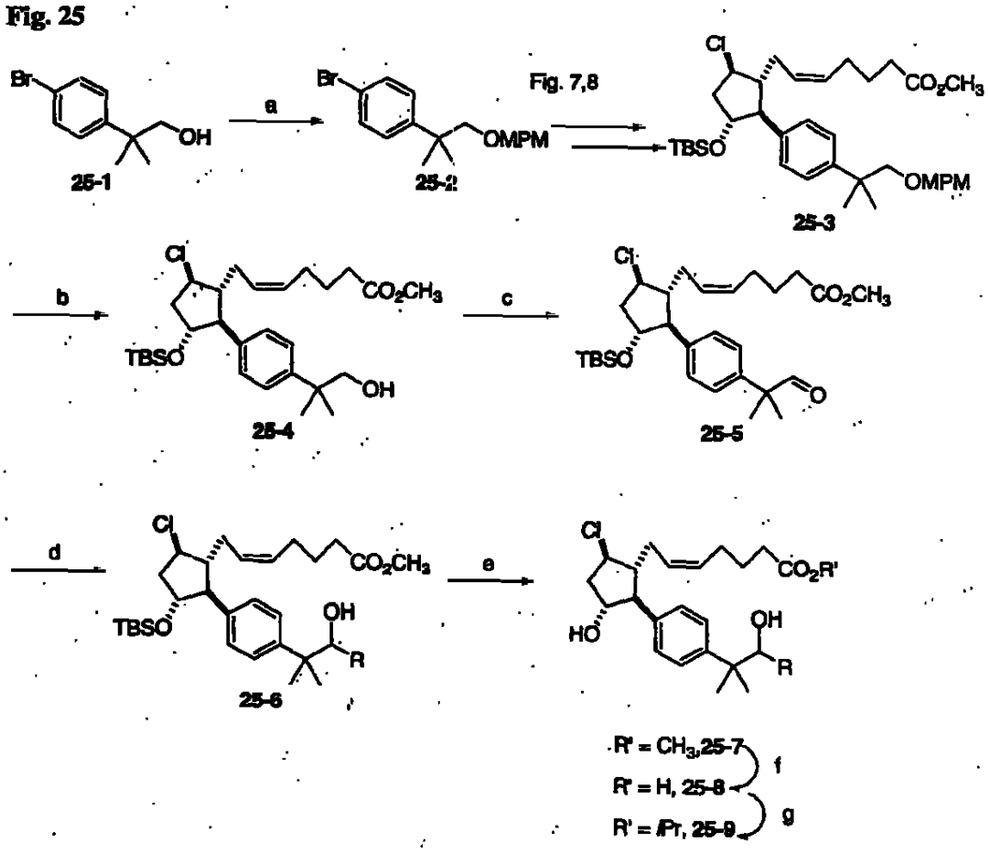
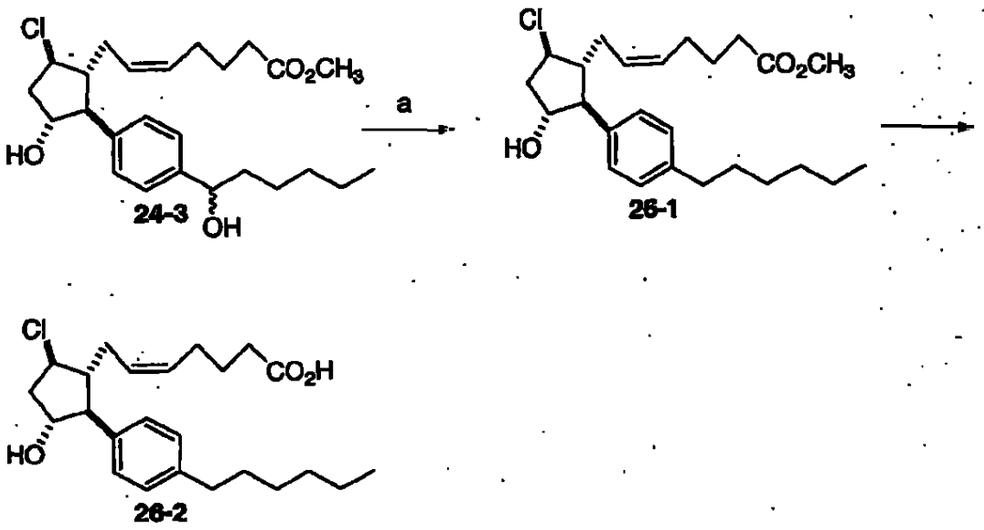
Fig. 25



(a) cloruro de 4-metoxibencilo, NaH; (b) DDQ; (c) TPAP, NMO; (d) RMgX; (e) HF-piridina 0 °C;
(f) 1 M LiOH, THF; (g) 2-yodopropano, DBU, acetona

Fig. 26



(a) Et_3SiH, TFA, $ClCH_2CH_2Cl$; (b) aq. LiOH, THF.

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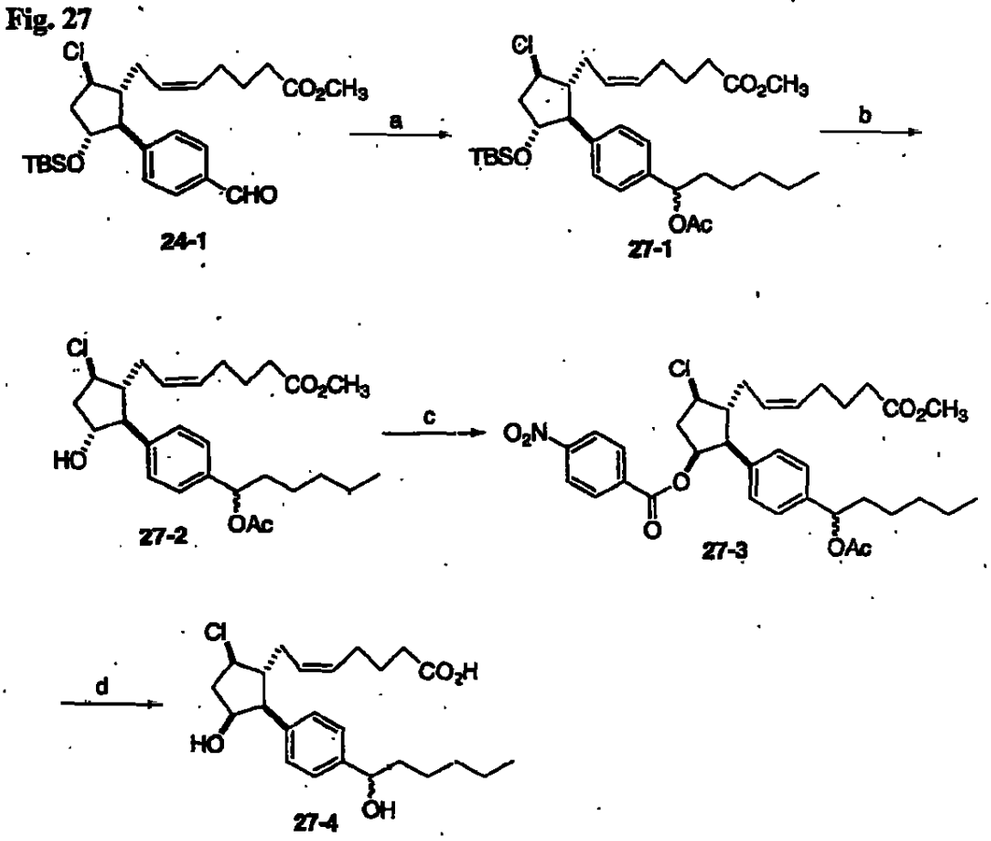
Fig. 27



(a) *n*-pentilMgBr;EtOAc; (b) HF-piridina 0 °C; (c) Ph_3P, diisopropil azodicarboxilato, ácido 4-nitrobenzoico, THF; (d) 1 M LiOH, THF

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-055671- -00000-0000
Fecha: 2007-06-01 16:23:04 Dep: 2020 NUECREACION
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 411 PRESENTACION Folios: 361

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 44,530
FECHA : JUNIO 1 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-055671- -00000-0000
Fecha: 2007-06-01 16:23:04 Dep: 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 361

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CASTILLO PINEDA	CONSIGNACION	BANCO POPULAR	050-00110-6	63495462	01/06/2007	482.000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN		482,000.00
		TOTAL :	$	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-055671- -00000-0000

Fecha. 2007-06-01 16:23:04 Dep. 2020 NUECREACION
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-055671- -00000-0000

Fecha: 2007-06-01 16:23:04 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 361

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REQUISITOS MINIMOS PARA AD PCT

PATENTE DE INVENCION [/] MODELO DE UTILIDAD [ ]

- ◇ Indicación de que se solicita la concesión de una patente [/]
- ◇ Datos de identificación del solicitante o de la persona que 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 se solicita el registro de un Esquema de Trazado [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representación gráfica del esquema trazado [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Edgar Noguera

Firma Responsable

Fecha 01-06-07

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CASTILLO BONILLA JERONIMO
Apoderado(a) y/o Representante de
ALLERGAN, INC.

REFERENCIA	Radicación No.	7 55671
	Solicitud internacional	PCT/US2005/044501
	Fecha inicio fase nacional	12/07/2007
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	10143

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486. Cuando se trate de documentos otorgados en el extranjero, deben legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 24 AGO 2007
adpa11