



Organización CSA Ltda

07

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Industria y Comercio
SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIVISIÓN DE NUEVAS CREACIONES

08-79189

SOLICITUD DE PATENTE DE
INVENCION

TITULO: DERIVADOS DE BENZOINDOL PARA EL TRATAMIENTO DEL
DOLOR

SOLICITANTE: GLAXO GROUP LIMITED

DIRECCIÓN: Glaxo Wellcome House, Berkeley Avenue, Greenford,
Middlesex UB6 ONN Inglaterra

AGK 31/4035

APODERADO: CARLOS R. OLARTE

BOGOTÁ 30 de Julio de 2008

SS

P2008/000137

OLARTE RAISBECK



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-079189- -00000-0000

Fecha: 2008-07-30 16:26:58 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYI Eve: 378 FASENACIONAL
Act. 411 PRESENTACION Folios: 202

PETITORIO - FORMULARIO ÚN PATENTE PCT

ENTRADA EN FASE NACIONAL

P2008/000137

SOLICITUD DE:

1



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

SOLICITANTE (71)

Nombre: GLAXO GROUP LIMITEDDirección: Glaxo Wellcome House, Berkeley
Avenue, Greenford, Middlesex UB06 0NNNacionalidad o Domicilio: EstadounidenseLugar de Constitución: Estados Unidos de
America.

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTEDirección: World Trade Center Torre A,
Calle 100 No. 8A-37 Piso 10Teléfono: 601-7700 Fax: 601-7799E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: 1) Mark, Patrick HEALY, 2) Gerard, Martin, Paul, GIBLIN,
3) Helen, Susanne, PRICE,Dirección: GlaxoSmithKline, New Frontiers Science Park South, Third
Avenue, Harlow, Essex CM19 5AW Gran BretañaNacionalidad o Domicilio: Británicos

5

PCT (86)

Solicitud Internacional No. PCT/EP2007/050991Fecha Febrero 1, 2007Publicación Internacional No. WO 2007/088189Fecha Agosto 9, 2007

6

Título (54) DERIVADOS DE BENZOISOINDOL PARA EL TRATAMIENTO DEL DOLOR

Clasificación Internacional (51) C07D 209/64, C07D 209/66, A61k 31/4035, A61P
25/02Prioridad
SI ☒ NO ☐

(33) País de Origen

GB

GB

Fecha

Febrero 3, 2006

Julio 28, 2006

(31) Número de Solicitud

0602238.8

0615094.0

9

Comprobante de pago No. 08-60,783Fecha Julio 29, 2008

10

ANEXOS

Comprobante de pago de la tasa de presentación de la solicitud.



Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

Poderes, si fuere el caso. *Adjunto copia simple. Ver Expediente No. 06-002051*

Documento de cesión del inventor al solicitante o a su causante.



Declaraciones.



Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).



Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).



Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).



Traducción del examen preliminar internacional efectuado por la IPEA.



De ser el caso, copia del contrato de acceso.



De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.



De ser el caso, certificado de depósito del material biológico.



Arte final 12 x 12.



De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.



De ser el caso, modificaciones efectuadas a la solicitud internacional.



Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-079189- -00000-0000

Fecha: 2008-07-30 16:26:58 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 202

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 60,783
FECHA : JULIO 29 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGD	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	81230225	28/07/2008	2,505,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
		TOTAL :	\$ 501,000.00

SON: QUINIENTOS UN MIL PESOS



RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

GLAXO GROUP LIMITED

PODER DE REPRESENTACION

Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español firmado por James Kerr Milligan

APOSTILLA

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

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229474
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.

Marlen Neira C


MARLEN NEIRA CASTRO
Traductor e Intérprete Oñ.
Inglés - Español - Inglés
Resolución No. 2117 del 7 O

Yo, el infrascrito **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

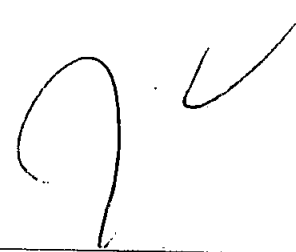
CERTIFICO:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada "**GLAXO GROUP LIMITED**", Sociedad legalmente constituida y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **305979**, con domicilio social en Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debidamente suficientemente autorizado para firmar documentos de esta clase en nombre y representación de dicha Sociedad en virtud de un Poder otorgado por la referida Sociedad fechado 3 de julio de 2002.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy vece de agosto del año dos mil tres.


JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



6

APOSTILLE

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

This public document / Le présent acte public

2. Has been signed by **James Kerr Milligan**
a été signé par

3. Acting in the capacity of **Notary Public**
agissant en qualité de

4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

5. at London/à Londres
6. the/le **14 August 2003**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G229474**

9. Stamp:
timbre: 10. Signature: **J. Garbrah**



[Handwritten signature]

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

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

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

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

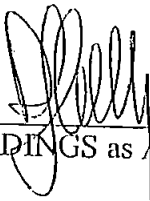
Glaxo Group Limited

El suscrito,

domiciliado en

Greenford, Middlesex UB6 0NN, GB
por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:


Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City/Country/Ciudad,País: Brentford, Middlesex, England

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 August 2007 (09.08.2007)

PCT

(10) International Publication Number
WO 2007/088189 A1

(51) International Patent Classification:

C07D 209/64 (2006.01) A61K 31/4035 (2006.01)
C07D 209/66 (2006.01) A61P 25/02 (2006.01)

(74) Agents: KING, Lawrence et al.; GlaxoSmithKline, 980
Great West Road, Brentford, Middlesex TW8 9GS (GB).

(21) International Application Number:

PCT/EP2007/050991

(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, GT, HN, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS,
LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY,
MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS,
RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date: 1 February 2007 (01.02.2007)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

0602238.8 3 February 2006 (03.02.2006) GB
0615094.0 28 July 2006 (28.07.2006) GB

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SI, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, 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).

(71) Applicant (for all designated States except US): **GLAXO
GROUP LIMITED** [GB/GB]; Glaxo Wellcome House,
Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

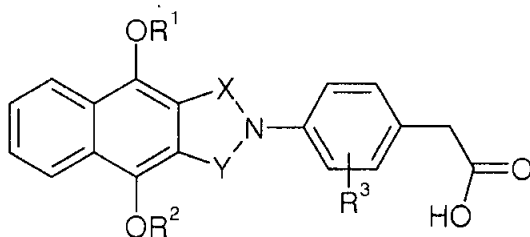
(75) Inventors/Applicants (for US only): **HEALY, Mark,
Patrick** [GB/GB]; GlaxoSmithKline, New Frontiers
Science Park South, Third Avenue, Harlow, Essex CM19
5AW (GB). **GIBLIN, Gerard, Martin, Paul** [GB/GB];
GlaxoSmithKline, New Frontiers Science Park South,
Third Avenue, Harlow, Essex CM19 5AW (GB). **PRICE,
Helen, Susanne** [GB/GB]; GlaxoSmithKline, New Fron-
tiers Science Park South, Third Avenue, Harlow, Essex
CM19 5AW (GB).

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

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

(54) Title: BENZOISINDOLE DERIVATIVES FOR THE TREATMENT OF PAIN



(I)

(57) Abstract: A compound of formula (I) or a
pharmaceutically acceptable derivative thereof,
wherein, R¹, R², R³, X and Y are as defined in the
specification; a process for preparing such com-
pounds; a pharmaceutical composition compris-
ing such compounds; and the use of such com-
pounds in medicine.

BENZOISOINDOLE DERIVATIVES FOR THE TREATMENT OF PAIN.

a

This invention relates to naphthalene derivatives, to processes for their
5 preparation, to pharmaceutical compositions containing them and to their use in
medicine.

The compounds of the present invention are EP₄ receptor agonists.

10 A number of review articles describe the characterization and therapeutic relevance of
the prostanoid receptors as well as the most commonly used selective agonists and
antagonists: *Eicosanoids; From Biotechnology to Therapeutic Applications*, Folco,
Samuelsson, Macclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-
154 and *Journal of Lipid Mediators and Cell Signalling*, 1996, 14, 83-87 and
15 *Prostanoid Receptors, Structure, Properties and Function*, S Narumiya et al,
Physiological Reviews 1999, 79(4), 1193-126.

The EP₄ receptor is a 7-transmembrane receptor and its natural ligand is the
prostaglandin PGE₂. PGE₂ also has affinity for the other EP receptors (types
20 EP₁, EP₂ and EP₃). The prostanoid EP₄ receptor falls into a group of receptors
normally associated with elevation of intracellular cyclic adenosine
monophosphate (cAMP) levels. The EP₄ receptor is associated with smooth
muscle relaxation, intraocular pressure, pain (in particular inflammatory,
neuropathic and visceral pain), inflammation, neuroprotection, lymphocyte
25 differentiation, bone metabolic processes, allergic activities, promotion of sleep,
renal regulation, gastric or enteric mucus secretion and duodenal bicarbonate
secretion. The EP₄ receptor plays an important role in closure of the ductus
arteriosus, vasodepression, inflammation and bone remodeling as reviewed by
Narumiya in *Prostaglandins & Other Lipid Mediators* 2002, 68-69 557-73.

30 A number of publications have demonstrated that PGE₂ acting through the EP₄
receptor subtype, and EP₄ agonists alone, can regulate inflammatory cytokines after

①

an inflammatory stimulus. Takayama *et al* in the *Journal of Biological Chemistry* 2002, 277(46), 44147-54 showed PGE₂ modulates inflammation during inflammatory diseases by suppressing macrophage derived chemokine production via the EP₄ receptor. In *Bioorganic & Medicinal Chemistry* 2002, 10(7), 2103-2110, Maruyama *et al* demonstrate the selective EP₄ receptor agonist (ONO-AE1-437) suppresses LPS induced TNF- α in human whole blood whilst increasing the levels of IL-10. An article in *Anesthesiology*, 2002, 97, 170-176 suggests that a selective EP₄ receptor agonist (ONO-AE1-329) effectively inhibited mechanical and thermal hyperalgesia and inflammatory reactions in acute and chronic monoarthritis.

10

Two independent articles from Sakuma *et al* in *Journal of Bone and Mineral Research* 2000, 15(2), 218-227 and Miyaura *et al* in *Journal of Biological Chemistry* 2000, 275(26), 19819-23, report impaired osteoclast formation in cells cultured from EP₄ receptor knock-out mice. Yoshida *et al* in *Proceedings of the National Academy of Sciences of the United States of America* 2002, 99(7), 4580-4585, by use of mice lacking each of the PGE₂ receptor EP subtypes, identified EP₄ as the receptor that mediates bone formation in response to PGE₂ administration. They also demonstrated a selective EP₄ receptor agonist (ONO-4819) consistently induces bone formation in wild type mice. Additionally, Terai *et al* in *Bone* 2005, 37(4), 555-562 have shown the presence of a selective EP₄ receptor agonist (ONO-4819) enhanced the bone-inducing capacity of rhBMP-2, a therapeutic cytokine that can induce bone formation.

15

20

Further research by Larsen *et al* shows the effects of PGE₂ on secretion in the second part of the human duodenum is mediated through the EP₄ receptor (*Acta. Physiol. Scand.* 2005, 185, 133-140). Also, it has been shown a selective EP₄ receptor agonist (ONO-AE1-329) can protect against colitis in rats (Nitta *et al* in *Scandinavian Journal of Immunology* 2002, 56(1), 66-75).

25

Doré *et al* in *The European Journal of Neuroscience* 2005, 22(9), 2199-206 have shown that PGE₂ can protect neurons against amyloid beta peptide toxicity by acting on EP₂ and EP₄ receptors. Furthermore Doré has demonstrated in *Brain*

30

Research 2005, 1066(1-2), 71-77 that an EP₄ receptor agonist (ONO-AE1-329) protects against neurotoxicity in an acute model of excitotoxicity in the brain.

Woodward et al in Journal of Lipid Mediators 1993, 6(1-3), 545-53 found
5 intraocular pressure could be lowered using selective prostanoid agonists. Two
papers in *Investigative Ophthalmology & Visual Science* have shown the
prostanoid EP₄ receptor is expressed in human lens epithelial cells
(Mukhopadhyay et al 1999, 40(1), 105-12), and suggest a physiological role for
the prostanoid EP₄ receptor in modulation of flow in the trabecular framework of
10 the eye (Hoyng et al 1999, 40(11), 2622-6).

Compounds exhibiting EP₄ receptor binding activity and their uses have been
described in, for example, WO98/55468, WO00/18744, WO00/03980,
WO00/15608, WO00/16760, WO00/21532, WO01010426, EP0855389,
15 EP0985663, WO02/047669, WO02/50031, WO02/50032, WO02/50033,
WO02/064564, WO03/103604, WO03/077910, WO03/086371, WO04/037813,
WO04/067524, WO04/085430, US04/142969, WO05/021508, WO05/105733,
WO05/105732, WO05/080367, WO05/037812, WO05/116010 and
WO06/122403.

20

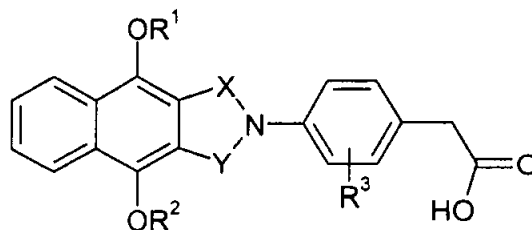
Derivatives of indoprofen such as [4-(1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]-2-propionic acid, sodium salt have been described by Rufer et. al. in
Eur. J. Med. Chem. – Chimica Therapeutica, **1978**, 13, 193.

25

30

12

The present invention provides compounds of formula (I) and/or pharmaceutically acceptable derivatives thereof,



(I)

5

wherein,

R¹ and R² independently represent C₁₋₄ alkyl or difluoromethyl provided that at least one of R¹ and R² represents difluoromethyl;

R³ represents H, F, Cl or Br; and

10 X and Y independently represent C=O or CH₂ provided that at least one of X and Y represents C=O.

In one embodiment of the invention one of R¹ and R² represents C₁₋₄ alkyl and the other represents difluoromethyl. In one embodiment of the invention one of R¹ and R² represents methyl and the other represents difluoromethyl. In one
15 embodiment of the invention one of R¹ and R² represents ethyl and the other represents difluoromethyl. In one embodiment of the invention one of R¹ and R² represents n-propyl and the other represents difluoromethyl. In one embodiment of the invention one of R¹ and R² represents *iso*-propyl and the other represents
20 difluoromethyl. In another embodiment of the invention both R¹ and R² represent difluoromethyl.

In one embodiment of the invention R³ represents F. In another embodiment of the invention R³ represents Cl. In another embodiment of the invention R³
25 represents H. In another embodiment of the invention R³ represents H, F or Cl. In another embodiment of the invention R³ represents F or Cl.

3

In one embodiment of the invention X represents CH₂ and Y represents C=O. In another embodiment of the invention X represents C=O and Y represents CH₂. In another embodiment of the invention both X and Y represent C=O.

- 5 In another embodiment of the invention there is provided a compound of formula (I) selected from the group consisting of:

- (4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;
- 10 (4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid;
- (4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
- (4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;
- 15 (4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
- (4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid;
- 20 (4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;
- (4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;
- {4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- 25 {4-[4-[(Difluoromethyl)oxy]-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- {4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
- 30 {3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

14

- {4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;
- {4-[4-[(Difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
- 5 {3-Chloro-4-[4-[(difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- {4-[4-[(Difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;
- (4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
- 10 (3-Chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;
- (4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;
- 15 {3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- {3-Chloro-4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- {4-[9-[(Difluoromethyl)oxy]-4-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- 20 {4-[4-[(Difluoromethyl)oxy]-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- {4-[9-[(Difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
- 25 {4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
- {4-[9-[(Difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;
- 4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;
- 30 {3-Chloro-4-[4-[(difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

S

- {4-[9-[(Difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
- {4-[4-[(Difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
- 5 {4-[9-[(Difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;
- {4-[4-[(Difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;
- (3-Chloro-4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-
- 10 benzo[f]isoindol-2-yl}phenyl)acetic acid;
- (3-Chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;
- (4-{9-[(Difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
- 15 (4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
- (4-{9-[(Difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;
- (4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-
- 20 benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid; or a pharmaceutically acceptable derivative thereof.

The present invention covers all combinations of particular and preferred embodiments as described herein.

25

As used herein, the term 'C₁₋₄ alkyl' includes straight chain and branched chain alkyl groups containing 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, *iso*-propyl, butyl and *iso*-butyl. The term 'C₁₋₆ alkyl' may be interpreted accordingly.

30

As used herein the term difluoromethyl means -CHF₂.

As used herein F means fluoro, Cl means chloro and Br means bromo.

16

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt, solvate or ester, or salt or solvate of such ester of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof. In one embodiment of the invention pharmaceutically acceptable derivative means salt, solvate or ester, or salt or solvate of such ester. In another embodiment of the invention pharmaceutically acceptable derivative means salt or ester, or salt of such ester.

10

It will be appreciated that, for pharmaceutical use, the salts referred to above will be the pharmaceutically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the pharmaceutically acceptable salts thereof.

15

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary, and tertiary amines; substituted amines including naturally occurring substituted amines; and cyclic amines. Particular pharmaceutically acceptable organic bases include arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tris(hydroxymethyl)aminomethane, and the like. Salts may also be formed from basic ion exchange resins, for example polyamine resins.

30



It will be appreciated that the compound of formula (I) may be produced in vivo by metabolism of a suitable prodrug. Such prodrugs may be for example physiologically acceptable metabolically labile esters of compounds of the general formula (I). These may be formed by esterification of the carboxylic acid group in the parent compound of general formula (I) with, where appropriate, prior protection of any other reactive groups present in the molecule followed by deprotection if required. Examples of such metabolically labile esters include C₁₋₄ alkyl esters e.g. methyl ethyl or t-butyl esters, C₃₋₆ alkenyl esters e.g. allyl substituted or unsubstituted aminoalkyl esters (e.g. aminoethyl, 2-(N,N-diethylamino) ethyl, or 2-(4-morpholino)ethyl esters or acyloxyalkyl esters such as, acyloxymethyl or 1-acyloxyethyl e.g. pivaloyloxymethyl, 1-pivaloyloxyethyl, acetoxymethyl, 1-acetoxyethyl, 1-(1-methoxy-1-methyl)ethyl, carbonyloxyethyl, 1-benzoyloxyethyl, isopropoxycarbonyloxymethyl, 1-isopropoxycarbonyloxyethyl, cyclohexylcarbonyloxymethyl, 1-cyclohexylcarbonyloxyethyl ester, cyclohexyloxycarbonyloxymethyl, 1-cyclohexyloxycarbonyloxyethyl, 1-(4-tetrahydropyranyloxy)carbonyloxyethyl or 1-(4-tetrahydropyranyl)carbonyloxyethyl.

It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures).

Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I) may be used for preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever

✓ 9b

possible, the compounds of the present invention are obtained in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are
5 recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates
10 as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of formula (I).

15

The present invention also includes within its scope all isotopically-labelled compounds of formula (I). Such compounds are identical to those recited in formula (I) except that one or more atoms therein are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass
20 number usually found in nature. Examples of isotopes that can be incorporated into compounds of formula (I) and pharmaceutically acceptable derivatives thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as 2H , 3H , 11C , 13C , 14C , 15N , 17O , 18O , 18F and 36Cl .

25 Isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as 3H , 14C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., 3H , and carbon-14, i.e., 14C , isotopes are particularly preferred for their ease of preparation and detectability. 11C and 18F isotopes are particularly useful in PET (positron
30 emission tomography) and are useful in brain imaging. Further substitution with heavier isotopes such as deuterium, i.e., 2H , can afford certain therapeutic

19

advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula (I) may be prepared by carrying out the synthetic procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The compounds of the invention are EP₄ receptor agonists and may therefore be useful in treating EP₄ receptor mediated diseases.

10

In particular the compounds of formula (I) may be useful in the treatment of pain, for example, chronic articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

20

The compounds of formula (I) may be particularly useful in the treatment of neuropathic pain and symptoms associated therewith. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. Symptoms of neuropathic pain include spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is included pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following

25

30



innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

5

The compounds of formula (I) may also be useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, COPD; gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varioliforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease, diarrhoea, constipation); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthesia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) may also be useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) may also be effective in increasing the latency of HIV infection.

The compounds of formula (I) may also be useful in the treatment of diseases of excessive or unwanted platelet activation such as intermittent claudication, unstable angina, stroke, and acute coronary syndrome (e.g. occlusive vascular diseases).

The compounds of formula (I) may also be useful as a drug with diuretic action, or may be useful to treat overactive bladder syndrome.

5 The compounds of formula (I) may also be useful in the treatment of impotence or erectile dysfunction.

The compounds of formula (I) may also be useful in the treatment of bone disease characterised by abnormal bone metabolism or resorption such as osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, 10 osteoarthritis, ostealgia, osteopenia, calculosis, lithiasis (especially urolithiasis), gout and ankylosing spondylitis, tendinitis and bursitis.

15 The compounds of formula (I) may also be useful in bone remodelling and/or promoting bone generation and/or promoting fracture healing.

The compounds of formula (I) may also be useful for attenuating the hemodynamic side effects of NSAIDs and COX-2 inhibitors.

20 The compounds of formula (I) may also be useful in the treatment of cardiovascular diseases such as hypertension or myocardial ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).

25 The compounds of formula (I) may also be useful in the treatment of neurodegenerative diseases such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, 30 Amyotrophic lateral sclerosis (ALS), motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions

v2

(including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

5 The compounds of formula (I) may also be useful in the treatment of neurological disorders and may be useful as neuroprotecting agents. The compounds of the invention may also be useful in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

10

The compounds of formula (I) may also be useful in the treatment of complications of Type 1 diabetes (e.g. diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy, macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

15

The compounds of formula (I) may also be useful in the treatment of a kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), a liver dysfunction (hepatitis, cirrhosis) and gastrointestinal dysfunction (diarrhoea).

20

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment.

According to a further embodiment of the invention, there is provided a
25 compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another embodiment of the invention, there is provided a compound
of formula (I) or a pharmaceutically acceptable derivative thereof for use in the
30 treatment of a condition which is mediated by the action, or loss of action, of PGE₂ at EP₄ receptors.

23

According to a further embodiment of the invention, there is provided a method of treating a human or animal subject suffering from a condition which is mediated by the action, or by loss of action, of PGE₂ at EP₄ receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further embodiment of the invention there is provided a method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological or bone disease, a neurodegenerative disease or a kidney dysfunction, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to another embodiment of the invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE₂ at EP₄ receptors.

According to another embodiment of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or kidney disorder.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

Thus, in another aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.



While it is possible for the compounds of formula (I) or a pharmaceutically acceptable derivative thereof to be administered as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The formulations of the present invention comprise the compounds of formula (I) or a pharmaceutically acceptable derivative thereof together with one or more acceptable carriers or diluents therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous e.g. by injection or by depot tablet, intradermal, intrathecal, intramuscular e.g. by depot and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy (see for example methods disclosed in 'Remington – The Science and Practice of Pharmacy', 21st Edition, Lippincott, Williams & Wilkins, USA, 2005 and references therein). All methods include the step of bringing into association the compound of formula (I) or a pharmaceutically acceptable derivative thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets (e.g. chewable tablets in particular for paediatric administration) each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an



oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

5 A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert
10 liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

15 Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials,
20 and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

25 Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, hard fat or polyethylene glycol.

30 Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

26

- The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for
- 5 example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.
- 10 In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.
- 15 The EP₄ receptor compounds for use in the present invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, rofecoxib, valdecoxib or parecoxib; 5-lipoxygenase inhibitors; analgesics such as paracetamol; NSAID's, such as diclofenac, indomethacin, nabumetone, naproxen or ibuprofen; leukotriene receptor antagonists; DMARD's
- 20 such as methotrexate; sodium channel blockers, such as lamotrigine; N-type calcium channel antagonists; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin, pregabalin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local
- 25 anaesthetics; 5HT₁ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; EP₁ receptor ligands; EP₂ receptor ligands; EP₃ receptor ligands; EP₁ antagonists; EP₂ antagonists and EP₃ antagonists; cannabinoid receptor agonists; VR1 antagonists. When the compounds are used in combination with other
- 30 therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.



The invention thus provides, in a further embodiment, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

- 5 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either
- 10 sequentially or simultaneously in separate or combined pharmaceutical formulations.

- When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the
- 15 same disease, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

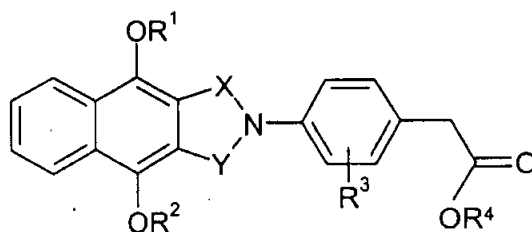
- A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable salts for the treatment of man is from 0.001 to 30 mg/kg body weight
- 20 per day and more particularly 0.1 to 3 mg/kg body weight per day, calculated as the free acid, which may be administered as a single or divided dose, for example one to four times per day. The dose range for adult human beings is generally from 0.1 to 1000 mg/day, such as from 10 to 800 mg/day, preferably 10
- 25 to 200 mg/day, calculated as the free acid.

- The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the
- 30 age and sex of the patient, the precise condition being treated and its severity, the route of administration, and any possible combination therapy that may be being undertaken.

The present invention also provides a process for preparing compounds of formula (I) and pharmaceutically acceptable derivatives thereof.

- 5 Thus, in one embodiment of the invention there is provided a process for preparing a compound of formula (I) wherein one of X and Y represents C=O and the other represents CH₂, and R¹, R² and R³ are as hereinbefore defined in relation to formula (I), which process comprises reacting a compound of formula (II),

10



(II)

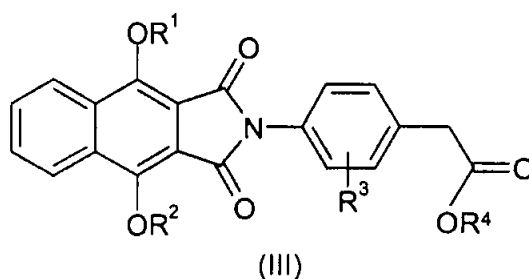
- 15 wherein, one of X and Y represents C=O and the other represents CH₂; R¹, R² and R³ are as hereinbefore defined in relation to formula (I); and R⁴ represents C₁₋₆ alkyl; with a suitable base, such as sodium hydroxide, and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

20

In one embodiment the above-mentioned reaction comprising a compound of formula (II) is performed in a suitable solvent, such as ethanol, under reflux.

- 25 In another embodiment of the present invention there is provided a process for preparing a compound of formula (I), wherein X and Y represent C=O and R¹, R² and R³ are as hereinbefore defined in relation to formula (I), which process comprises adding a compound of formula (III),

29



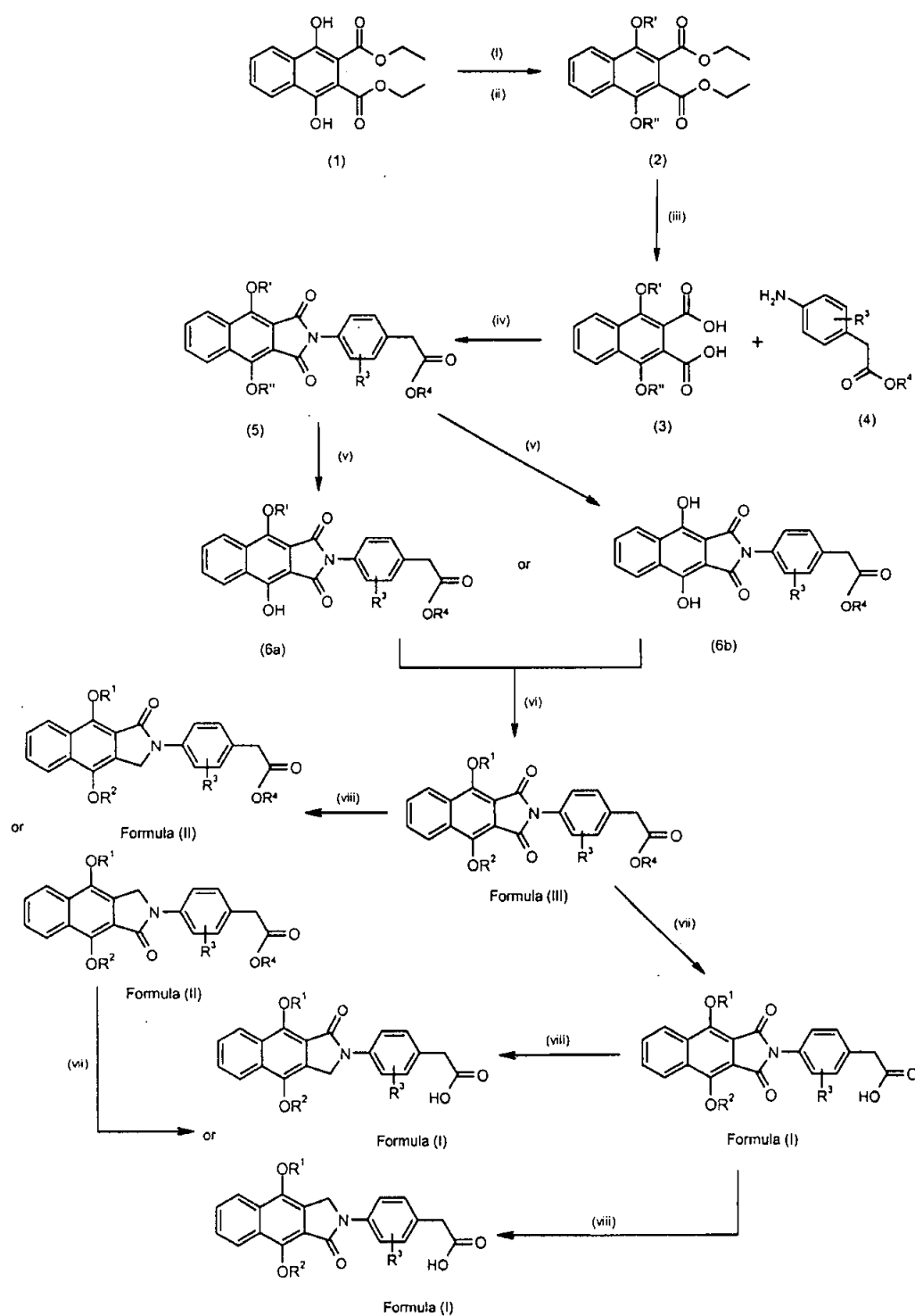
wherein, R^1 , R^2 and R^3 are as hereinbefore defined in relation to formula (I); and
5 R^4 represents C_{1-6} alkyl; to a suitable acid or mixture of acids, such as glacial acetic acid in the presence of hydrochloric acid, and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

10 In one embodiment the above-mentioned reaction comprising a compound of formula (III) is performed at a temperature in the range from about 50 to 110 °C, for a time period in the range from about 2 to 70 hours. In one embodiment, the molar ratio of glacial acetic acid to acid, such as hydrochloric acid, present in the reaction mixture is 1:1.

15

Compounds of formula (II) and (III) may be prepared according to Scheme 1 below:

Scheme 1



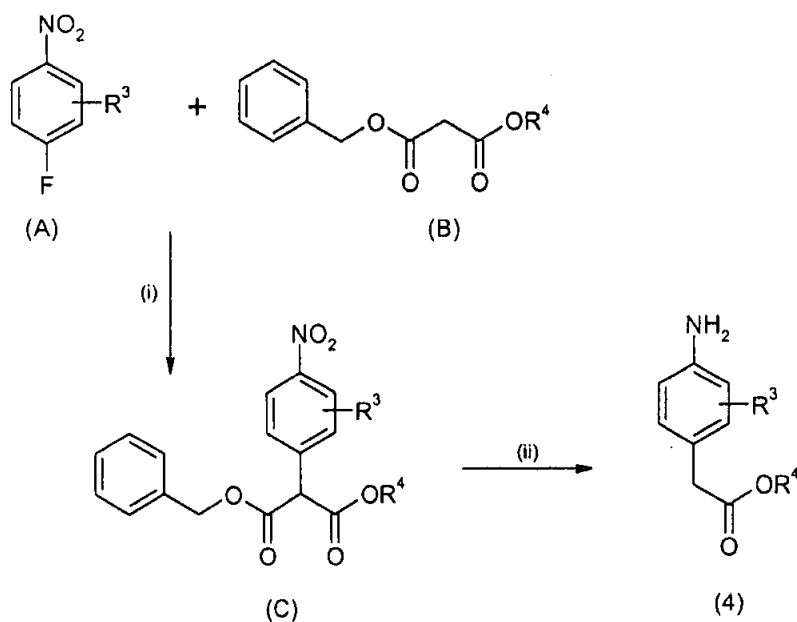
31

- (i) $R'-Br$, K_2CO_3 , $(CH_3)_2CO$; (ii) $R''-Br$, K_2CO_3 , $(CH_3)_2CO$; (iii) $NaOH$, $EtOH/H_2O$; (iv) CH_3CO_2H ; (v) Pd/C , H_2 , $EtOH$ or BBR_3 , CH_2Cl_2 ; (vi) $CClF_2CO_2Na$, Na_2CO_3 , DMF ; or $CHClF_2$, K_2CO_3 , KI , DMF ; (vii) $NaOH$, $EtOH$ or HCl , CH_3CO_2H ; (viii) $NaBH_4$, $MeOH$ or $EtOH$ then TFA , Et_3SiH ; (wherein R' and R'' may be the same or different and represent suitable protecting groups such as $-CH_2Ph$, or one of R' and R'' represents a suitable protecting group and the other represents R^1 or R^2).

Compound (1) may be prepared in accordance with the method disclosed in International Patent Application, Publication Number WO 02/064564.

Compounds of formula (4) where R^3 is F and R^4 is as hereinbefore defined in relation to formulae (II) and (III) may be prepared according to Schemes 2 and 3 below:

15

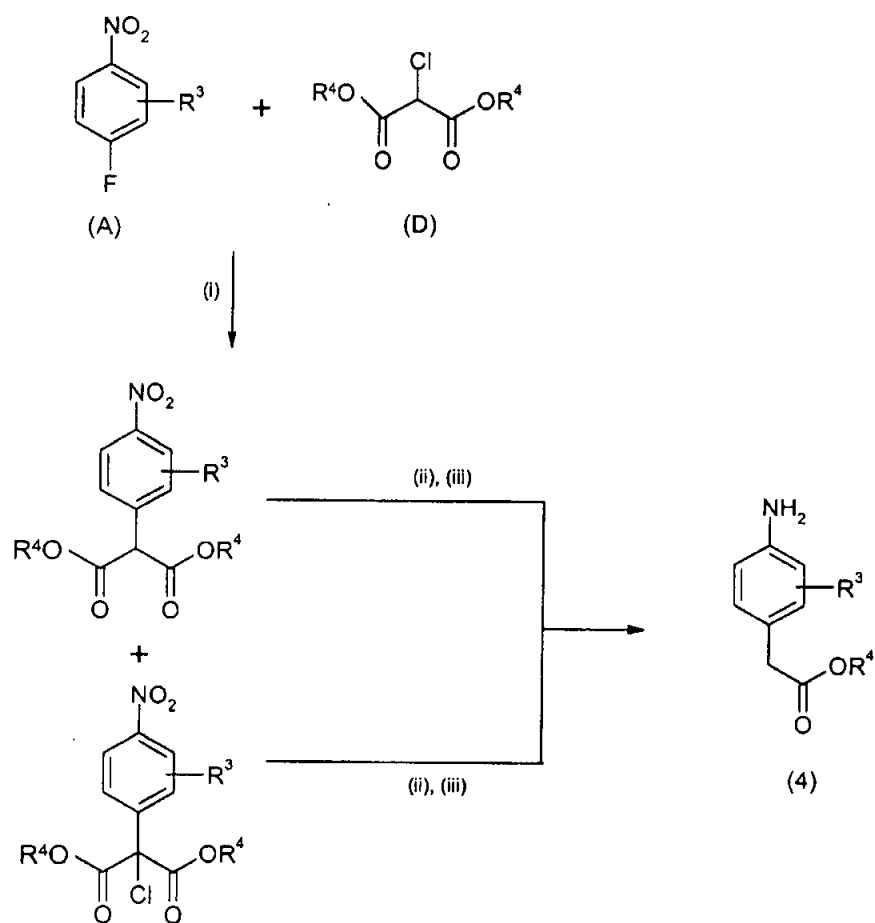
Scheme 2

20

32

(i) NaH, dry DMF; (ii) $\text{NH}_4\text{CO}_2\text{H}$, EtOH, Pd/C.

Scheme 3

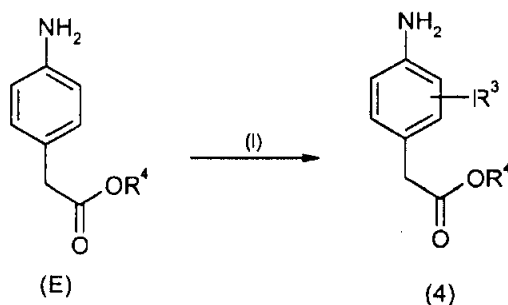


5

(i) NaOH, dry DMF; (ii) $\text{NH}_4\text{CO}_2\text{H}$, EtOH, Pd/C; (iii) NaOH, H_2O , EtOH.

Compounds of formula (4) where R^3 is Br or Cl and R^4 is as hereinbefore defined in relation to formulae (II) and (III) may be prepared according to Scheme 4 below:

15

Scheme 4

5

(i) N-Chlorosuccinamide or N-Bromosuccinamide.

Compounds of formula (A) are commercially available or may be prepared in accordance with methods known in the art (for example, 3,4-difluoronitrobenzene may be purchased from Sigma-Aldrich Co. Ltd.).

Compounds of formula (B) are commercially available or may be prepared in accordance with methods known in the art (for example, benzyl ethyl malonate may be purchased from Sigma-Aldrich Co. Ltd.).

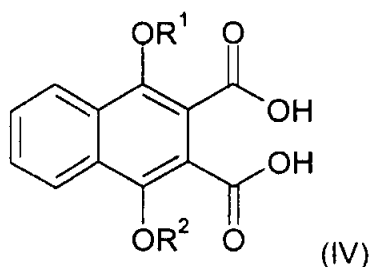
Compounds of formula (D) are commercially available or may be prepared in accordance with methods known in the art (for example, diethylchloromalonate may be purchased from Sigma-Aldrich Co. Ltd.).

20

Compounds of formula (E) are commercially available or may be prepared in accordance with methods known in the art (for example, ethyl 4-aminophenyl acetate may be purchased from Avocado Research).

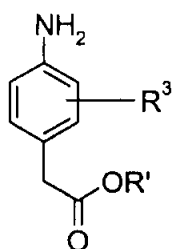
In another embodiment of the invention there is provided a process for preparing a compound of formula (I) or a pharmaceutically acceptable derivative thereof, which process comprises reacting a compound of formula (IV),

34



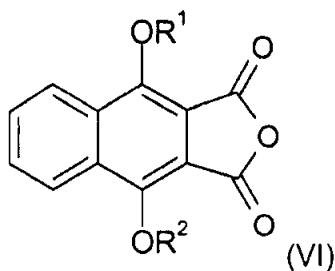
wherein R¹ and R² are as hereinbefore defined in relation to formula (I), with a compound of formula (V),

5



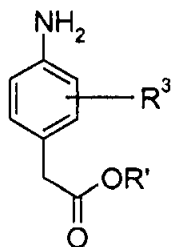
wherein R³ is as hereinbefore defined in relation to formula (I) and R' represents H or C₁₋₆ alkyl, and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

In another embodiment of the invention there is provided a process for preparing a compound of formula (I) or a pharmaceutically acceptable derivative thereof, which process comprises reacting a compound of formula (VI),





wherein R^1 and R^2 are as hereinbefore defined in relation to formula (I), with a compound of formula (V),



(V)

5

wherein R^3 is as hereinbefore defined in relation to formula (I) and R' represents H or C_{1-6} alkyl, and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

10

Compounds of formula (IV), (V) and (VI) are commercially available or may be prepared in accordance with methods known in the art

15

The following Descriptions and Examples illustrate the preparation of the compounds of the invention. Descriptions refer to intermediate compounds.

Abbreviations

	DCM	Dichloromethane
	DMF	Dimethylformamide
20	DMSO	Dimethylsulfoxide
	EtOH	Ethanol
	LC/MS	Liquid chromatography/Mass spectroscopy
	MDAP	Mass Directed Auto Preparation
	MeOH	Methanol
25	TFA	Trifluoroacetic acid

26

Analytical procedures**LC/MS****Column**

- 5 Waters Atlantis (4.6mm x 50mm). Stationary phase particle size, 3 μ m.

Solvents

A: Aqueous solvent = Water + 0.05% Formic Acid

B: Organic solvent = Acetonitrile + 0.05% Formic Acid

10

Method

Time / min	%B
0	3
0.1	3
4	97
4.8	97
4.9	3
5.0	3

- Flow rate, 3ml/mins.
- 15 • Injection volume, 5 μ l.
- Column temperature, 30°C.
- UV detection range, 220 to 330nm.

All retention times are measured in minutes.

20

NMR

¹H NMR spectra were recorded on a Bruker AVANCE 400 NMR spectrometer or a Bruker DPX250 NMR spectrometer. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants (*J*) are in units of hertz (Hz). Splitting

- 25 patterns describe apparent multiplicities and are designated as s (singlet), d

(doublet), t (triplet), q (quartet), dd (double doublet), ddd (double, double doublet), dt (double triplet), m (multiplet), br (broad).

Purification Techniques

- 5 Purification of the Examples may be carried out by conventional methods such as chromatography and/or recrystallisation using suitable solvents. Chromatographic methods include column chromatography, flash chromatography, HPLC (high performance liquid chromatography), SFC (supercritical fluid chromatography), and MDAP (mass directed autopreparation).

10

The term "Biotage" when used herein refers to commercially available pre-packed silica gel cartridges.

Mass Directed Auto Preparation (MDAP)

15 **Column**

Waters Atlantis: 19mm x 100mm (small scale); and 30mm x 100mm (large scale).

Stationary phase particle size, 5µm.

20 **Solvents**

A: Aqueous solvent = Water + 0.1% Formic Acid

B: Organic solvent = Acetonitrile + 0.1% Formic Acid

Make up solvent = Methanol : Water 80:20

Needle rinse solvent = Methanol

25

Methods

Five methods were used depending on the analytical retention time of the compound of interest:

- 30 (1) Large/Small Scale 1.0-1.5 = 5-30% B
(2) Large/Small Scale 1.5-2.2 = 15-55% B
(3) Large/Small Scale 2.2-2.9 = 30-85% B



(4) Large/Small Scale 2.9-3.6 = 50-99% B

Runtime, 13.5 minutes, comprising 10-minute gradient followed by a 3.5 minute column flush and re-equilibration step.

5

(5) Large/Small Scale 3.6-5.0 = 80-99% B

Runtime, 13.5 minutes, comprising 6-minute gradient followed by a 7.5 minute column flush and re-equilibration step.

10

Flow rate

20mls/min (Small Scale) or 40mls/min (Large Scale).

Specification of HPLC purification system:

15

- Column: Supelco LCABZ++, 100mm x 20mm ID, particle size 5µm
- Flow rate: 20ml/min
- Injection volume: 0.5ml
- Temp: RT
- Solvents: A - Aqueous solvent = Water + 0.1% Formic Acid; B - Organic solvent = MeCN/Water 95:5 +0.05% Formic Acid
- Run time: 9 min gradient followed by 5 min column flush and re-equilibration
- Gradient: 30-80% B

20

25

SFC (Super Critical Fluid Chromatography)

Column: Chiralcel OD-H S.F.C. (250 mm x 21.2mm ID; 5 micron particle size) or Ethyl-pyridine column (150 mm length x 21.2 mm ID; 6 micron particle size) or Chiralpak AD (355 and 438) (250 mm length x 21.2 mm ID; 10 micron particle size)

30

Mobile phase: A = Carbon dioxide (supercritical)
B = Methanol
A:B (70:30 - 85:15 w/w isocratic)

35

Flow-rate: 39.4 gmin⁻¹ (= 50 mLmin⁻¹ approx.)
Temperature: 40 °C

39

Back pressure: 100 bar
Detection: U.V. absorbance at 215 nm
Run-time: 25 minutes or 20 minutes

- 5 Sample concentration: 100 mgmL⁻¹ in dimethylformamide
Injection volume: VARIABLE

HPLC purification 1

- 10 Stationary phase: Chiralcel OD
(250 mm length x 21.2 mm ID; 10 micron particle size)

- Mobile phase: Heptane : Ethanol
(ranging from 50:50 v/v isocratic to 90:10 v/v isocratic)
320 = 50:50 v/v
15 353 = 70:30 v/v
354 = 90:10 v/v
356 = 70:30 v/v

- Flow-rate: 17 mLmin⁻¹
Temperature: Ambient
20 Detection: U.V. absorbance at 215 nm
Injection volume: 0.9 mL

HPLC purification 2

- 25 Column: Phenomenex Luna C18 (2) (50 mm x 21.2mm ID;
10 micron particle size)

Mobile phase: A = Acetonitrile + 0.1% v/v trifluoroacetic acid
B = Water + 0.1% v/v trifluoroacetic acid
(Gradient and isocratic methodologies)

- Flow-rate: 20 mLmin⁻¹ approx.
30 Temperature: Ambient
Detection: U.V. absorbance at 215 nm (0 nm band-width)

AD

Sample concentration: 100 mgmL⁻¹ in dimethylformamide

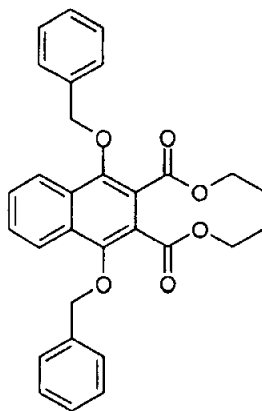
Injection volume: VARIABLE

ID = internal diameter

5

Description 1

Diethyl 1,4-bis[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate

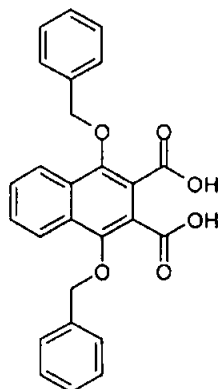


- 10 Benzylbromide (2.95ml, 24.7mmol) was added to a stirred solution of diethyl 1,4-dihydroxy-2,3-naphthalenedicarboxylate (3g, 9.87mmol) and potassium carbonate (3.40g, 24.7mmol) in acetone (100ml). The reaction mixture was refluxed for 18 hours under an atmosphere of argon. The resulting mixture was evaporated and the reaction mixture triturated with water. The resulting tan
- 15 coloured solid was collected by filtration and washed with water then dried under vacuum to give the title compound (5.23g, 10.8mmol). LC/MS: $R_t=4.13$, $[MH]^+$ 485.

Description 2

- 20 *1,4-Bis[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid*

2/1

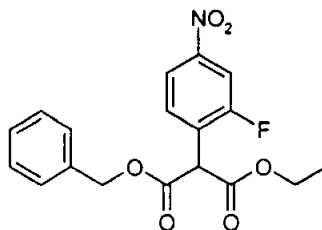


- 5 A mixture of diethyl 1,4-bis[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate (4.78g, 9.88mmol), ethanol (75ml), and 2N aqueous sodium hydroxide solution (75ml) was refluxed for 2 hours. The reaction mixture was cooled and evaporated. This was acidified with HCl (2N) and the resulting cream solid was collected by filtration and washed with water. This was dried under vacuum to
10 give the title compound (3.79g, 8.86mmol). LC/MS: Rt=3.15, [MH]⁺ 427.

Description 3

Ethyl phenylmethyl (2-fluoro-4-nitrophenyl)propanedioate

15



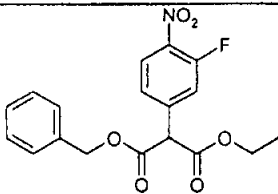
- Sodium hydride (504mg, 12.6mmol) was added portionwise to an ice bath chilled
20 solution of benzyl ethyl malonate (2.9g, 12.6mmol) in dry DMF (20ml) and stirred for 10 minutes. At room temperature 3,4-difluoronitrobenzene (2g, 12.6mmol) was added and stirred under argon. Heated at 100°C for 20 hours. The reaction mixture was cooled and partitioned between 2N Hydrochloric acid (75ml) and ethyl acetate (75ml). The aqueous layer was extracted with ethyl acetate (2x
25 75ml) and the combined organics were evaporated to a yellow oil. Purified by

JL2

chromatography on silica gel eluting with ethyl acetate/hexane (1:4) to give the title compound as a yellow oil (3.86g, 10.6mmol). LC/MS: Rt=3.40, [MH]⁺ 362.

The following compound was prepared in a similar manner to ethyl phenylmethyl (2-fluoro-4-nitrophenyl)propanedioate using the appropriate starting materials.

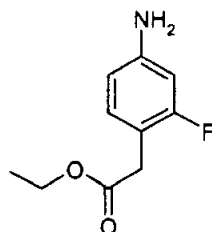
5

	Name	LC/MS
	<i>Ethyl phenylmethyl (3-fluoro-4-nitrophenyl)propanedioate</i>	Rt=3.30 [MH] ⁺ 362

Description 4

Ethyl (4-amino-2-fluorophenyl)acetate

10

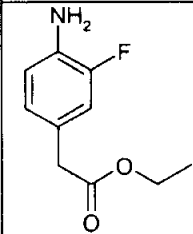


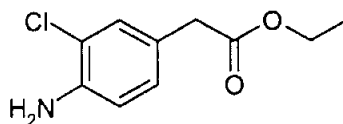
- 15 Ethyl phenylmethyl (2-fluoro-4-nitrophenyl)propanedioate (3.86g, 10.6mmol) dissolved in ethanol, was treated with ammonium formate (6.7g, 10.6mmol) and palladium on carbon 10% paste (380mg) was added under argon. The reaction mixture was refluxed for 3 hours, cooled and filtered. Evaporated and purified by chromatography on silica gel eluting with ethyl acetate/hexane (1:1) to give the
- 20 title compound as a yellow oil (1.26g). LC/MS: Rt=2.10, [MH]⁺ 198.

The following compound was prepared in a similar manner to ethyl (4-amino-2-fluorophenyl)acetate, using the appropriate starting materials.

25

N3

	Name	LC/MS
	<i>Ethyl (4-amino-3-fluorophenyl)acetate</i>	Rt=2.20 [MH] ⁺ 198

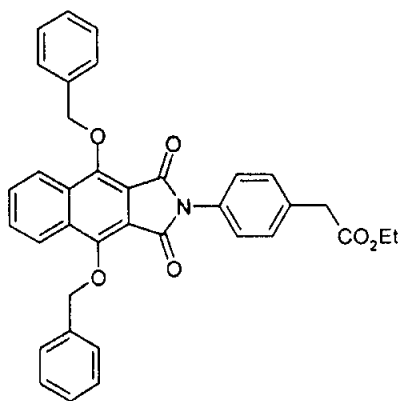
Description 5*Ethyl (4-amino-3-chlorophenyl)acetate*

5 Ethyl-4-aminophenylacetate (20g, 112mmol) was dissolved in chloroform (300ml) and treated with N-chlorosuccinimide (14.92g, 112mmol) and stirred for 15 minutes at room temperature under argon. Reaction mixture was washed with water, brine and dried over magnesium sulphate. Evaporated to a brown oil

10 which was purified by chromatography on silica gel eluting with ethyl acetate (0-45%) in hexane to give the title compound as a orange oil (10.12g, 47.4mmol). LC/MS: Rt=2.59, [MH]⁺ 214.

Description 6

15 *Ethyl (4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*

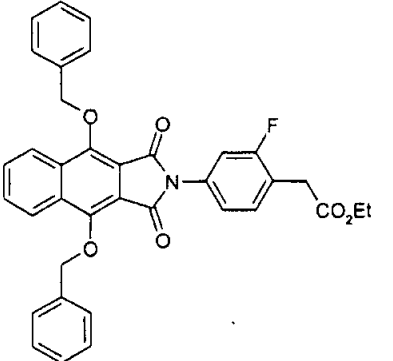


A mixture of 1,4-bis[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid (2.0g, 4.67mmol) and ethyl (4-aminophenyl)acetate (1.67g, 9.35mmol) were heated to 120°C in acetic acid (30ml) for 2 hours. The mixture solidified on standing at room temperature overnight. Water was added and the solid collected by filtration and washed with water. This was dried under vacuum to give the title compound (2.65g, 4.64mmol). LC/MS: Rt=4.24, [MH]⁺ 572.

The following compounds were prepared in a similar manner to ethyl (4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate using the appropriate starting materials.

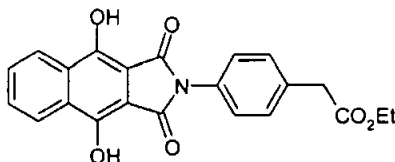
	Name	LC/MS
	<i>Ethyl (3-chloro-4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate</i>	Rt=4.15 [MH] ⁺ 606
	<i>Ethyl (4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate</i>	Rt=4.08 [MH] ⁺ 590

MS

	<i>Ethyl 4-(4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate</i>	Rt=4.10 $[MH]^+ 590$
---	--	-------------------------

Description 7

Ethyl [4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate

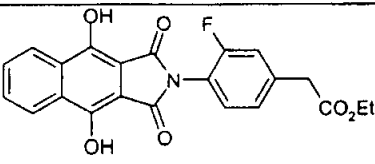
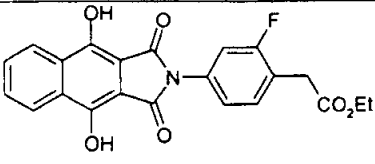


5

10% Palladium on carbon (0.265g) was suspended in ethanol (250ml), to this was added ethyl 4-(4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate (2.65g, 4.64mmol). The reaction was stirred at room temperature under an atmosphere of hydrogen for 3 hours. This was filtered through a bed of celite under a blanket of argon, and washed with dichloromethane. The filtrate was evaporated to give a tan solid (1.52g, 3.89mmol). LC/MS: Rt=3.25, $[MH]^+ 392$.

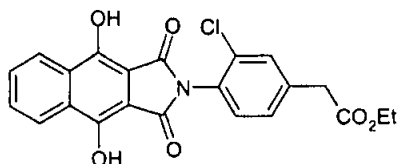
15 The following compounds were prepared in a similar manner to ethyl [4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate using the appropriate starting materials.

20

	Name	LC/MS
	<i>Ethyl [4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-fluorophenyl]acetate</i>	Rt=3.16 [MH] ⁺ 410
	<i>Ethyl [4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-2-fluorophenyl]acetate</i>	Rt=3.24 [MH] ⁺ 410

Description 8

5 *Ethyl [3-chloro-4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate*



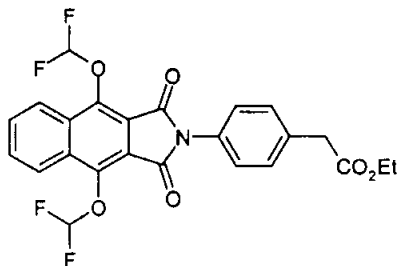
10

To a solution of ethyl (3-chloro-4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate (0.505g, 0.84mmol) in DCM (30ml), cooled to -78°C under an atmosphere of argon, was added boron tribromide (0.24ml, 2.50mmol) drop wise. Stirred at -78°C for 25 minutes. The reaction mixture was quenched with water and warmed to room temperature. This was extracted twice with DCM using a hydrophobic frit. The organic phase was evaporated to an orange solid. Hot trituration in DCM resulted in a yellow solid which was collected by filtration (0.189g, 0.44mmol). The filtrate was purified by chromatography on silica gel, eluting with ethyl acetate (0-70%) in hexane to give the title compound as a yellow solid (0.035g, 0.082mmol). LC/MS: Rt=3.22, [MH]⁺ 426.

47

Description 9

Ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate



5 To a solution of ethyl [4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate (0.200g, 0.51mmol) in dimethylformamide (7ml) was added sodium carbonate (0.163g, 1.53mmol) followed by sodium chlorodifluoroacetate (0.233g, 1.53mmol). The mixture was heated to 100°C for
 10 2.5 hours. Further sodium carbonate (0.054g, 0.51mmol) and sodium chlorodifluoroacetate (0.078g, 0.51mmol) was added, heating continued for 1 hour, and the same amounts added again and heating continued for 30 minutes. The mixture was cooled to room temperature and water added. The resulting brown solid was collected by filtration and washed with water. This was purified
 15 by chromatography on silica gel, eluting with ethyl acetate (0-30%) in hexane to give the title compound as white solid (0.032g, 0.065mmol). LC/MS: Rt=3.61, [MH]⁺ 492.

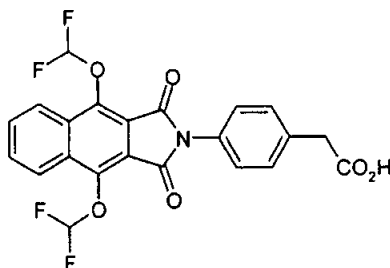
The following compounds were prepared in a similar manner to ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate using the appropriate starting materials.

	Name	LC/MS
	<i>Ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetate</i>	Rt=3.64 [MH] ⁺ 526

	<i>Ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate</i>	Rt=3.61 [MH] ⁺ 510
	<i>Ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate</i>	Rt=3.63 [MH] ⁺ 510

Example 1

5 (4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid



10 Ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate (0.03g, 0.061mmol) was heated to 100°C in a 1:1 mixture of acetic acid : 2N aqueous hydrochloric acid (4ml) for 2 hours. The reaction was cooled to room temperature. On addition of water, the resulting white solid was collected by filtration and washed with water. This was purified by MDAP to give the desired product (0.017g, 0.037mmol). LC/MS: Rt=3.28, [MH]⁺ 464.

15

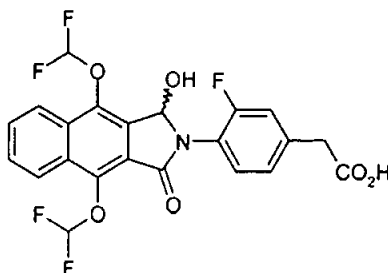
The following compounds were prepared in a similar manner to (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid using the appropriate starting materials.

		Name	LC/MS
Example 2		(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid	Rt=3.23 [MH] ⁺ 498
Example 3		(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid	Rt=3.15 [MH] ⁺ 482
Example 4		(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid	Rt=3.18 [MH] ⁺ 482

Description 10

(4-{4,9-Bis[(difluoromethyl)oxy]-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid

5



To a solution of (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid (0.041g, 0.085mmol) in ethanol
 10 (2ml) and tetrahydrofuran (4ml), was added sodium borohydride (0.019g,

0.51mmol). This was stirred at 0°C for 5 minutes. The mixture was evaporated and then quenched with aqueous saturated ammonium chloride solution until the mixture was pH7. This was extracted x 2 with ethyl acetate, washed with brine, dried over magnesium sulphate and evaporated to give the crude product

5 (0.035g, 0.072mmol). LC/MS: Rt=2.88, [MH]⁺484.

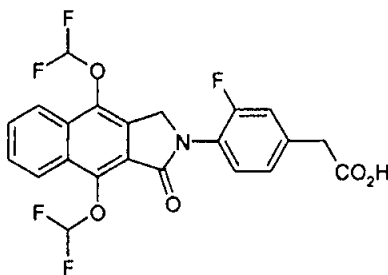
The following compounds were prepared in a similar manner to (4-{4,9-bis[(difluoromethyl)oxy]-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid using the appropriate starting materials.

10

	Name	LC/MS
	(4-{4,9-Bis[(difluoromethyl)oxy]-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid	Rt=2.95 [MH] ⁺ 500
	(4-{4,9-Bis[(difluoromethyl)oxy]-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid	Rt=3.03 [MH] ⁺ 484

Example 5

(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid

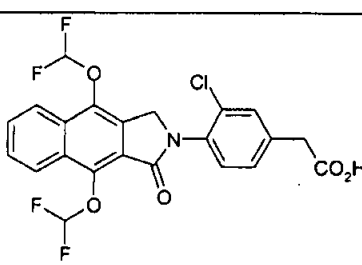
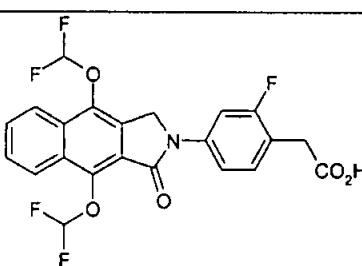


15

51

To a solution of (4-{4,9-bis[(difluoromethyl)oxy]-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid (0.035g, 0.072mmol) in trifluoroacetic acid (2ml) cooled to 0°C, was added triethylsilane (0.019ml, 0.110mmol). Stirring continued at 0°C for 5 minutes and then the mixture was
 5 evaporated. The crude mixture was purified using MDAP. The clean fractions were evaporated to give the title compound (0.015g, 0.033mmol). LC/MS: Rt=3.15, [MH]⁺468.

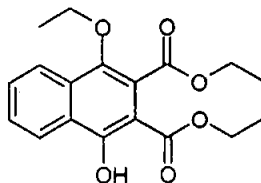
The following compounds were prepared in a similar manner to (4-{4,9-bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid using the appropriate starting materials.
 10

		Name	LC/MS
Example 6		(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid	Rt=3.21 [MH] ⁺ 484
Example 7		(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid	Rt=3.27 [MH] ⁺ 468

Description 11

15 Diethyl 1-(ethyloxy)-4-hydroxy-2,3-naphthalenedicarboxylate

52

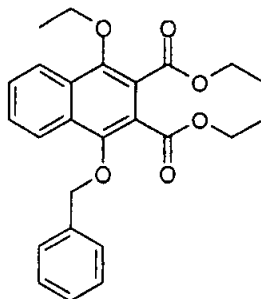


Bromoethane (0.359g, 3.29mmol) was added to a stirred solution of diethyl 1,4-dihydroxy-2,3-naphthalenedicarboxylate (1g, 3.29mmol) and potassium carbonate (0.454g, 3.29mmol) in acetone (25ml). The reaction mixture was refluxed for 24 hours under an atmosphere of argon. The resulting mixture was evaporated and the residue was partitioned between 2 x ethylacetate and water. The combined organics were washed with water and dried over magnesium sulphate. The orange oil was purified by chromatography on silica gel, eluting with ethyl acetate (0-10%) in hexane to give the title compound as a clear oil (0.661g, 1.99mmol). LC/MS: Rt=3.63, [MH]⁺ 331.

The following compounds were prepared in a similar manner to diethyl 1-(ethoxy)-4-hydroxy-2,3-naphthalenedicarboxylate using the appropriate starting materials.

	Name	LC/MS
	<i>Diethyl 1-hydroxy-4-(methoxy)-2,3-naphthalenedicarboxylate</i>	Rt=3.50 [MH] ⁺ 317
	<i>Diethyl 1-hydroxy-4-[(methylethoxy)-2,3-naphthalenedicarboxylate</i>	Rt=3.69 [MH] ⁺ 345
	<i>Diethyl 1-hydroxy-4-(propyloxy)-2,3-naphthalenedicarboxylate</i>	Rt=3.80 [MH] ⁺ 345

53

Description 12*Diethyl 1-(ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate*

5 Benzyl bromide (1.32ml, 11.1mmol) was added to a stirred solution of diethyl 1-(ethyloxy)-4-hydroxy-2,3-naphthalenedicarboxylate (2.45g, 7.38mmol) and potassium carbonate (1.53g, 11.1mmol) in acetone (50ml). The reaction mixture was refluxed for 1 hour under an atmosphere of argon. The resulting mixture was
10 evaporated and the residue was partitioned between 2 x ethylacetate and brine. The combined organics were washed with water and dried over magnesium sulphate. The clear oil was purified by chromatography on silica gel, eluting with ethyl acetate (0-40%) in hexane to give the title compound as clear oil (3.05g, 7.23mmol). LC/MS: Rt=3.77, [MH]⁺ 423.

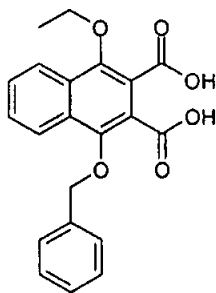
15 The following compounds were prepared in a similar manner to diethyl 1-(ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate using the appropriate starting materials.

	Name	LC/MS
	<i>Diethyl 1-(methoxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate</i>	Rt=3.80 [MH] ⁺ 409
	<i>Diethyl 1-[methylethoxy]-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate</i>	Rt=3.83 [MNH ₄] ⁺ 454
	<i>Diethyl 1-[(phenylmethyl)oxy]-4-(propyloxy)-2,3-naphthalenedicarboxylate</i>	Rt=3.98 [MH] ⁺ 436.9 8

Description 13

1-(Ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid

5



10

A mixture of diethyl 1-(ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate (3.05g, 7.23mmol), ethanol (30ml), and 2N aqueous sodium hydroxide solution (35ml) was refluxed for 3 hours. The reaction mixture was cooled and evaporated. This was acidified with HCl (2N) and extracted with ethyl acetate twice. Combined organics were dried over magnesium sulphate

15

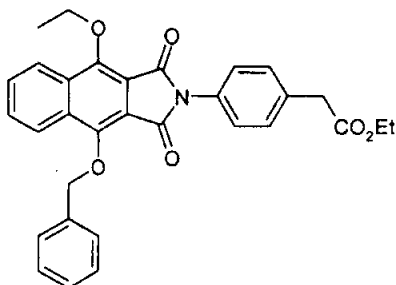
and the solvent evaporated to give the title compound as a white solid (2.55g, 6.97mmol). LC/MS: Rt=2.76, [MH]⁺ 365.

- The following compounds were prepared in a similar manner to 1-(ethyloxy)-4-
 5 [(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid using the appropriate starting materials.

	Name	LC/MS
	1-(Methyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid	Rt=2.62 [MH] ⁺ 351
	1-[Methylethoxy]-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid	Rt=2.87 [MH] ⁺ 381
	1-[(Phenylmethyl)oxy]-4-(propyloxy)-2,3-naphthalenedicarboxylic acid	Rt=2.95 [MH] ⁺ 379

10 Description 14

Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate



A mixture of 1-(ethoxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid (2.55g, 6.97mmol) and ethyl (4-aminophenyl)acetate (2.49g, 13.9mmol) were heated to 120°C in acetic acid (20ml) for 18 hours. The reaction mixture was diluted with brine and extracted with ethyl acetate twice. Combined organics were washed with water then dried over magnesium sulphate, the solvent evaporated to give a brown oil. This was purified by chromatography on silica gel, eluting with ethyl acetate (0-30%) in hexane to give the title compound as a peach coloured solid (2.63g, 5.17mmol). LC/MS: Rt=3.95, [MH]⁺ 510.

The following compounds were prepared in a similar manner to ethyl (4-{4-(ethoxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate using the appropriate starting materials and on some occasions, MDAP was included (denoted by *).

	Name	LC/MS
	Ethyl (4-{4-(methoxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate	Rt=3.94 [MH] ⁺ 496

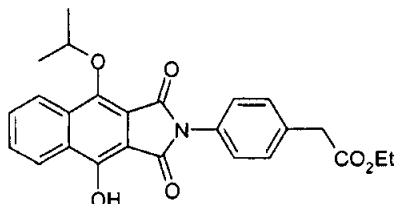
	<i>Ethyl (4-{4-[(methylethoxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=3.96 [MH] ⁺ 524
	<i>Ethyl (3-chloro-4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*</i>	Rt=4.04 [MH] ⁺ 544
	<i>Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate*</i>	Rt=3.95 [MH] ⁺ 528
	<i>Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate*</i>	Rt=3.96 [MH] ⁺ 528
	<i>Ethyl {3-chloro-4-[1,3-dioxo-4-[(phenylmethyl)oxy]-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=4.07 [MH] ⁺ 558

58

	<i>Ethyl {4-[1,3-dioxo-4-[(phenylmethyl)oxy]-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i>	Rt=4.11 [MH] ⁺ 542
	<i>Ethyl {4-[1,3-dioxo-4-[(phenylmethyl)oxy]-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate</i>	Rt=4.13 [MH] ⁺ 542
	<i>Ethyl (3-chloro-4-{4-[(1-methylethyl)oxy]-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*</i>	Rt=4.13 [MH] ⁺ 558
	<i>Ethyl (3-fluoro-4-{4-[(1-methylethyl)oxy]-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*</i>	Rt=3.98 [MH] ⁺ 542
	<i>Ethyl (2-fluoro-4-{4-[(1-methylethyl)oxy]-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*</i>	Rt=4.01 [MH] ⁺ 542

Description 15

Ethyl (4-{4-hydroxy-9-[methylethoxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate



5

10% Palladium on carbon (0.365g) was suspended in ethanol (500ml), to this was added ethyl (4-{4-[methylethoxy]-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate (3.65g, 6.98mmol). The reaction was stirred at room temperature under an atmosphere of hydrogen for 3 hours.

10 This was filtered through a bed of celite under a blanket of argon, and washed with ethanol and dichloromethane. The filtrate was evaporated to give an orange solid (3.05g, 7.04mmol). LC/MS: Rt=3.72, [MH]⁺ 434.

The following compounds were prepared in a similar manner to ethyl (4-{4-hydroxy-9-[methylethoxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate using the appropriate starting materials.

15

	Name	LC/MS
	<i>Ethyl (4-{4-hydroxy-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate</i>	Rt=3.51 [MH] ⁺ 406
	<i>Ethyl (4-{4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate</i>	Rt=3.56 [MH] ⁺ 420

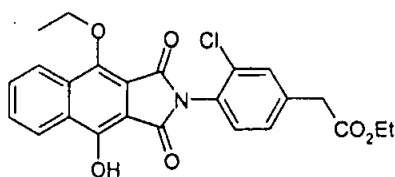
60

	<i>Ethyl {4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i>	Rt=3.50 [MH] ⁺ 437.99
	<i>Ethyl {4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate</i>	Rt=3.63 [MH] ⁺ 438
	<i>Ethyl {3-fluoro-4-[4-hydroxy-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=3.76 [MH] ⁺ 450
	<i>Ethyl {2-fluoro-4-[4-hydroxy-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=3.81 [MH] ⁺ 450
	<i>Ethyl (3-fluoro-4-{4-hydroxy-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate</i>	Rt=3.69 [MH] ⁺ 450
	<i>Ethyl (2-fluoro-4-{4-hydroxy-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate</i>	Rt=3.74 [MH] ⁺ 452

Description 16

Ethyl {3-chloro-4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2 yl]phenyl}acetate

61



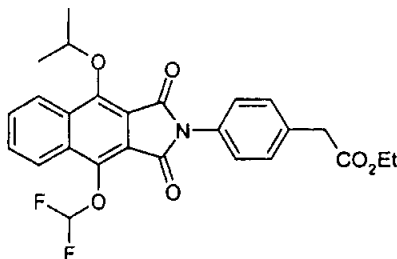
- To a solution of ethyl (3-chloro-4-{4-(ethoxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate (1.75g, 3.22mmol) in DCM (40ml), cooled to -78°C under an atmosphere of argon, was added boron tribromide (0.31ml, 3.22mmol) drop wise. Stirred at -78°C for 12 minutes. A further addition of boron tribromide (0.31ml, 3.22mmol) was made drop wise. The reaction mixture was quenched with water and warmed to room temperature. This was extracted twice with DCM using a hydrophobic frit. The organic phase was evaporated to an yellow solid. This was purified by chromatography on silica gel, eluting with ethyl acetate (0-60%) in hexane to give the title compound as a orange oily solid (0.920g, 2.03mmol). LC/MS: Rt=3.65, [MH]⁺ 454.
- The following compounds were prepared in a similar manner to ethyl (3-chloro-4-[4-(ethoxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl)acetate using the appropriate starting materials.

	Name	LC/MS
	Ethyl (3-chloro-4-[4-hydroxy-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl)acetate	Rt=3.80 [MH] ⁺ 468
	Ethyl (3-chloro-4-{4-[(1-methylethyl)oxy]-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate	Rt=3.77 [MH] ⁺ 468

62

Description 17

Ethyl (4-{4-[(difluoromethyl)oxy]-9-[methylethoxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate



5

To a solution of ethyl (4-{4-hydroxy-9-[methylethoxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate (0.25g, 0.577mmols) in dimethylformamide (10ml), was added potassium carbonate (0.120g, 0.866mmol) followed by potassium iodide (0.048g, 0.289mmol). Chloro(difluoro)methane was bubbled through the solution at 80°C for 2 hours. Bubbling was ceased and heating continued for 25 hours. The cooled mixture was partitioned between 2x ethyl acetate and brine, the combined organics were washed with water, dried over sodium sulphate and evaporated down to a yellow oil. This was purified by chromatography on silica gel, eluting with ethyl acetate (0-30%) in hexane to give the title compound as a white coloured solid (0.142g, 0.294mmol). LC/MS: Rt=3.82, [MH]⁺ 484.

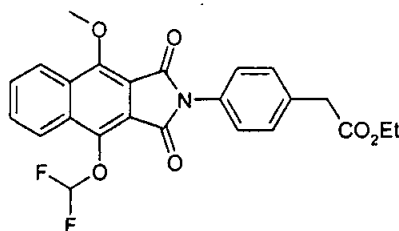
10

15

Description 18

Ethyl (4-{4-[(difluoromethyl)oxy]-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate

20

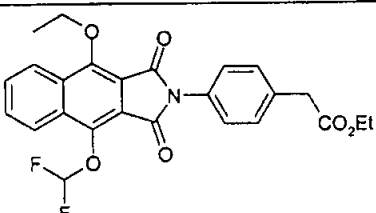
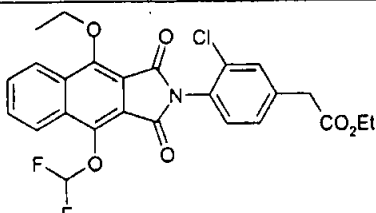
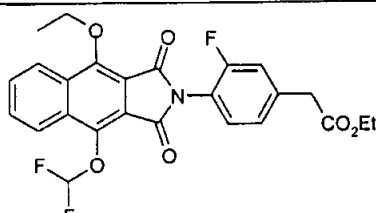


To a solution of ethyl (4-{4-hydroxy-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate (0.700g, 1.73mmol) in dimethylformamide

b7

- (25ml) was added sodium carbonate (0.220g, 2.07mmol) followed by sodium chlorodifluoroacetate (0.315g, 2.07mmol). The mixture was heated to 100°C for 1.5 hours. Further sodium carbonate (0.220g, 2.07mmol) and sodium chlorodifluoroacetate (0.315g, 2.07mmol) was added, heating continued for 2 hours, and the same amounts added again. The mixture was cooled to room temperature and water added. The resulting beige solid was collected by filtration and washed with water. This was dried under vacuum (0.680g, 1.49mmol). LC/MS: Rt=3.62, [MH]⁺ 456.

- 10 The following compounds was prepared in a similar manner to ethyl {4-[(difluoromethyl)oxy]-9-(methoxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl}acetate using the appropriate starting materials.

	Name	LC/MS
	<i>Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethoxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=3.77 [MH] ⁺ 470
	<i>Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-9-(ethoxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=3.69 [MH] ⁺ 503.89
	<i>Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethoxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i>	Rt=3.73 [MH] ⁺ 488

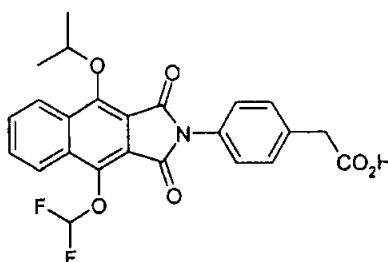
	<i>Ethyl {4-[4-((difluoromethyl)oxy)-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate</i>	Rt=3.62 [MH] ⁺ 488
	<i>Ethyl {3-chloro-4-[4-((difluoromethyl)oxy)-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=3.86 [MH] ⁺ 516
	<i>Ethyl {4-[4-((difluoromethyl)oxy)-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i>	Rt=3.83 [MH] ⁺ 502
	<i>Ethyl {4-[4-((difluoromethyl)oxy)-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate</i>	Rt=3.85 [MH] ⁺ 502
	<i>Ethyl {3-chloro-4-[4-((difluoromethyl)oxy)-9-((1-methylethyl)oxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=3.84 [MH] ⁺ 516
	<i>Ethyl {4-[4-((difluoromethyl)oxy)-9-((1-methylethyl)oxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i>	Rt=3.76 [MH] ⁺ 502

69

	<i>Ethyl (4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate</i>	Rt=3.75 [MH] ⁺ 502
--	--	----------------------------------

Example 8

(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid



5

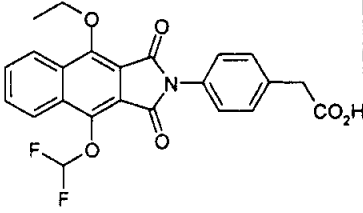
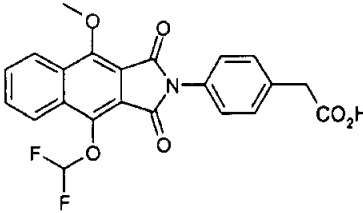
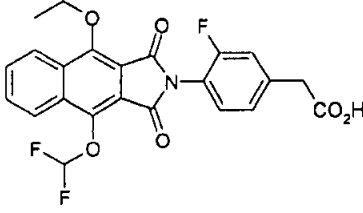
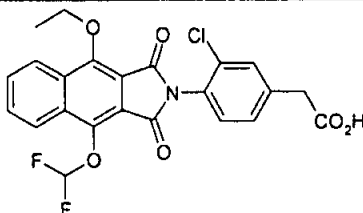
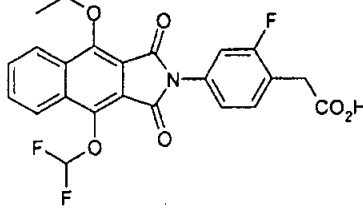
Ethyl (4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate (0.14g, 0.289mmol) was heated to 100°C in a 1:1 mixture of acetic acid : 2N aqueous hydrochloric acid (8ml) for 1 hour. The reaction was cooled to room temperature. On addition of water, the resulting white solid was collected by filtration and washed with water. This was dried in the vacuum oven to give the title compound (0.120g, 0.026mmol). LC/MS: Rt=3.36, [MH]⁺ 456.

15

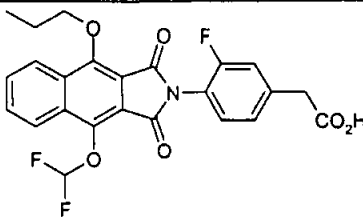
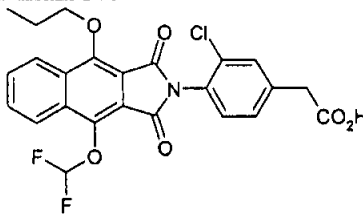
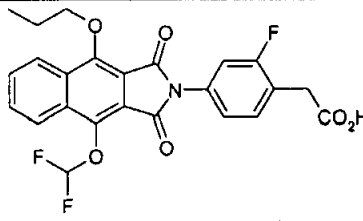
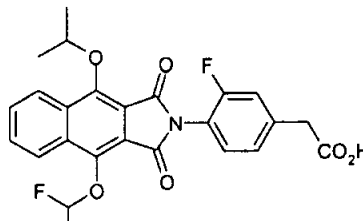
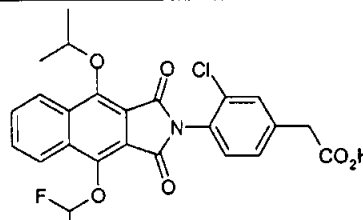
The following compounds were prepared in a similar manner to (4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid using the appropriate starting materials.

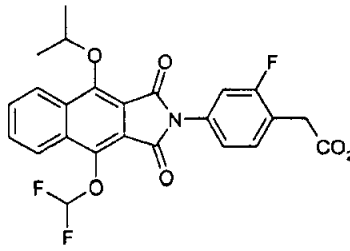
20

fb

		Name	LC/MS
Example 9		{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid	Rt=3.29 [MH] ⁺ 442
Example 10		{4-[4-[(Difluoromethyl)oxy]-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid	Rt=3.14 [MH] ⁺ 428
Example 11		{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid	Rt=3.33 [MH] ⁺ 460
Example 12		{3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid	Rt=3.33 [MH] ⁺ 476
Example 13		{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid	Rt=3.25 [MH] ⁺ 460

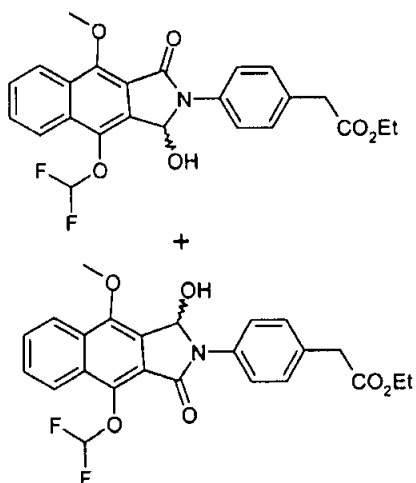
62

Example 14		{4-[4- [(Difluoromethyl)oxy]- 1,3-dioxo-9- (propyloxy)-1,3- dihydro-2H- benzo[f]isoindol-2-yl]- 3-fluorophenyl}acetic acid	Rt=3.39 [MH] ⁺ 474
Example 15		{3-chloro-4-[4- [(Difluoromethyl)oxy]- 1,3-dioxo-9- (propyloxy)-1,3- dihydro-2H- benzo[f]isoindol-2- yl]phenyl}acetic acid	Rt=3.51 [MH] ⁺ 490
Example 16		{4-[4- [(Difluoromethyl)oxy]- 1,3-dioxo-9- (propyloxy)-1,3- dihydro-2H- benzo[f]isoindol-2-yl]- 2-fluorophenyl}acetic acid	Rt=3.41 [MH] ⁺ 474
Example 17		(4-[4- [(Difluoromethyl)oxy]- 9-[(1-methylethyl)oxy]- 1,3-dioxo-1,3-dihydro- 2H-benzo[f]isoindol-2- yl]-3- fluorophenyl)acetic acid	Rt=3.34 [MH] ⁺ 474
Example 18		(3-Chloro-4-[4- [(difluoromethyl)oxy]-9- [(1-methylethyl)oxy]- 1,3-dioxo-1,3-dihydro- 2H-benzo[f]isoindol-2- yl]phenyl)acetic acid	Rt=3.41 [MH] ⁺ 490

Example 19		(4-{4- [(Difluoromethyl)oxy]- 9-{(1-methylethyl)oxy}- 1,3-dioxo-1,3-dihydro- 2H-benzo[f]isoindol-2- yl}-2- fluorophenyl)acetic acid	Rt=3.36 [MH] ⁺ 474
-----------------------	---	--	----------------------------------

Description 19

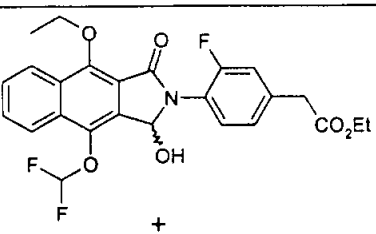
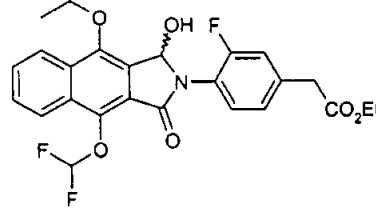
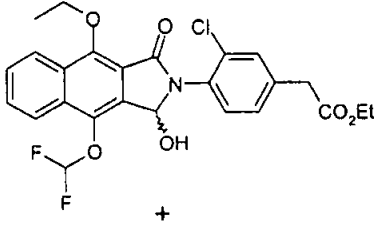
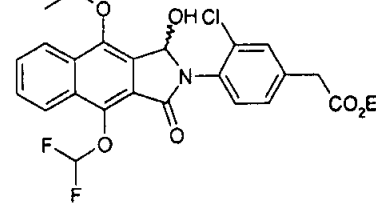
Ethyl {4-[4-[(difluoromethyl)oxy]-1-hydroxy-9-(methyloxy)-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate and Ethyl {4-[4-[(difluoromethyl)oxy]-3-hydroxy-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate



To a solution of ethyl {4-[4-[(difluoromethyl)oxy]-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate (0.455g, 1.00mmol) in ethanol (4ml) and tetrahydrofuran (8ml), was added sodium borohydride (0.114g, 3.0mmol) portion wise. The reaction was stirred for 1 hour then a further portion of sodium borohydride (0.114g, 3.0mmol) was added, stirring continued at room temperature for 1 hour. The mixture was quenched with aqueous saturated ammonium chloride solution and then evaporated. This was extracted with ethyl acetate twice, dried over magnesium sulphate and evaporated to give the crude product (0.515g, 1.13mmol). LC/MS: Rt=3.21 & 3.26, [MH]⁺457.97.

69

The following compounds were prepared in a similar manner to ethyl {4-[4-
 [(difluoromethyl)oxy]-1-hydroxy-9-(methyloxy)-3-oxo-1,3-dihydro-2H-
 benzo[f]isoindol-2-yl]phenyl}acetate and ethyl {4-[4-[(difluoromethyl)oxy]-3-
 5 hydroxy-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate
 using the appropriate starting materials.

	Name	LC/MS
 	<i>Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i> <i>Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-3-hydroxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i>	Rt=3.35, 3.38 [MH] ⁺ 490
 	<i>Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i> <i>Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-3-hydroxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=3.43, 3.47 [MH] ⁺ 506

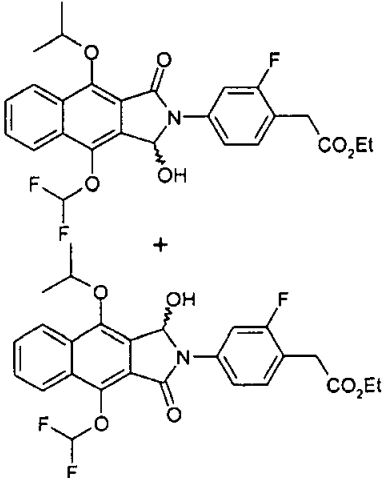
20

	<i>Ethyl {4-[4-((difluoromethyl)oxy)-9-(ethyloxy)-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate</i> <i>Ethyl {4-[4-((difluoromethyl)oxy)-9-(ethyloxy)-3-hydroxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate</i>	Rt=3.43 [MH]⁺490
	<i>Ethyl {3-chloro-4-[4-((difluoromethyl)oxy)-1-hydroxy-3-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i> <i>Ethyl {3-chloro-4-[4-((difluoromethyl)oxy)-3-hydroxy-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=3.60 [MH]⁺520
	<i>Ethyl {4-[4-((difluoromethyl)oxy)-1-hydroxy-3-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate –</i> <i>Ethyl {4-[4-((difluoromethyl)oxy)-3-hydroxy-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i>	Rt=3.52 [MH]⁺504

21

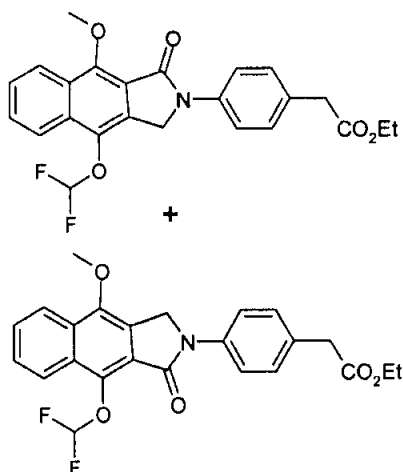
	<i>Ethyl {4-[4-[(difluoromethyl)oxy]-1-hydroxy-3-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate -</i> <i>Ethyl {4-[4-[(difluoromethyl)oxy]-3-hydroxy-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate</i>	Rt=3.64 [MH]⁺504
	<i>Ethyl (3-chloro-4-{4-[(difluoromethyl)oxy]-1-hydroxy-9-[(1-methylethyl)oxy]-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate</i> <i>Ethyl (3-chloro-4-{4-[(difluoromethyl)oxy]-3-hydroxy-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate</i>	Rt=3.53 [MH]⁺520
	<i>Ethyl (4-{4-[(difluoromethyl)oxy]-1-hydroxy-9-[(1-methylethyl)oxy]-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl)acetate</i> <i>Ethyl (4-{4-[(difluoromethyl)oxy]-3-hydroxy-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl)acetate</i>	Rt=3.44 [MH]⁺504

52

	<i>Ethyl 4-[4-[(difluoromethyl)oxy]-1-hydroxy-9-[(1-methylethyl)oxy]-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl]acetate</i> <i>Ethyl 4-[4-[(difluoromethyl)oxy]-3-hydroxy-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl]acetate)</i>	Rt=3.57 [MH]⁺504
---	--	--

Description 20

Ethyl 4-[4-[(difluoromethyl)oxy]-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl]acetate and ethyl 4-[9-[(difluoromethyl)oxy]-4-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl]acetate

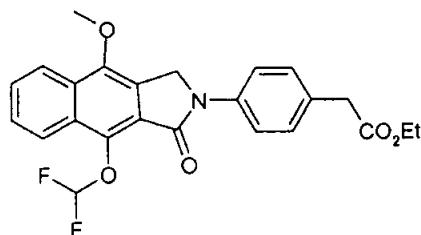


To a solution of ethyl 4-[4-[(difluoromethyl)oxy]-3-hydroxy-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl]acetate and ethyl 4-[4-[(difluoromethyl)oxy]-1-hydroxy-9-(methyloxy)-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl]acetate (0.457g, 1.00mmol) in trifluoroacetic acid (5ml) cooled to 0°C, was added triethylsilane (0.089ml, 0.561mmol). Stirring continued at 0°C for 15 minutes, and then the mixture was evaporated. The

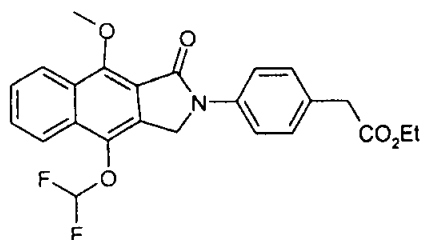
73

crude mixture was purified using chromatography on silica gel, eluting with ethyl acetate (0-30%) in hexane. The isomers were then separated using super critical fluid chromatography.

- 5 *Ethyl {4-[9-[(difluoromethyl)oxy]-4-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate* (0.036g, 0.082mmol). LC/MS: Rt=3.75, [MH]⁺442



- 10 *Ethyl {4-[4-[(difluoromethyl)oxy]-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate* (0.036g, 0.082mmol). LC/MS: Rt=3.60, [MH]⁺442

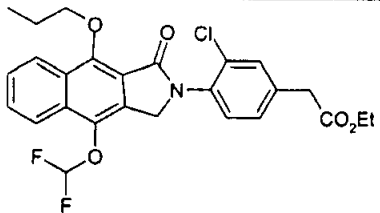
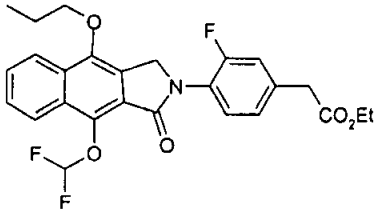
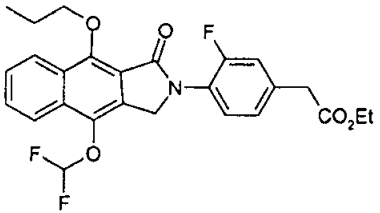
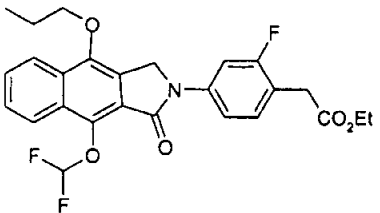
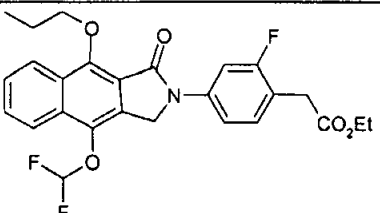
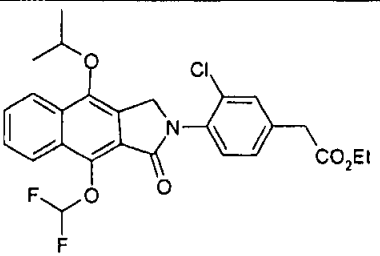


- 15 The following compounds were prepared in a similar manner to ethyl {4-[4-[(difluoromethyl)oxy]-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate and ethyl {4-[9-[(difluoromethyl)oxy]-4-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate using the appropriate starting
20 materials and the isomers separated using high performance liquid chromatography or super critical fluid chromatography.

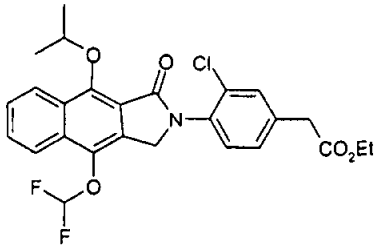
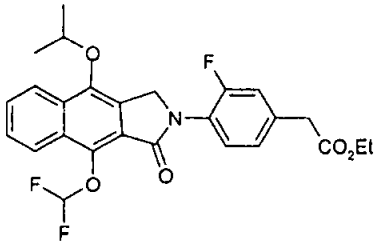
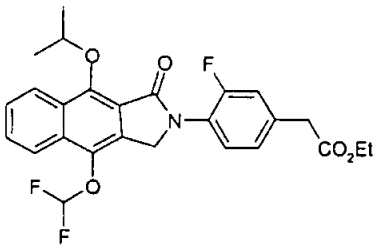
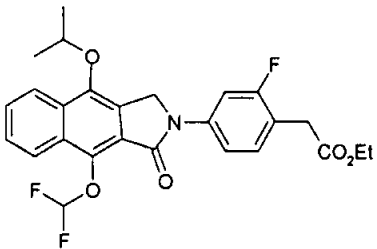
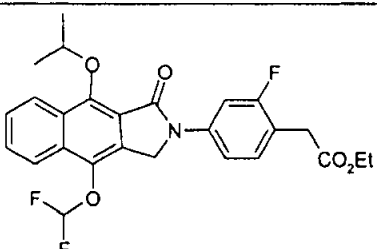
25

	Name	LC/MS
	<i>Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=3.69 [MH] ⁺ 490
	<i>Ethyl {3-chloro-4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate</i>	Rt=3.75 [MH] ⁺ 490
	<i>Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i>	Rt=3.60 [MH] ⁺ 474
	<i>Ethyl {4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i>	Rt=3.65 [MH] ⁺ 474
	<i>Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate</i>	Rt=3.70 [MH] ⁺ 474
	<i>Ethyl {4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate</i>	Rt=3.73 [MH] ⁺ 474

7/5

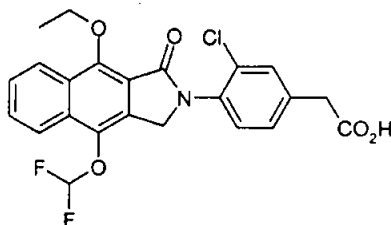
	<i>Ethyl (3-chloro-4-[(difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl}acetate</i>	Rt=3.83 [MH] ⁺ 504
	<i>Ethyl (4-[9-[(difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i>	Rt=3.89 [MH] ⁺ 488
	<i>Ethyl (4-[4-[(difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate</i>	Rt=3.84 [MH] ⁺ 488
	<i>Ethyl (4-[9-[(difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate</i>	Rt=3.93 [MH] ⁺ 488
	<i>Ethyl (4-[4-[(difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate</i>	Rt=3.93 [MH] ⁺ 488
	<i>Ethyl (3-chloro-4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl}acetate</i>	Rt=3.81 [MH] ⁺ 504

26

	<i>Ethyl (3-chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate</i>	Rt=3.76 [MH] ⁺ 504
	<i>Ethyl (4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate</i>	Rt=3.77 [MH] ⁺ 488
	<i>Ethyl (4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate</i>	Rt=3.73 [MH] ⁺ 488
	<i>Ethyl (4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate</i>	Rt=3.88 [MH] ⁺ 488
	<i>Ethyl (4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate</i>	Rt=3.91 [MH] ⁺ 488

**Example 20**

{3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid



5

Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate (0.141g, 0.288mmol) was heated to reflux in a 1:1 mixture of 2N sodium hydroxide : ethanol (6ml) for 1.5 hours. The reaction was cooled to room temperature. The ethanol was evaporated and the mixture
 10 acidified with 2N aqueous hydrochloric acid. The resulting white solid was collected by filtration, washed with water and dried under vacuum to give the title compound (0.125g, 0.271mmol). LC/MS: Rt=3.19, [MH]⁺ 462.

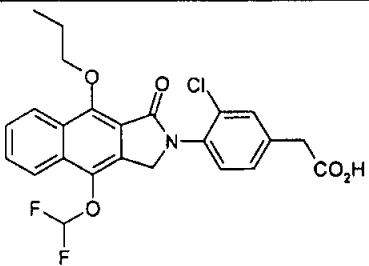
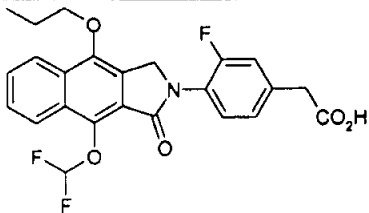
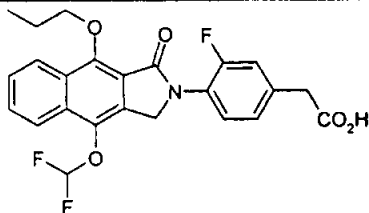
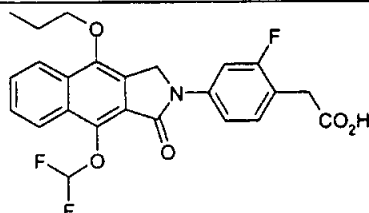
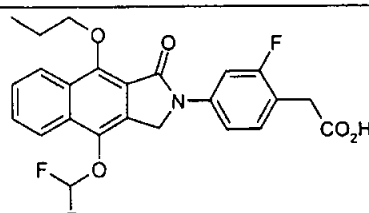
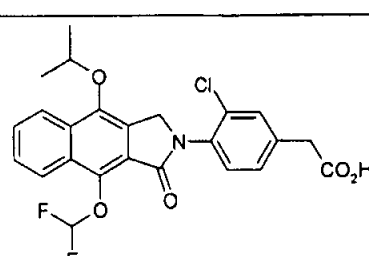
The following compounds were prepared in a similar manner to {3-Chloro-4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid using the appropriate starting materials. Some compounds
 15 underwent an alternative aqueous work-up with ethyl acetate extraction followed by purification by MDAP (denoted by *), or were purified by trituration with diethyl ether (denoted by #).

20

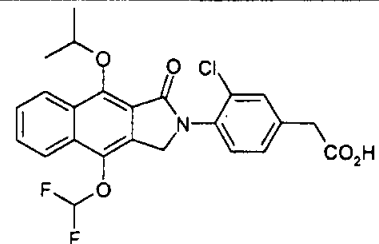
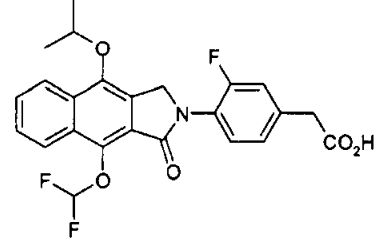
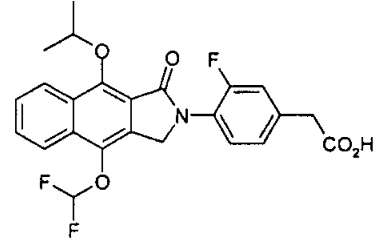
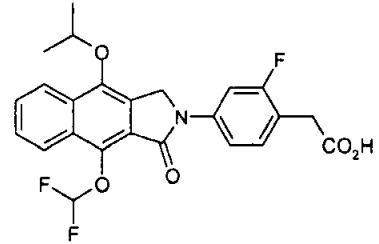
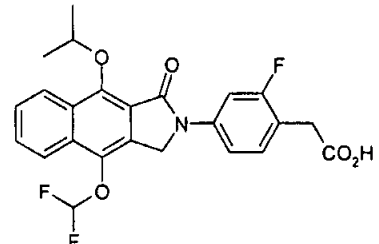
		Name	LC/MS
Example 21		{3-Chloro-4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid	Rt=3.28 [MH] ⁺ 462

Example 22		{4-[9- [(Difluoromethyl)oxy]- 4-(methoxy)-1-oxo- 1,3-dihydro-2H- benzo[f]isoindol-2- yl]phenyl}acetic acid	Rt=3.16 [MH] ⁺ 414
Example 23		{4-[4- [(Difluoromethyl)oxy]- 9-(methoxy)-1-oxo- 1,3-dihydro-2H- benzo[f]isoindol-2- yl]phenyl}acetic acid	Rt=3.11 [MH] ⁺ 414
Example 24		{4-[9- [(Difluoromethyl)oxy]- 4-(ethoxy)-1-oxo-1,3- dihydro-2H- benzo[f]isoindol-2-yl]- 3-fluorophenyl}acetic acid	Rt=3.20 [MH] ⁺ 446
Example 25		{4-[4- [(Difluoromethyl)oxy]- 9-(ethoxy)-1-oxo-1,3- dihydro-2H- benzo[f]isoindol-2-yl]- 3-fluorophenyl}acetic acid	Rt=3.10 [MH] ⁺ 446
Example 26		{4-[9- [(Difluoromethyl)oxy]- 4-(ethoxy)-1-oxo-1,3- dihydro-2H- benzo[f]isoindol-2-yl]- 2-fluorophenyl}acetic acid*	Rt=3.31 [MH] ⁺ 446
Example 27		{4-[4- [(Difluoromethyl)oxy]- 9-(ethoxy)-1-oxo-1,3- dihydro-2H- benzo[f]isoindol-2-yl]- 2-fluorophenyl}acetic acid#	Rt=3.28 [MH] ⁺ 446

A

Example 28		{3-Chloro-4-[4- [(difluoromethyl)oxy]-1- oxo-9-(propyloxy)-1,3- dihydro-2H- benzo[f]isoindol-2- yl]phenyl}acetic acid*	Rt=3.38 [MH] ⁺ 476
Example 29		{4-[9- [(Difluoromethyl)oxy]- 1-oxo-4-(propyloxy)- 1,3-dihydro-2H- benzo[f]isoindol-2-yl]- 3-fluorophenyl}acetic acid*	Rt=3.42 [MH] ⁺ 460
Example 30		{4-[4- [(Difluoromethyl)oxy]- 1-oxo-9-(propyloxy)- 1,3-dihydro-2H- benzo[f]isoindol-2-yl]- 3-fluorophenyl}acetic acid	Rt=3.32 [MH] ⁺ 460
Example 31		{4-[9- [(Difluoromethyl)oxy]- 1-oxo-4-(propyloxy)- 1,3-dihydro-2H- benzo[f]isoindol-2-yl]- 2-fluorophenyl}acetic acid	Rt=3.51 [MH] ⁺ 460
Example 32		{4-[4- [(Difluoromethyl)oxy]- 1-oxo-9-(propyloxy)- 1,3-dihydro-2H- benzo[f]isoindol-2-yl]- 2-fluorophenyl}acetic acid*	Rt=3.46 [MH] ⁺ 460
Example 33		(3-Chloro-4-{9- [(difluoromethyl)oxy]-4- [(1-methylethyl)oxy]-1- oxo-1,3-dihydro-2H- benzo[f]isoindol-2- yl}phenyl)acetic acid*	Rt=3.39 [MH] ⁺ 476

80

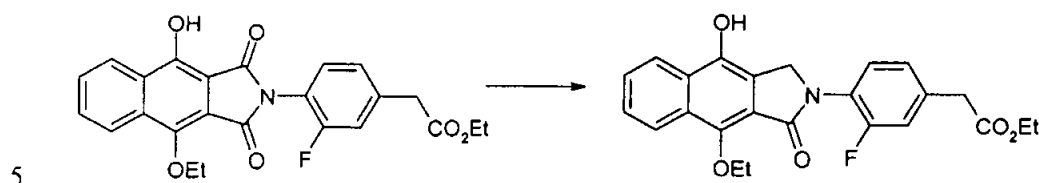
Example 34		(3-Chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid*	Rt=3.32 [MH] ⁺ 476
Example 35		(4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid*	Rt=3.32 [MH] ⁺ 460
Example 36		(4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid*	Rt=3.36 [MH] ⁺ 460
Example 37		(4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid*	Rt=3.44 [MH] ⁺ 460
Example 38		(4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid*	Rt=3.41 [MH] ⁺ 460

{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid [Example 25] has also been conveniently prepared using a regioselective methodology as follows:

A

Description 21

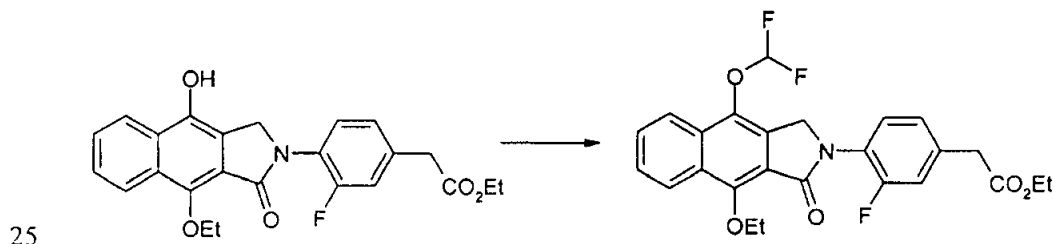
Ethyl {4-[9-(ethyloxy)-4-hydroxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate



To a solution of ethyl {4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate (2.50g, 5.72mmol) in THF (50ml) under an argon atmosphere, was added sodium borohydride (0.217g, 5.72mmol) followed by borane THF complex solution (1.0M in THF, 5.72ml, 5.72mmol). This was stirred at room temperature for 2 hours. A further 5.72mmol of sodium borohydride and borane THF complex was added to the reaction mixture and stirring continued for 2 hours. Finally, a further 2.86mmol addition of sodium borohydride and borane THF complex was made and stirring continued for 1.5 hours until the reaction was complete. This was quenched with ethyl acetate (100ml) and methanol (3ml) then washed with 2N HCl (100ml). The aqueous was re-extracted with ethyl acetate (200ml). The combined organics were washed with brine (200ml), dried over magnesium sulphate, filtered and evaporated to give the title compound as a pale yellow solid (2.45g, 5.79mmol).
LC/MS: Rt=3.04, [MH]⁺ 424.

Description 22

Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate



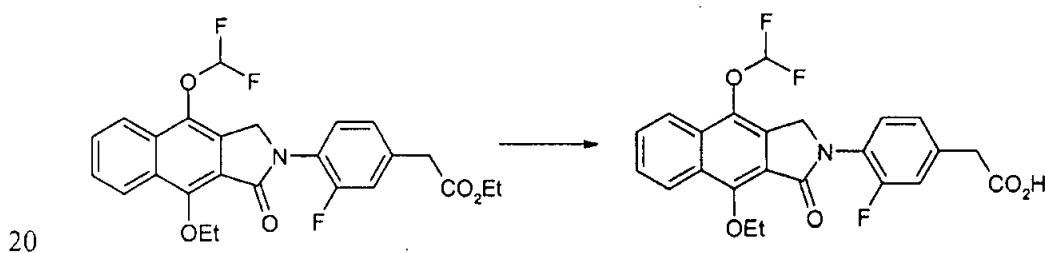
52

To a solution of ethyl {4-[9-(ethyloxy)-4-hydroxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate (2.40g, 5.67mmols) in DMF (30ml) was added sodium chlorodifluoroacetate (1.72g, 11.34mmol) and sodium carbonate (1.20g, 11.34mmol). The mixture was heated to 100°C for 3 hours. Further sodium chlorodifluoroacetate (1.72g, 11.34mmol) was added, heating continued for 1.5 hours, and the same amount added again and heating continued for 30 minutes. The mixture was cooled to room temperature and partitioned between ethyl acetate x2 and water. The combined organics were washed with water x3 and brine. This was dried over magnesium sulphate, filtered and evaporated to a brown oil. This was purified by chromatography on silica gel, eluting with ethyl acetate (5-40%) in hexane to give the title compound as a yellow solid (0.60g, 1.27mmol).
LC/MS: Rt=3.49, [MH]⁺ 474.

15

Example 25

{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid



Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate (0.60g, 1.27mmol) was heated to 100°C in a 1:1 mixture of acetic acid : 2N aqueous hydrochloric acid (20ml) for 50 minutes. The reaction was cooled to room temperature. On addition of water, the resulting white solid was collected by filtration, washed with water and dried under vacuum to give the title compound (0.516g, 1.09mmol).
LC/MS: Rt=3.13, [MH]⁺ 446.



¹H-NMR (DMSO) δ8.42 (1H, ddd, J=8.4,1.1,0.6Hz), δ8.12 (1H, d, J=8.5Hz), δ7.84 (1H, ddd, J=8.2,6.9,1.3Hz), δ7.74 (1H, ddd, J=8.4, 6.8, 1.2Hz), δ7.63 (1H, t, J=8.1Hz), δ 7.32 (1H, dd, 11.5,1.9Hz), δ7.22 (1H, dd, 8.1,1.8Hz), δ7.30 (1H, t, 73.6Hz), δ5.06 (2H, s), δ 4.50 (2H, q, J=7.0Hz), δ3.67 (2H, s), δ1.44 (3H, t, 7.0Hz).

Biological data

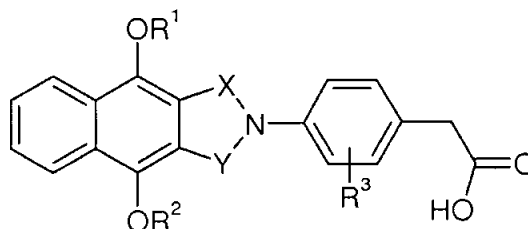
Studies were performed using HEK-293(T) cells expressing the recombinant human prostanoid EP₄ receptor (HEK-EP₄ cells). Cells were grown as a monolayer culture in DMEM-F12/F12 containing glutamax II (Gibco) and supplemented with 10% foetal bovine serum and 0.4mg.ml⁻¹ G418. HEK-EP₄ cells were pre-treated 24hr and 30mins prior to the experiment with 10μM indomethacin and harvested using Versene containing 10μM indomethacin. The cells were resuspended in assay buffer (DMEM:F12, 10μM indomethacin and 200μM IBMX) at 1×10⁶ cells per ml and incubated for 20min at 37°C. Thereafter, 50μl of cells were added to 50ul agonist (compound of Formula (I)) and incubated at 37°C for 4 minutes before stopping reactions with 100μl of 1% triton X-100. cAMP levels in the cell lysates were determined using a competition binding assay. In this assay the ability of cell lysates to inhibit 3H-cAMP (Amersham) binding to the binding subunit of protein kinase A was measured and cAMP levels were calculated from a standard curve. The data for each compound were expressed as a % of the response to a 10nM maximal concentration of the standard agonist PGE₂. For each compound the maximal response and concentration of compound causing 50% of its maximal response were calculated. Intrinsic activity is expressed relative to the maximal response to PGE₂. Unless stated, reagents were purchased commercially from Sigma.

The examples of the present invention were tested in the above-mentioned assay and exhibited pEC₅₀ values of 6.1 or higher. Certain examples exhibited pEC₅₀ values of 7 or higher and intrinsic activities of 50% or higher.

81

Claims

1. A compound of formula (I) or a pharmaceutically acceptable derivative thereof,



(I)

wherein,

R¹ and R² independently represent C₁₋₄ alkyl or difluoromethyl provided that at least one of R¹ and R² represents difluoromethyl;

R³ represents H, F, Cl or Br; and

X and Y independently represent C=O or CH₂ provided that at least one of X and Y represents C=O.

2. A compound of formula (I), according to claim 1, wherein one of R¹ and R² represents C₁₋₄ alkyl and the other represents difluoromethyl.
3. A compound of formula (I), according to claim 1, wherein both R¹ and R² represent difluoromethyl.
4. A compound of formula (I), according to any of claims 1 to 3, wherein both X and Y represent C=O.
5. A compound of formula (I), according to any of claims 1 to 4, wherein R³ represents H, F or Cl.

85

6. A compound of formula (I), according to claim 1, selected from the group consisting of:

(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;

5 (4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid;

(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;

10 (4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;

(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;

(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid;

15 (4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;

(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;

20 {4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;

25 {3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;

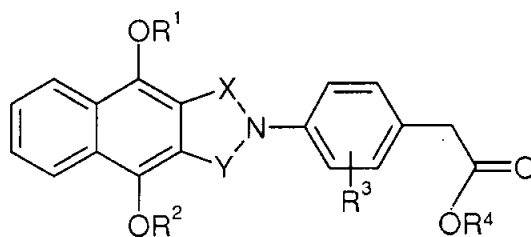
30 {4-[4-[(Difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;

{3-Chloro-4-[4-[(difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

- {4-[4-[(Difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;
- (4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
- 5 (3-Chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;
- (4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;
- {3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- 10 {3-Chloro-4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- {4-[9-[(Difluoromethyl)oxy]-4-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- 15 {4-[4-[(Difluoromethyl)oxy]-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- {4-[9-[(Difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
- {4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
- 20 {4-[9-[(Difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;
- 4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;
- 25 {3-Chloro-4-[4-[(difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
- {4-[9-[(Difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
- {4-[4-[(Difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
- 30 {4-[9-[(Difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-
 benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;
 (3-Chloro-4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-
 dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;
 5 (3-Chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-
 dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;
 (4-{9-[(Difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-
 benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
 (4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-
 10 benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
 (4-{9-[(Difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-
 benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;
 (4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-
 benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid; or a pharmaceutically
 15 acceptable derivative thereof.

7. A process for preparing a compound of formula (I), according to claim 1,
 wherein one of X and Y represents C=O and the other represents CH₂,
 and R¹, R² and R³ are as defined in claim 1, which process comprises
 20 reacting a compound of formula (II),



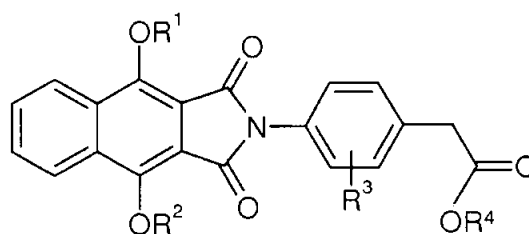
(II)

25 wherein, one of X and Y represents C=O and the other represents CH₂;
 R¹, R² and R³ are as hereinbefore defined in claim 1; and R⁴ represents

56

C₁₋₆ alkyl; with a suitable base and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

- 5 8. A process for preparing a compound of formula (I), according to claim 1, wherein X and Y represent C=O and R¹, R² and R³ are as defined in claim 1, which process comprises adding a compound of formula (III),



(III)

10

wherein, R¹, R² and R³ are as defined in claim 1; and R⁴ represents C₁₋₆ alkyl; to a suitable acid or mixture of acids, and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

15

9. A compound of formula (I), according to claim 1, for use in human or veterinary medicine.
10. A compound of formula (I), according to claim 1, for use in the treatment of a condition which is mediated by the action, or loss of action, of PGE₂ at EP₄ receptors.
11. A method of treating a human or animal subject suffering from a condition which is mediated by the action, or by loss of action, of PGE₂ at EP₄ receptors which comprises administering to said subject an effective amount of a compound of formula (I), according to claim 1.

20

25

12. Use of a compound of formula (I), according to claim 1, for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE₂ at EP₄ receptors.

5 13. A pharmaceutical composition comprising a compound of formula (I), according to claim 1, and one or more acceptable carriers or diluents therefor.

10 14. A pharmaceutical composition according to claim 13, comprising one or more additional therapeutic agents.

15

20

25

30

90

DERIVADOS DE BENZOISOINDOL PARA EL TRATAMIENTO DEL DOLOR

MEMORIA DESCRIPTIVA

5 Esta invención se refiere a derivados de naftaleno, a procedimientos para su preparación, a composiciones farmacéuticas que los contienen, y a su uso en medicina.

Los compuestos de la presente invención son agonistas del receptor EP₄.

10 Varios artículos de revisión describen la caracterización y relevancia terapéutica de los receptores prostanoideos y sus agonistas y antagonistas selectivos usados más comúnmente: "Eicosanoids: From Biotechnology to Therapeutic Applications, Folco, Samuelsson, Maclouf, y Velo, eds, Plenum Press, Nueva York, 1996, cap. 14, 137- 154; y *Journal of*
15 *Lipid Mediators and Cell Signalling*, 1996, 14, 83-87, y "Prostanoid Receptors, Structure, Properties and Function", S Narumiya y otros, *Physiological Reviews* 1999, 79(4), 1193-126.

El receptor EP₄ es un receptor 7-transmembrana y su ligando natural es la prostaglandina PGE₂. La PGE₂ también tiene afinidad por otros
20 receptores de EP (tipos EP₁, EP₂ y EP₃). El receptor prostanoide EP₄ pertenece a un grupo de receptores asociados normalmente con la elevación de la concentración de adenosina monofosfato cíclico (AMPc) intracelular. El receptor EP₄ está asociado con la relajación del músculo liso, la presión

al

intraocular, dolor (en particular dolor inflamatorio, neuropático y visceral), inflamación, neuroprotección, diferenciación de linfocitos, procesos metabólicos del hueso, actividades alérgicas, promoción del sueño, regulación renal, secreción de moco gástrico o entérico y secreción de bicarbonato duodenal. El receptor EP₄ tiene una función importante en el cierre de los ductos arteriosos, la vasodepresión, inflamación y remodelación de hueso, como lo revisa Narumiya en *Prostaglandins & Other Lipid Mediators*, 2002, 68-69 557-73.

Varias publicaciones han demostrado que la PGE₂ que actúa por medio del receptor subtipo EP₄, y los agonistas de EP₄ solos, pueden regular citocinas inflamatorias después de un estímulo inflamatorio. Takayama y otros en el *Journal of Biological Chemistry*, 2002, 277(46), 44147-54, mostraron que la PGE₂ modula la inflamación durante las enfermedades inflamatorias suprimiendo la producción de quimocina derivada de macrófago por medio del receptor EP₄. En *Bioorganic & Medicinal Chemistry*, 2002, 10(7), 2103-2110, Maruyama y otros muestran que el agonista selectivo del receptor EP₄ (ONO-AE1-437) suprime el TNF- α inducido por LPS en sangre completa humana, aumentando la concentración de IL-10. Un artículo en *Anesthesiology*, 2002, 97, 170-176, sugiere que un agonista selectivo del receptor EP₄ (ONO-AE1-329) inhibe eficientemente la hiperalgesia mecánica y térmica y las reacciones inflamatorias en monoartritis aguda y crónica.

Dos artículos independientes de Sakuma y otros en el *Journal of Bone and Mineral Research*, 2000, 15(2), 218-227, y Miyaura y otros en el

92

Journal of Biological Chemistry, 2000, 275(26), 19819-23, informaron el deterioro en la formación de osteoclasto en células cultivadas de ratones receptor EP₄-knock-out. Yoshida y otros en *Proceedings of the National Academy of Sciences of the United States of America*, 2002, 99(7), 4580-4585, usando ratones que carecen de los subtipos EP del receptor de PGE₂, identificaron a EP₄ como el receptor que media la formación de hueso en respuesta a la administración PGE₂. También mostraron que un agonista selectivo del receptor EP₄ (ONO-4819) induce consistentemente la formación de hueso en ratones de tipo silvestre. Adicionalmente, Terai y otros en *Bone*, 2005, 37(4), 555-562, han mostrado que la presencia de un agonista selectivo del receptor EP₄ (ONO-4819) aumentó la capacidad inductora de hueso de rhBMP-2, una citocina terapéutica que puede inducir la formación de hueso.

Una investigación adicional de Larsen y otros muestra que los efectos de PGE₂, sobre la secreción en la segunda parte del duodeno humano es mediada por el receptor EP₄ (*Acta Physiol. Scand.* 2005, 185, 133-140). También se ha mostrado que un agonista selectivo del receptor EP₄ (ONO-AE1-329) puede proteger contra la colitis en las ratas (Nitta y otros en *Scandinavian Journal of Immunology* 2002, 56(1), 66-75).

Doré y otros en *The European Journal of Neuroscience*, 2005, 22(9), 2199-206, han mostrado que la PGE₂ puede proteger a las neuronas contra la toxicidad del péptido beta-amiloide actuando sobre los receptores EP₂ y EP₄. Además, Doré ha mostrado en *Brain Research*, 2005, 1066(1-2), 71-77, que el antagonista del receptor EP₄ (ONO-AE1-329) protege contra la

93

neurotoxicidad en un modelo de excitotoxicidad aguda en el cerebro.

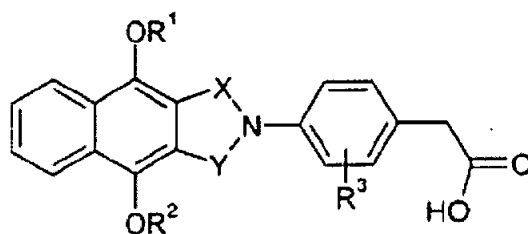
Woodward y otros en el *Journal of Lipid Mediators*, 1993, 6(1-3), 545-53, encontraron que la presión intraocular se podría disminuir usando agonistas selectivos de prostanoide. Dos documentos de *Investigative*
5 *Ophthalmology & Visual Science* han mostrado que el receptor prostanoide EP₄ es expresado en células epiteliales del cristalino humano (Mukhopadhyay y otros, 1999, 40(1), 105-12), y sugieren una función del receptor prostanoide EP₄ en la modulación del flujo en la estructura trabecular del ojo (Hoyng y otros, 1999, 40(11), 2622-6).

10 Se han descrito compuestos que exhiben actividad de unión del receptor EP₄ y sus usos, por ejemplo en WO98/55468, WO00/18744, WO00/03980, WO00/15608, WO00/16760, WO00/21532, WO01010426, EP0855389, EP0985663, WO02/047669, WO02/50031, WO02/50032, WO02/50033, WO02/064564, WO03/103604, WO03/077910, WO03/086371,
15 WO04/037813, WO04/067524, WO04/085430, US04/142969, WO05/021508, WO05/105733, WO05/105732, WO05/080367, WO05/037812, WO05/116010 y WO06/122403.

Derivados de indoprofeno tales como la sal de sodio del ácido [4-(1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il)fenil]-2-propiónico han sido
20 descritos por Rufer y otros en el *Eur. J. Med. Chem. - Chimica Therapeutica*, 1978, 13, 193.

La presente invención provee compuestos de fórmula (I), y derivados farmacéuticamente aceptables de los mismos,

an



5

(I)

en donde:

R^1 y R^2 representan independientemente alquilo de C_{1-4} o difluorometilo, siempre que por lo menos uno de R^1 y R^2 represente difluorometilo;

10

R^3 representa H, F, Cl o Br; y

X y Y representan independientemente C=O o CH_2 , siempre que por lo menos uno de X y Y represente C=O.

15

En una modalidad de la invención, uno de R^1 y R^2 representa alquilo de C_{1-4} y el otro representa difluorometilo. En una modalidad de la invención, uno de R^1 y R^2 representa metilo y el otro representa difluorometilo.

20

En una modalidad de la invención, uno de R^1 y R^2 representa etilo y el otro representa difluorometilo. En una modalidad de la invención, uno de R^1 y R^2 representa n-propilo y el otro representa difluorometilo. En una modalidad de la invención, uno de R^1 y R^2 representa *iso*-propilo y el otro representa difluorometilo. En otra modalidad de la invención, tanto R^1 como R^2 representan difluorometilo.

En una modalidad de la invención, R^3 representa F. En otra modalidad de la invención, R^3 representa Cl. En otra modalidad de la

invención, R³ representa H. En otra modalidad de la invención, R³ representa H, F, o Cl. En otra modalidad de la invención, R³ representa F o Cl.

En otra modalidad de la invención, X representa CH₂ y Y representa C=O. En otra modalidad de la invención, X representa C=O y Y representa CH₂. En otra modalidad de la invención, tanto X como Y representan C=O.

En otra modalidad de la invención, se provee un compuesto de fórmula (I) seleccionado del grupo que consiste en:

ácido (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acético;

ácido (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-clorofenil)acético;

ácido (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético;

ácido (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acético;

ácido (4-{4,9-bis[(difluorometil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético;

ácido (4-{4,9-bis[(difluorometil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-clorofenil)acético;

ácido (4-{4,9-bis[(difluorometil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acético;

ácido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-

dihidro-2H-benzo[f]isoindol-2-il}fenil}acético;

ácido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético;

ácido {4-[4-[(difluorometil)oxi]-9-(metiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético;

ácido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético;

ácido {3-cloro-4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético;

ácido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético;

ácido {4-[4-[(difluorometil)oxi]-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético;

ácido {3-cloro-4-[4-[(difluorometil)oxi]-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético;

ácido {4-[4-[(difluorometil)oxi]-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético;

ácido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil}acético;

ácido (3-cloro-4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético;

ácido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil}acético;

ácido {3-cloro-4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acético;

ácido {3-cloro-4-[9-[(difluorometil)oxi]-4-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acético;

5 ácido {4-[9-[(difluorometil)oxi]-4-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acético;

ácido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acético;

10 ácido {4-[9-[(difluorometil)oxi]-4-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético;

ácido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético;

ácido {4-[9-[(difluorometil)oxi]-4-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético;

15 ácido 4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético;

ácido {3-cloro-4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acético;

20 ácido {4-[9-[(difluorometil)oxi]-1-oxo-4-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético;

ácido {4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético;

ácido {4-[9-[(difluorometil)oxi]-1-oxo-4-(propiloxi)-1,3-dihidro-2H-

benzo[f]isoindol-2-il]-2-fluorofenil}acético;

ácido {4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético;

ácido (3-cloro-4-{9-[(difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acético;

ácido (3-cloro-4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acético;

ácido (4-{9-[(difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético;

10 ácido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético;

ácido (4-{9-[(difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acético;

15 ácido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acético; o un derivado farmacéuticamente aceptable de los mismos.

La presente invención cubre todas las combinaciones de modalidades particulares y preferidas que se describen en la presente.

20 Como se usa aquí, el término "alquilo de C₁₋₄" incluye grupos alquilo de cadena recta y cadena ramificada que contienen de 1 a 4 átomos de carbono, tales como metilo, etilo, n-propilo, iso-propilo, butilo e iso-butilo. El término "alquilo de C₁₋₆" se puede interpretar en consecuencia.

Como se usa aquí, el término difluorometilo significa -CHF₂.

Como se usa aquí, F significa flúor, Cl significa cloro y Br significa bromo.

Por derivado farmacéuticamente aceptable se entiende cualquier sal, solvato o éster farmacéuticamente aceptable, o sal o solvato de dicho éster de los compuestos de fórmula (I), o cualquier otro compuesto que por administración al receptor sea capaz de proveer (directa o indirectamente) un compuesto de fórmula (I) o un metabolito o residuo activo del mismo. En una modalidad de la invención, el derivado farmacéuticamente aceptable significa la sal, solvato o éster, o la sal o solvato de dicho éster. En otra modalidad de la invención, el derivado farmacéuticamente aceptable significa la sal o éster, o la sal de dicho éster.

Se apreciará que para uso farmacéutico las sales anteriormente mencionadas serán las sales farmacéuticamente aceptables; sin embargo, se pueden usar otras sales, por ejemplo en la preparación de los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables.

Las sales farmacéuticamente aceptables incluyen las descritas por Berge, Bighley y Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. El término "sales farmacéuticamente aceptables" se refiere a las sales preparadas de bases farmacéuticamente aceptables que incluyen bases inorgánicas y bases orgánicas. Las sales derivadas de bases inorgánicas incluyen las sales de aluminio, amonio, calcio, cobre, férrica, ferrosa, litio, magnesio, mangánica, manganosa, potasio, sodio, zinc, etcétera. Las sales derivadas de bases orgánicas farmacéuticamente aceptables incluyen las sales de aminas

V02

primarias, secundarias y terciarias; aminos sustituidas que incluyen aminos sustituidas naturales; y aminos cíclicas. Las bases orgánicas farmacéuticamente aceptables particulares incluyen arginina, betaína, cafeína, colina, N,N'-dibenciletilendiamina, dietilamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilendiamina, N-etil-morfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, isopropilamina, lisina, metilglucamina, morfolina, piperazina, piperidina, procaína, purinas, teobromina, trietilamina, trimetilamina, tripropilamina, tris(hidroximetil)aminometano, etcétera. Las sales también se pueden formar

10 de resinas de intercambio iónico básicas, por ejemplo resinas de poliamina.

Se apreciará que los compuestos de fórmula (I) pueden ser producidos *in vivo* por el metabolismo de un profármaco adecuado. Dichos profármacos pueden ser por ejemplo ésteres metabólicamente lábiles, fisiológicamente aceptables, de los compuestos de fórmula general (I). Estos

15 se pueden formar por esterificación del grupo de ácido carboxílico en el compuesto original de fórmula general (I), con protección previa de cualquier otro grupo reactivo presente en la molécula cuando sea necesario, seguido por desprotección, si así se requiere. Los ejemplos de dichos ésteres metabólicamente lábiles incluyen ésteres de alquilo de C₁₋₄, por ejemplo,

20 ésteres de metilo, etilo o t-butilo, ésteres de alquenilo de C₃₋₆ por ejemplo ésteres de alilo de aminoalquilo sustituido o no sustituido (por ejemplo aminoetilo, 2-(N,N-dietilamino)etilo), o ésteres de 2-(4-morfolino)etilo, o ésteres de aciloxialquilo tales como aciloximetilo o 1-aciloxietilo, por ejemplo

101

éster de pivaloiloimetilo, 1-pivaloiloietilo, acetoiimetilo, 1-acetoiietilo, 1-(1-metoxi-1-metil)etilcarboniloietilo, 1-benzoiloietilo, isopropoxicarboniloimetilo, 1-isopropoxicarboniloietilo, ciclohexilcarboniloimetilo, 1-ciclohexilcarboniloietilo, ciclohexiloxicarboniloimetilo, 1-ciclohexiloxicarboniloietilo, 1-(4-tetrahidropiraniilo)carboniloietilo, o 1-(4-tetrahidropiraniil)carboniloietilo.

Se entiende que la presente invención abarca todos los isómeros de los compuestos de fórmula (I) y sus derivados farmacéuticamente aceptables, incluyendo todas las formas geométricas, tautoméricas y ópticas, y mezclas de los mismos (por ejemplo mezclas racémicas).

Puesto que los compuestos de la presente invención, en particular los compuestos de fórmula (I), están destinados a usarse en composiciones farmacéuticas, se entenderá que se proveen en forma sustancialmente pura, por ejemplo por lo menos 50% pura, convenientemente por lo menos 75% pura, de preferencia por lo menos 95% pura (el porcentaje en una base de peso/peso). Las preparaciones impuras de los compuestos de fórmula (I) se pueden usar para preparar las formas más puras usadas en las composiciones farmacéuticas. Aunque la pureza de los compuestos intermediarios de la presente invención es menos crítica, se entenderá fácilmente que se prefiere la forma sustancialmente pura para los compuestos de fórmula (I). Preferiblemente, siempre que sea posible, los compuestos de la presente invención se obtienen en forma cristalina.

Cuando algunos de los compuestos de esta invención se dejan

cristalizar o se recristalizan de disolventes orgánicos, el disolvente de la cristalización puede estar presente en el producto cristalino. Esta invención incluye dentro de su alcance tales solvatos. Similarmente, algunos de los compuestos de esta invención se pueden cristalizar o recristalizar de disolventes que contienen agua. En dichos casos se puede formar agua de hidratación. Esta invención incluye dentro de su alcance hidratos estequiométricos y compuestos que contienen cantidades variables de agua, que pueden ser producidos por procedimientos tales como liofilización. Además, diferentes condiciones de cristalización pueden llevar a la formación de formas polimórficas diferentes de los productos cristalinos. Esta invención incluye dentro de su alcance todas las formas polimórficas de los compuestos de fórmula (I).

La presente invención también incluye dentro de su alcance todos los compuestos de fórmula (I) marcados con isótopos. Dichos compuestos son idénticos a los de fórmula (I), excepto que uno o más átomos están reemplazados con un átomo que tiene una masa atómica o número de masa diferente de la masa atómica o número de masa encontrados usualmente en la naturaleza. Los ejemplos de isótopos que se pueden incorporar en los compuestos de fórmula (I) y sus derivados farmacéuticamente aceptables incluyen los isótopos de hidrógeno, carbono, nitrógeno, oxígeno, flúor y cloro, tales como 2H , 3H , 11C , 13C , 14C , 15N , 17O , 18O , 18F y 36Cl .

Los compuestos marcados con isótopos de la presente

V03

invención, por ejemplo en los que se incorporan isótopos radioactivos tales como ^3H , ^{14}C , son útiles para las pruebas de distribución de fármaco o substrato en los tejidos. Los isótopos tritiados, es decir, ^3H , y de carbono 14, es decir, ^{14}C , son particularmente preferidos por su facilidad de preparación y detección. Los isótopos ^{11}C y ^{18}F son particularmente útiles en PET (tomografía de emisión de positrones), y son útiles en el análisis de imagen del cerebro. La sustitución adicional con isótopos más pesados tales como deuterio, es decir, ^2H , puede producir ciertas ventajas terapéuticas que se originan de una mayor estabilidad metabólica, por ejemplo un incremento de la vida media *in vivo* o una reducción de la dosis requerida, y por lo tanto se pueden preferir en ciertas circunstancias. Los compuestos de fórmula (I) marcados con isótopos se pueden preparar realizando los procedimientos sintéticos que se describen en los esquemas o los ejemplos más abajo, sustituyendo con un reactivo marcado con isótopo, fácilmente disponible, un reactivo no marcado con isótopo.

Los compuestos de la invención son agonistas del receptor EP_4 y por lo tanto pueden ser útiles para el tratamiento de enfermedades mediadas por el receptor EP_4 .

En particular, los compuestos de fórmula (I) pueden ser útiles en el tratamiento del dolor, por ejemplo dolor articular crónico (por ejemplo, artritis reumatoide, osteoartritis, espondilitis reumatoide, artritis gotosa y artritis juvenil), incluyendo la propiedad de modificación de la enfermedad y conservación de la estructura de la articulación; dolor musculoesquelético;

col

lumbalgia y dolor de cuello; esguinces y torceduras; dolor neuropático; dolor mantenido simpáticamente; miositis; dolor asociado con cáncer y fibromialgia; dolor asociado con migraña; dolor asociado con influenza u otras infecciones virales, tales como el resfriado común; fiebre reumática; dolor asociado con trastornos funcionales del intestino, tales como dispepsia no ulcerosa, dolor de pecho no cardíaco y síndrome de intestino irritable; dolor asociado con isquemia miocárdica; dolor postoperatorio; cefalea; dolor dental; y dismenorrea.

Los compuestos de fórmula (I) pueden ser particularmente útiles en el tratamiento del dolor neuropático y los síntomas asociados con el mismo. Los síndromes de dolor neuropático incluyen: neuropatía diabética; ciática; lumbalgia inespecífica; dolor de esclerosis múltiple; fibromialgia; neuropatía relacionada con VIH; neuralgia postherpética; neuralgia del trigémino; y dolor originado de trauma físico, amputación, cáncer, toxinas o condiciones inflamatorias crónicas. Los síntomas del dolor neuropático incluyen dolor de disparo espontáneo y lacerante, o dolor quelante persistente. Además, se incluye el dolor asociado con sensaciones normalmente no dolorosas, tales como "hormigueo" (parestias y disestesias), incremento de la sensibilidad del tacto (hiperestesia), sensación dolorosa posterior a estimulación inocua (alodinia dinámica, estática o térmica), incremento de la sensibilidad a estímulos nocivos (hiperalgesia térmica, al frío, mecánica), sensación de dolor continuo después de retirar un estímulo (hiperpatía), o ausencia o déficit de las rutas sensoriales selectivas

LOS

(hipoalgesia).

Los compuestos de fórmula (I) también pueden ser de utilidad en el tratamiento de la inflamación, por ejemplo en el tratamiento de condiciones de la piel (por ejemplo, quemaduras solares, quemaduras, eczema, dermatitis, soriasis); enfermedades oftálmicas tales como glaucoma, retinitis, retinopatía, uveítis y lesión aguda del tejido del ojo (por ejemplo conjuntivitis); trastornos del pulmón (por ejemplo asma, bronquitis, enfisema, rinitis alérgica, síndrome de dificultad respiratoria, enfermedad del criador de pichones, enfermedad del pulmón del granjero, COPD; trastornos del tracto gastrointestinal (por ejemplo úlcera aftosa, enfermedad de Crohn, gastritis atópica, gastritis varioliforme, colitis ulcerativa, enfermedad celiaca, ileítis regional, síndrome del intestino irritable, enfermedad inflamatoria del intestino, enfermedad de reflujo gastrointestinal, diarrea, constipación); trasplante de órgano; otras condiciones con un componente inflamatorio, tales como enfermedad vascular, migraña, periarteritis nudosa, tiroiditis, anemia aplásica, enfermedad de Hodgkin, esclerodoma, miastenia grave, esclerosis múltiple, sarcoidosis, síndrome nefrótico, síndrome de Bechet, polimiositis, gingivitis, isquemia miocárdica, pirexia, lupus eritematoso sistémico, polimiositis, tendinitis, bursitis y síndrome de Sjogren.

Los compuestos de fórmula (I) también pueden ser útiles en el tratamiento de enfermedades inmunes tales como enfermedades autoinmunes, enfermedades de deficiencia inmune o trasplante de órgano. Los compuestos de fórmula (I) también pueden ser eficaces para tratar la

Cob

latencia de la infección de VIH.

Los compuestos de fórmula (I) también pueden ser útiles en el tratamiento de enfermedades de activación excesiva o indeseable de plaquetas, tales como claudicación intermitente, angina inestable, ataque cerebral y síndrome coronario agudo (por ejemplo, enfermedades vasculares oclusivas).

Los compuestos de fórmula (I) también pueden ser útiles como un fármaco con acción diurética, o pueden ser útiles para tratar el síndrome de vejiga sobreactiva.

Los compuestos de fórmula (I) también pueden ser útiles en el tratamiento de la impotencia o disfunción eréctil.

Los compuestos de fórmula (I) también pueden ser útiles en el tratamiento de la enfermedad del hueso caracterizada por metabolismo o resorción anormal del hueso, tal como osteoporosis (especialmente osteoporosis postmenopáusica), hipercalcemia, hiperparatiroidismo, enfermedades de hueso de Paget, osteólisis, hipercalcemia de malignidad con o sin metástasis de hueso, artritis reumatoide, periodontitis, osteoartritis, ostealgia, osteopenia, calculosis, litiasis (especialmente urolitiasis), gota y espondilitis anquilosante, tendinitis y bursitis.

Los compuestos de fórmula (I) también pueden ser útiles en la remodelación de hueso o promoción de la generación de hueso, o promoción de la cicatrización de fracturas.

Los compuestos de fórmula (I) también pueden ser útiles para

atenuar los efectos secundarios hemodinámicos de los AINE's e inhibidores de COX2.

Los compuestos de fórmula (I) también pueden ser útiles en el tratamiento de enfermedades cardiovasculares tales como hipertensión o
5 isquemia de miocardio; insuficiencia venosa funcional u orgánica; terapia varicosa; hemorroides; y estados de choque asociados con una caída sustancial de la presión arterial (por ejemplo choque séptico).

Los compuestos de fórmula (I) también pueden ser útiles en el tratamiento de enfermedades neurodegenerativas tales como demencia,
10 particularmente demencia degenerativa (incluyendo demencia senil, enfermedad de Alzheimer, enfermedad de Pick, córea de Huntington, enfermedad de Parkinson y enfermedad de Creutzfeldt-Jacob, esclerosis lateral amiotrófica (ALS), enfermedad de neurona motora); demencia vascular (incluyendo demencia de infarto múltiple); así como también demencia
15 asociada con lesiones que ocupan el espacio intracraneal; trauma; infecciones y condiciones relacionadas (que incluyen infección de VIH); metabolismo; toxinas; anoxia y deficiencia de vitamina; y deterioro cognitivo leve asociado con el envejecimiento, particularmente deterioro de la memoria asociado con la edad.

20 Los compuestos de fórmula (I) también pueden ser de utilidad en el tratamiento de trastornos neurológicos y se pueden usar como agentes neuroprotectores. Los compuestos de la invención también pueden ser útiles en el tratamiento de la neurodegeneración posterior al ataque cerebral, paro

cardiaco, derivación pulmonar, lesión traumática del cerebro, lesión de la médula espinal, o similares.

Los compuestos de fórmula (I) también se pueden usar en el tratamiento de las complicaciones de la diabetes de tipo (I) (por ejemplo
5 microangiopatía diabética, retinopatía diabética, nefropatía diabética, degeneración macular, glaucoma), síndrome nefrótico, anemia aplásica, uveítis, enfermedad de Kawasaki, y sarcoidosis.

Los compuestos de fórmula (I) también pueden ser útiles en el tratamiento de la disfunción renal (nefritis, particularmente glomerulonefritis
10 proliferativa mesangial, síndrome nefrítico), la disfunción hepática (hepatitis, cirrosis), y la disfunción gastrointestinal (diarrea).

Se entiende que la referencia al tratamiento incluye tanto el tratamiento de los síntomas establecidos como el tratamiento profiláctico.

De acuerdo con una modalidad adicional de la invención, se
15 provee un compuesto de fórmula (I), o un derivado farmacéuticamente aceptable del mismo, para usarse en la medicina humana o veterinaria.

De acuerdo con otra modalidad de la invención, se provee un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo, para usarse en el tratamiento de una condición que es mediada por la
20 acción o pérdida de acción de la PGE_2 en los receptores EP_4 .

De acuerdo con una modalidad adicional de la invención, se provee un método de tratamiento de un sujeto humano o animal que padece una condición mediada por la acción o por la pérdida de acción de la PGE_2 en

los receptores EP₄, que comprender administrar a dicho sujeto una cantidad efectiva de un compuesto de fórmula (I), o un derivado farmacéuticamente aceptable del mismo.

5 De acuerdo con una modalidad adicional de la invención, se provee un método de tratamiento de un sujeto humano o animal que padece de dolor, o una enfermedad inflamatoria, inmune, ósea, neurodegenerativa o renal, que comprender administrar a dicho sujeto una cantidad efectiva de un compuesto de fórmula (I), o un derivado farmacéuticamente aceptable del mismo.

10 De acuerdo con otra modalidad de la invención, se provee el uso de un compuesto de fórmula (I), o un derivado farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para el tratamiento de una condición que es mediada por la acción de la PGE₂ en los receptores EP₄.

15 De acuerdo con otra modalidad de la invención, se provee el uso de un compuesto de fórmula (I), o un derivado farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para el tratamiento o prevención de una condición tal como dolor, o un trastorno inflamatorio, inmune, óseo neurodegenerativo o renal.

20 El compuesto de fórmula (I) y sus derivados farmacéuticamente aceptables se administran convenientemente en forma de composiciones farmacéuticas. Dichas composiciones se pueden presentar convenientemente para usarse de la manera convencional en mezcla con uno o más vehículos o excipientes fisiológicamente aceptables.

10

De esta manera, en otro aspecto de la invención, se provee una composición farmacéutica que comprende un compuesto de fórmula (I) o un derivado farmacéuticamente aceptable del mismo, adaptado para usarse en medicina humana o veterinaria.

5 Aunque es posible administrar los compuestos de fórmula (I) o sus derivados farmacéuticamente aceptables como el agente químico en bruto, es preferible presentarlo como una formulación farmacéutica. Las formulaciones de la presente invención comprenden los compuestos de fórmula (I), o derivados farmacéuticamente aceptables de los mismos, junto
10 con uno o más vehículos o diluentes aceptables, y opcionalmente con otros ingredientes terapéuticos. El vehículo debe ser "aceptable" en el sentido de ser compatible con los otros ingredientes de la formulación y no debe ser nocivo para el receptor del mismo.

Las formulaciones incluyen las adecuadas para administración
15 oral, parenteral (que incluye subcutánea, por ejemplo por inyección o tableta de depósito, intradérmica, intratecal, intramuscular, por ejemplo por depósito, e intravenosa), rectal y tópica (incluyendo dérmica, bucal y sublingual), aunque la vía más adecuada puede depender, por ejemplo, de la condición y trastorno del receptor. Las formulaciones se pueden presentar
20 convenientemente en forma de dosis unitaria y se pueden preparar mediante cualquiera de los métodos conocidos en las ciencias farmacéuticas (véanse por ejemplo los métodos descritos en "Remington - The Science and Practice of Pharmacy", 21^a edición, Lippincott, Williams & Wilkins, USA, 2005, y las

W

referencias ahí citadas). Todos los métodos incluyen el paso de asociar el compuesto de fórmula (I), o un derivado farmacéuticamente aceptable del mismo ("ingrediente activo"), con el vehículo que constituye uno o más ingredientes accesorios. En general, las formulaciones se preparan asociando íntima y uniformemente el ingrediente activo con vehículos líquidos o vehículos sólidos finamente divididos, o ambos, y después si es necesario dando forma al producto en la formulación deseada.

Las formulaciones de la presente invención adecuadas para administración oral se pueden presentar como unidades discretas tales como cápsulas, saquitos o tabletas (por ejemplo tabletas masticables, en particular para administración pediátrica), cada una conteniendo una cantidad predeterminada del ingrediente activo; como polvo o gránulos; como una solución o suspensión en un líquido acuoso o no acuoso; o como una emulsión líquida de aceite en agua o una emulsión líquida de agua en aceite.

El ingrediente activo también se puede presentar como un bolo, electuario o pasta.

Una tableta se puede hacer por compresión o moldeo, opcionalmente con uno o más ingredientes accesorios. Se pueden preparar tabletas comprimidas comprimiendo en una máquina adecuada el ingrediente activo en forma de libre flujo, por ejemplo como un polvo o gránulos, mezclado opcionalmente con un aglutinante, lubricante, diluyente inerte, agente tensoactivo o agente dispersante. Las tabletas moldeadas se pueden hacer moldeando en una máquina adecuada una mezcla del compuesto pulverizado

u2

humedecido con un diluyente líquido inerte. Opcionalmente, las tabletas se pueden recubrir o ranurar y se pueden formular a fin de proveer la liberación lenta o controlada del ingrediente activo.

5 Las formulaciones para administración parenteral incluyen soluciones inyectables estériles no acuosas que pueden contener antioxidantes, amortiguadores, bacteriostáticos, y solutos que hacen a la formulación isotónica con la sangre del receptor deseado; y suspensiones estériles acuosas y no acuosas que pueden incluir agentes de suspensión y agentes espesantes. Las formulaciones se pueden presentar en recipientes
10 de dosis unitaria o de dosis múltiples, por ejemplo ampolletas y frascos sellados, y se pueden guardar en una condición secada por congelación (liofilizada) que solo requiere la adición de un vehículo líquido estéril, por ejemplo agua inyectable, inmediatamente antes de usarse. Se pueden preparar soluciones y suspensiones inyectables extemporáneas partiendo de
15 polvos, gránulos y tabletas estériles del tipo previamente descrito.

Las formulaciones para administración rectal se pueden presentar como un supositorio con los vehículos usuales tales como manteca de cacao, grasa sólida o polietilenglicol.

20 Las formulaciones para administración tópica en la boca, por ejemplo por vía bucal o sublingual, incluyen pastillas que comprenden el ingrediente activo saborizado en una base tal como sacarosa y acacia o tragacanto, y pastillas que comprenden el ingrediente activo en una base como gelatina y glicerina, o sacarosa y acacia.

113

Los compuestos de la invención se pueden formular como preparaciones de depósito. Tales formulaciones de acción prolongada se pueden administrar por implante (por ejemplo por vía subcutánea o intramuscular) o mediante inyección intramuscular. De esta manera, por ejemplo, los compuestos de la invención se pueden formular con materiales poliméricos o hidrofóbicos adecuados (por ejemplo como una emulsión en un aceite aceptable) o resinas de intercambio iónico, o como derivados escasamente solubles, por ejemplo como una sal escasamente soluble.

Además de los ingredientes particularmente mencionados más arriba, las formulaciones pueden incluir otros agentes convencionales relacionados con el tipo de formulación en cuestión; por ejemplo, los adecuados para administración oral pueden incluir agentes saborizantes.

Los compuestos de receptor EP₄ para usarse en la presente invención se pueden usar en combinación con otros agentes terapéuticos, por ejemplo inhibidores de COX-2, tales como celecoxib, rofecoxib, valdecoxib o parecoxib; inhibidores de 5-lipooxigenasa; analgésicos tales como paracetamol, AINE's tales como diclofenaco, indometacina, nabumetona, naproxeno o ibuprofeno; antagonistas del receptor de leucotrieno; DMARD's tales como metotrexate; bloqueadores del canal de sodio tales como lamotrigina; antagonistas del canal de calcio de tipo N; moduladores del receptor de NMDA, tales como antagonistas del receptor de glicina; gabapentina, pregabalina y compuestos relacionados; antidepresivos tricíclicos tales como amitriptilina; agentes antiepilépticos estabilizadores de

114

neurona; inhibidores de la incorporación mono-aminérgica tales como venlafaxina; analgésicos opioides; anestésicos locales; agonistas de 5HT₁ tales como triptanos, por ejemplo sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan o rizatriptan; ligandos del receptor EP₁; ligandos del receptor EP₂; ligandos del receptor EP₃; antagonistas de EP₁; antagonistas de EP₂ y antagonistas de EP₃; agonistas del receptor canabinoide; antagonistas de VR1. Cuando los compuestos se usan en combinación con otros agentes terapéuticos, los compuestos se pueden administrar secuencialmente o simultáneamente mediante cualquier vía conveniente.

Así, la invención provee, en una modalidad adicional, una combinación que comprende un compuesto de fórmula (I), o un derivado farmacéuticamente aceptable del mismo, junto con uno o más agentes terapéuticos adicionales.

Convenientemente, las combinaciones anteriormente mencionadas se pueden presentar para usarse en forma de una formulación farmacéutica, y de esta manera las formulaciones farmacéuticas que comprenden una combinación como se define arriba, junto con un vehículo o excipiente farmacéuticamente aceptable, comprenden un aspecto adicional de la invención. Los componentes individuales de dichas combinaciones se pueden administrar de forma secuencial o simultánea en formulaciones farmacéuticas separas o combinadas.

Cuando un compuesto de fórmula (I), o un derivado

MS

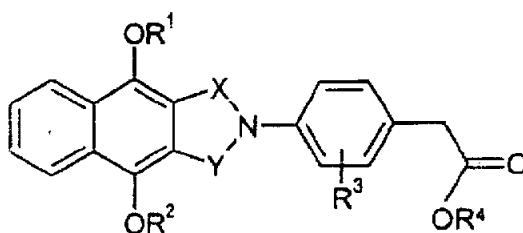
farmacéuticamente aceptable del mismo, se usa en combinación con un segundo agente terapéutico activo contra la misma enfermedad, la dosis de cada compuesto puede diferir de la dosis del compuesto cuando se usa solo. Las dosis adecuadas serán apreciadas fácilmente por los expertos en la materia.

Una dosis diaria propuesta de los compuestos de fórmula (I) o sus sales farmacéuticamente aceptables para terapia en humanos, es de 0.001 mg/kg a 30 mg/kg de peso corporal por día, particularmente de 0.1 mg/kg a 3 mg/kg de peso corporal por día, calculados como el ácido libre, que se puede administrar como una sola dosis o en dosis divididas, por ejemplo de una a cuatro veces al día. La escala de dosis para los seres humanos adultos es por lo general de 0.1 mg/día a 1000 mg/día, por ejemplo de 10 mg/día a 800 mg/día, de preferencia de 10 mg/día a 200 mg/día, calculados como el ácido libre.

La cantidad precisa administrada de los compuestos de fórmula (I) a un hospedero, particularmente a un paciente humano, será responsabilidad del médico a cargo. Sin embargo, la dosis usada dependerá de varios factores que incluyen la edad y sexo del paciente, la condición precisa tratada y su severidad, la vía de administración, y cualquier posible terapia de combinación que pueda estarse llevando a cabo.

La presente invención también provee un procedimiento para preparar los compuestos de fórmula (I) y derivados farmacéuticamente aceptables de los mismos.

De esta manera, en una modalidad de la invención, se provee un procedimiento para preparar un compuesto de fórmula (I) en donde uno de X y Y representa C=O y el otro representa CH₂, y R¹, R² y R³ son como se define arriba con respecto a la fórmula (I), dicho procedimiento comprende hacer reaccionar un compuesto de fórmula (II),



(II)

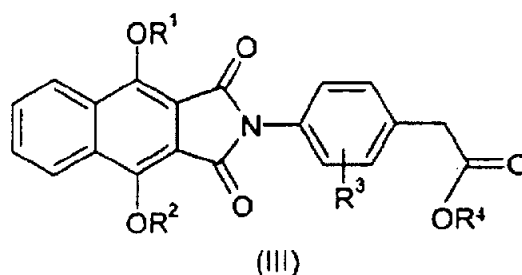
en donde uno de X y Y representa C=O y el otro representa CH₂; R¹, R² y R³ son como se define anteriormente con respecto a la fórmula (I); y R⁴ representa alquilo de C₁₋₆; con una base adecuada, tal como hidróxido de sodio, y opcionalmente formar un derivado farmacéuticamente aceptable del compuesto así formado, o convertir un compuesto de fórmula (I) en otro.

En una modalidad, la reacción anteriormente mencionada que comprende un compuesto de fórmula (II) se realiza en un disolvente adecuado, tal como etanol, bajo reflujo.

En otra modalidad de la presente invención, se provee un procedimiento para preparar un compuesto de fórmula (I) en donde X y Y representan C=O, y R¹, R² y R³ son como se define arriba con respecto a la fórmula (I), dicho procedimiento comprende agregar un compuesto de fórmula

117

(III),



5

10

en donde R¹, R² y R³ son como se define arriba con respecto a la fórmula (I); y R⁴ representa alquilo de C₁₋₆; a un ácido o mezcla de ácidos adecuados, tales como ácido acético glacial, en presencia de ácido clorhídrico, y opcionalmente formar un derivado farmacéuticamente aceptable del compuesto así formado, o convertir un compuesto de fórmula (I) en otro.

15

En una modalidad, la reacción anteriormente mencionada que comprende un compuesto de fórmula (III), se realiza a una temperatura en la escala de aproximadamente 50 °C a 110 °C, durante un periodo en la escala de aproximadamente 2 horas a 70 horas. En una modalidad, la relación molar de ácido acético glacial al otro ácido presente en la mezcla de reacción, tal como ácido clorhídrico, es 1:1.

Los compuestos de las fórmulas (II) y (III) se pueden preparar de acuerdo con el siguiente esquema 1:

118

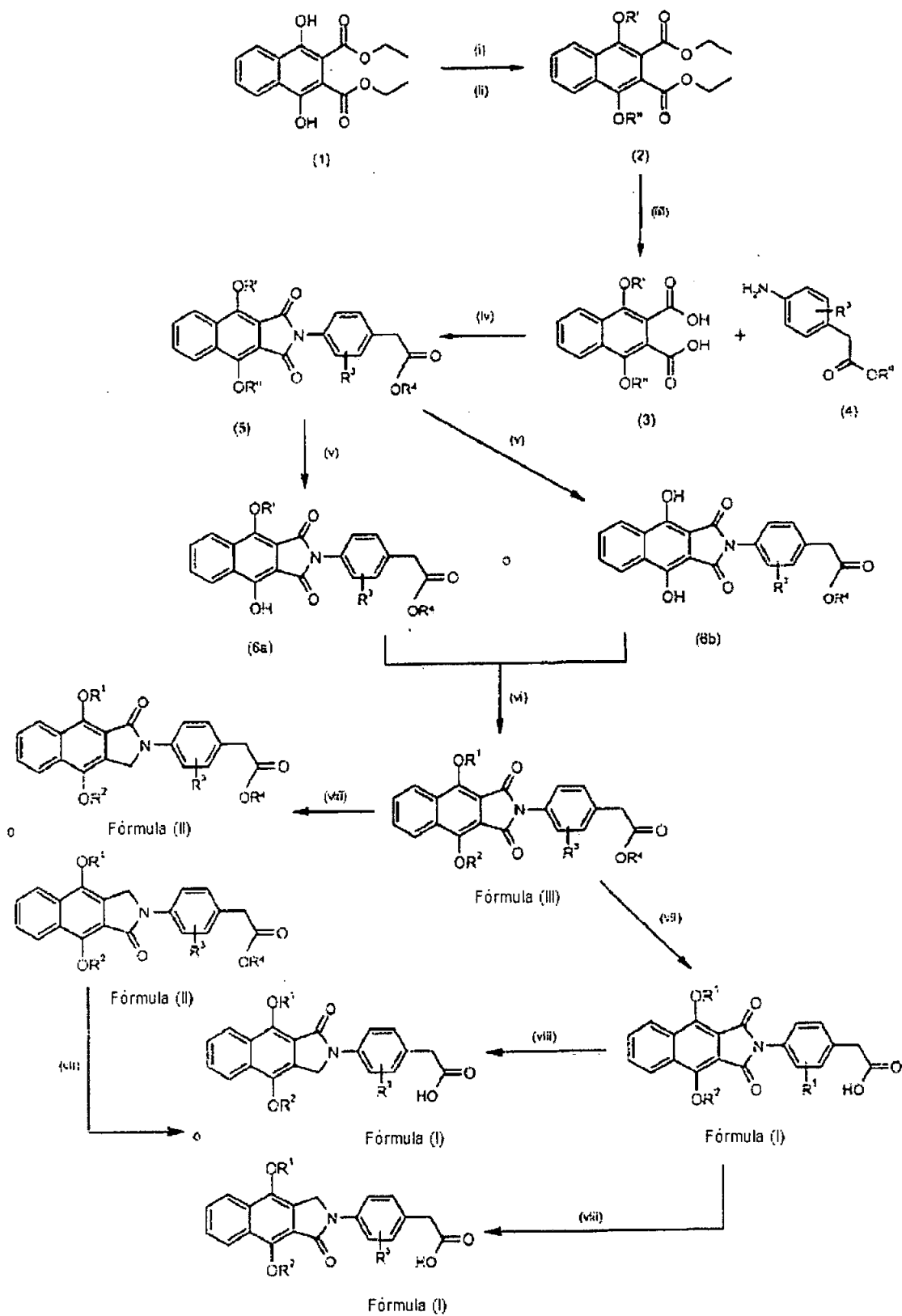
ESQUEMA 1

5

10

15

20

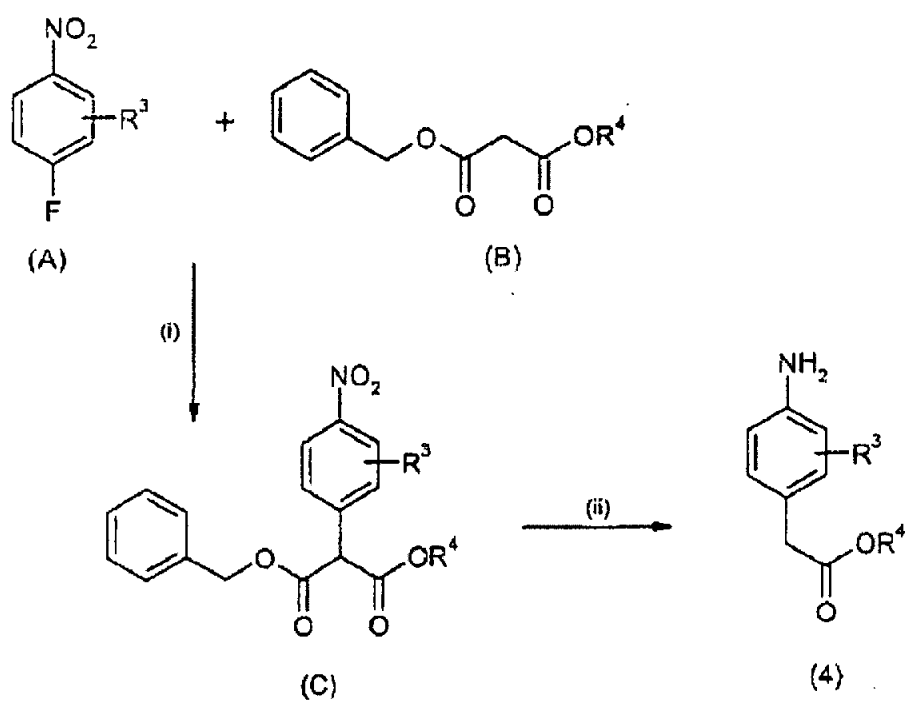


119

(i) $R'-Br$, K_2CO_3 , $(CH_3)_2CO$; (ii) $R''-Br$, K_2CO_3 , $(CH_3)_2CO$; (iii) $NaOH$, $EtOH/H_2O$; (iv) CH_3CO_2H ; (v) Pd/C , H_2 , $EtOH$ o BBr_3 , CH_2Cl_2 ; (vi) $CClF_2CO_2Na$, Na_2CO_3 , DMF ; o $CHClF_2$, K_2CO_3 , KI , DMF ; (vii) $NaOH$, $EtOH$ o HCl , CH_3CO_2H ; (viii) $NaBH_4$, $MeOH$ o $EtOH$ y después TFA , Et_3SiH ; (en donde R' y R'' pueden ser iguales o diferentes y representan grupos protectores adecuados tales como $-CH_2Ph$, o uno de R' y R'' representa un grupo protector adecuado y el otro representa R^1 o R^2).

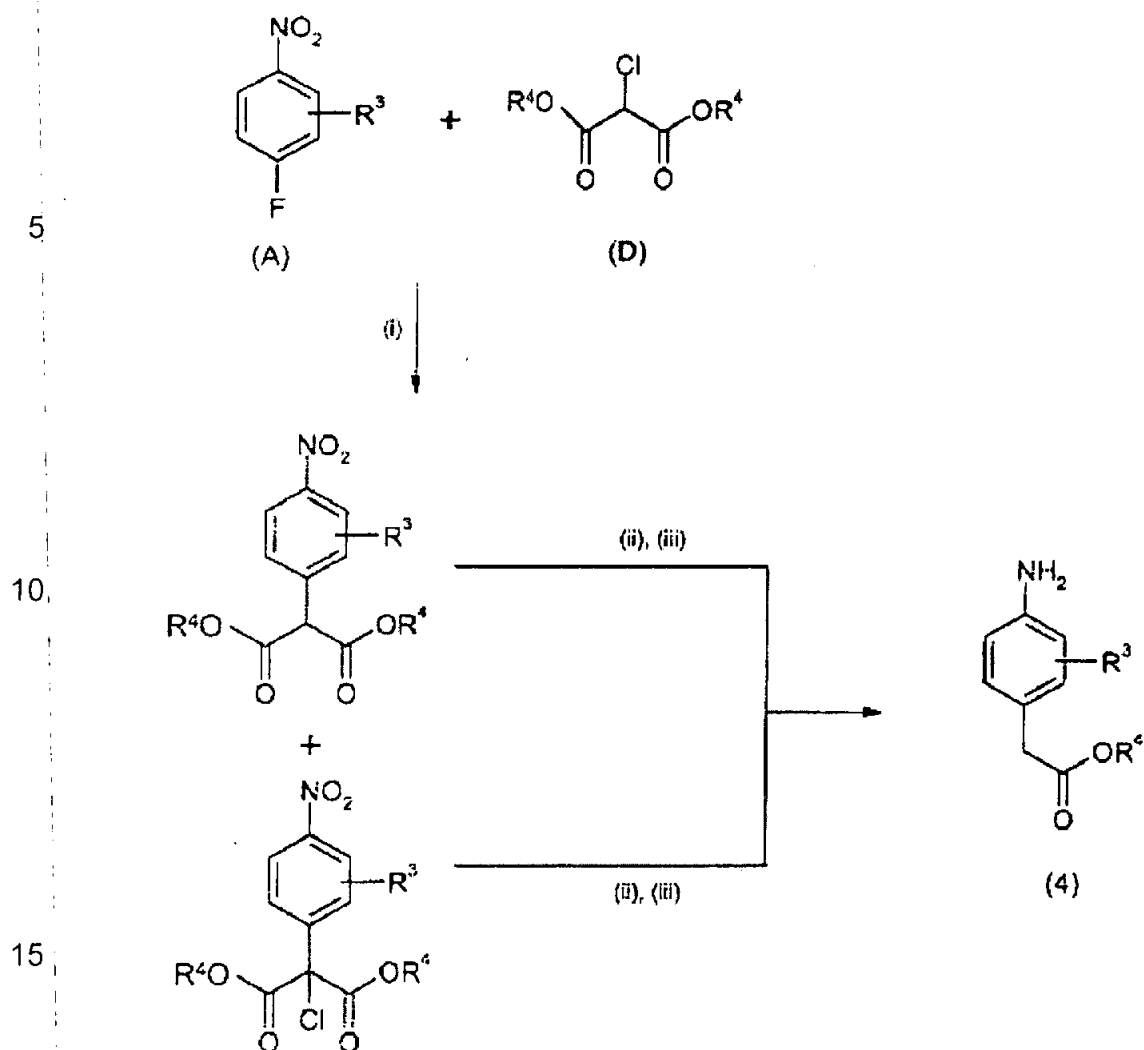
El compuesto (1) se puede preparar de acuerdo con el método descrito en la solicitud de patente internacional número de publicación WO 02/064564.

Los compuestos de fórmula (4) en donde R^3 es F y R^4 es como se define anteriormente con respecto a las fórmulas (II) y (III), se puede preparar de acuerdo con los esquemas 2 y 3 siguientes.

ESQUEMA 2

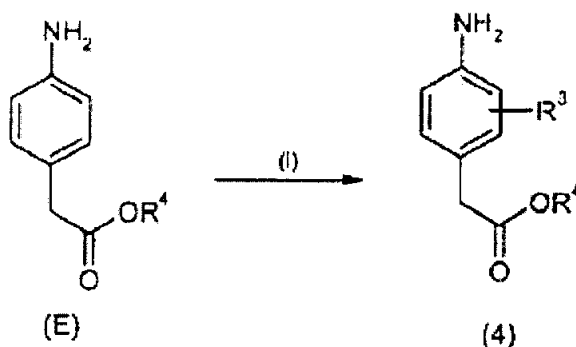
(i) NaH, DMF seca; (ii) NH₄CO₂H, EtOH, Pd/C.

121

ESQUEMA 3

(i) NaOH, DMF seca; (ii) $\text{NH}_4\text{CO}_2\text{H}$, EtOH, Pd/C; (iii) NaOH, H_2O , EtOH.

20 Los compuestos de fórmula (4) en donde R^3 es Br o Cl, y R^4 es como se define anteriormente con respecto a las fórmulas (II) y (III), se pueden preparar de acuerdo con el esquema 4 siguiente.

ESQUEMA 4

(i) N-Clorosuccinamida o N-Bromosuccinamida.

Los compuestos de fórmula (A) están disponibles comercialmente o se pueden preparar de acuerdo con los métodos conocidos (por ejemplo, el 3,4-difluoronitrobenzenceno se puede comprar de Sigma-Aldrich Co. Ltd.).

Los compuestos de fórmula (B) están disponibles comercialmente o se pueden preparar de acuerdo con los métodos conocidos (por ejemplo, el etil-malonato de bencilo se puede comprar de Sigma-Aldrich Co. Ltd.).

Los compuestos de fórmula (D) están disponibles comercialmente o se pueden preparar de acuerdo con los métodos conocidos (por ejemplo, el cloro-malonato de dietilo se puede comprar de Sigma-Aldrich Co. Ltd.).

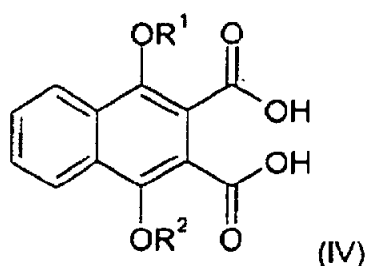
Los compuestos de fórmula (E) están disponibles comercialmente o se pueden preparar de acuerdo con los métodos conocidos

123

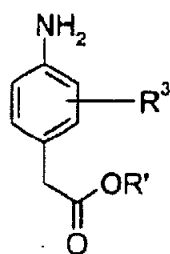
(por ejemplo, el 4-aminofenil-acetato de etilo se puede comprar de Avocado Research).

En otra modalidad de la invención, se provee un procedimiento para preparar un compuesto de fórmula (I), o un derivado farmacéuticamente aceptable del mismo, dicho procedimiento comprende hacer reaccionar un

5 compuesto de fórmula (IV),



en donde R^1 y R^2 son como se define anteriormente con respecto a la fórmula (I), con un compuesto de fórmula (V),

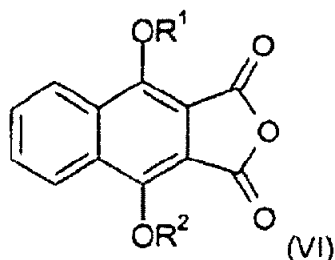


en donde R^3 es como se define anteriormente con respecto a la fórmula (I), y R' representa H o alquilo de C_{1-6} , y opcionalmente formar un

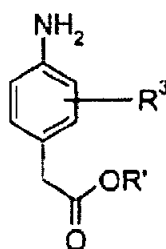
20 derivado farmacéuticamente aceptable del compuesto así formado, o convertir un compuesto de fórmula (I) en otro.

En otra modalidad de la invención, se provee un procedimiento

para preparar un compuesto de fórmula (I), o un derivado farmacéuticamente aceptable del mismo, dicho procedimiento comprende hacer reaccionar un compuesto de fórmula (VI),



en donde R^1 y R^2 son como se define anteriormente con respecto a la fórmula (I), con un compuesto de fórmula (V),



en donde R^3 es como se define anteriormente con respecto a la fórmula (I), y R' representa H o alquilo de C_{1-6} , y opcionalmente formar un derivado farmacéuticamente aceptable del compuesto así formado, o convertir un compuesto de fórmula (I) en otro.

Los compuestos de las fórmulas (IV), (V) y (VI) están disponibles comercialmente o se pueden preparar de acuerdo con los métodos conocidos.

Las siguientes descripciones y ejemplos ilustran la preparación de los compuestos de la invención. Las descripciones se refieren a

compuestos intermediarios.

Abreviaciones

DCM	Diclorometano
DMF	Dimetilformamida
DMSO	Sulfóxido de dimetilo
EtOH	Etanol
LC/MS	Cromatografía de líquido /Espectroscopía de masa
MDAP	Autopreparación dirigida de masa
MeOH	Metanol
TFA	Acido trifluoroacético

Procedimientos analíticos

LC/MS

Columna:

Waters Atlantis (4.6 mm x 50 mm). Fase estacionaria, tamaño de partícula, 3µm.

Disolventes:

A: Disolvente acuoso = agua + 0.05% de ácido fórmico

B: Disolvente orgánico = acetonitrilo + 0.05% de ácido fórmico

Método:

Tiempo / min %B

0	3
0.1	3
4	97
4.8	97
4.9	3
5.0	3

- Velocidad de flujo, 3 ml/min.
- Volumen de inyección, 5 µl.
- Temperatura de la columna, 30°C.
- Escala de detección UV, 220 nm a 330 nm.

Todos los tiempos de retención se midieron en minutos.

RMN

Se registraron los espectros de ^1H RMN en un espectrómetro de RMN Bruker AVANCE 400 o Bruker DPX250. Los desplazamientos químicos se expresan en partes por millón (ppm, unidades δ). Las constantes de acoplamiento (J) están en Hertz (Hz). Los patrones de división describen multiplicidades aparentes y se designan como s (singulete), d (doblete), t (triplete), q (cuarteto), dd (doblete doble), ddd (doblete doblete doble), dt (triplete doble), m (multiplete), br (amplio).

127

Técnicas de purificación

La purificación de los compuestos ejemplares se puede efectuar por los métodos convencionales, tales como cromatografía o recristalización, usando los disolventes adecuados. Los métodos cromatográficos incluyen

5 cromatografía en columna, cromatografía de vaporización instantánea, HPLC (cromatografía de líquidos de alto rendimiento), SFC (cromatografía de fluido supercrítico), y MDAP (autopreparación dirigida de masa).

El término "Biotage" usado en la presente se refiere a cartuchos de gel de sílice preempacados disponibles comercialmente.

10 Columna de Autopreparación Dirigida de Masa (MDAP):

Waters Atlantis: 19 mm x 100 mm (escala chica); y 30 mm x 100 mm (escala grande).

Tamaño de partícula de la fase estacionaria, 5 µm.

Disolventes:

15 A: Disolvente acuoso = agua + 0.1% ácido fórmico

B: Disolvente orgánico = acetonitrilo + 0.1 % ácido fórmico

Disolvente de preparación = metanol : agua, 80:20

Disolvente de enjuague de aguja = Metanol

Métodos:

20 Se usaron 5 métodos dependiendo del tiempo de retención analítico del compuesto de interés:

(1) Escala grande/chica 1.0-1.5 = 5-30% B

(2) Escala grande/chica 1.5-2.2 = 15-55% B

(3) Escala grande/chica 2.2-2.9 = 30-85% B

(4) Escala grande/chica 2.9-3.6 = 50-99% B

Tiempo de corrida, 13.5 minutos, que comprenden 10 minutos de gradiente seguidos por 3.5 minutos de inundación de la columna y un paso de reequilibrio.

(5) Escala grande/chica 3.6-5.0 = 80-99% B

Tiempo de corrida, 13.5 minutos, que comprenden 6 minutos de gradiente seguidos por 7.5 minutos de inundación de la columna y un paso de reequilibrio.

Velocidad de flujo:

20 ml/min (escala chica) o 40 ml/min (escala grande).

Especificación del sistema de purificación de HPLC:

- Columna: Supelco LCABZ++, DI 100 mm x 20 mm, tamaño de partícula, 5 μ m

- Velocidad de flujo: 20 ml/min

- Volumen de inyección: 0.5 ml

- Temperatura: ambiente

- Disolventes: A – disolvente acuoso = agua + 0.1 % ácido fórmico; B – disolvente orgánico = MeCN/agua, 95:5 +0.05% ácido fórmico

- Tiempo de corrida: 9 min de gradiente seguido por 5 min de inundación de columna y reequilibrio

- Gradiente: 30-80% B

129

SFC (Cromatografía de Fluido Supercrítico)

Columna: Chiralcel OD-H S.F.C. (250 mm x 21.2 mm DI; tamaño de partícula 5 micras), o

5 Columna de etilpiridina (150 mm de longitud x 21.2 mm DI; tamaño de partícula, 6 micras), o

Chiralpak AD (355 y 438)

(250 mm de longitud x 21.2 mm DI; tamaño de partícula 10 micras)

10 Fase móvil: A = Dióxido de carbono (supercrítico)

B = Metanol

A:B (70:30 - 85:15 p/p, isocrático)

Velocidad de flujo: 39.4 gmin^{-1} (= 50 mLmin^{-1} , aprox.)

Temperatura: 40 °C

Retropresión: 100 bar

15 Detección: absorbancia en U.V. a 215 nm

Tiempo de corrida: 25 minutos o 20 minutos

Concentración de la muestra: 100 mgmL^{-1} en dimetilformamida

Volumen de la inyección: VARIABLE

20 Purificación HPLC 1

Fase estacionaria: Chiralcel OD (250 mm longitud x 21.2 mm DI; tamaño de partícula, 10 micras)

Fase móvil: heptano : etanol (variando de isocrático 50:50 v/v a

130

isocrático 90:10 v/v):

320 = 50:50 v/v

353 = 70:30 v/v

354 = 90:10 v/v

5

356 = 70:30 v/v

Velocidad de flujo: 17 mLmin⁻¹

Temperatura: ambiente

Detección: absorbancia U.V. a 215 nm

Volumen de inyección: 0.9 mL

10

Purificación HPLC 2

Columna: Phenomenex Luna C18 (2) (50 mm x 21.2mm DI;

tamaño de partícula 10 micras)

Fase móvil: A = acetonitrilo + 0.1% v/v ácido trifluoroacético

B = agua + 0.1% v/v ácido trifluoroacético

15

(Métodos de gradiente e isocrático)

Velocidad de flujo: 20 mLmin⁻¹ aprox.

Temperatura: ambiente

Detección: absorbancia U.V. a 215 nm (ancho de banda 0 nm)

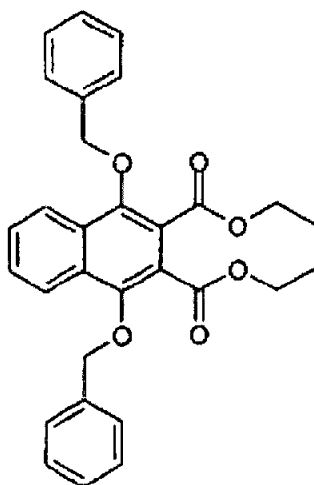
Concentración de la muestra: 100 mgml⁻¹ en dimetilformamida

20

Volumen de inyección: VARIABLE.

DI = diámetro interno

131

DESCRIPCION 1**1,4-bis[(Fenilmetil)oxi]-2, 3-naftalendicarboxilato de dietilo**

5

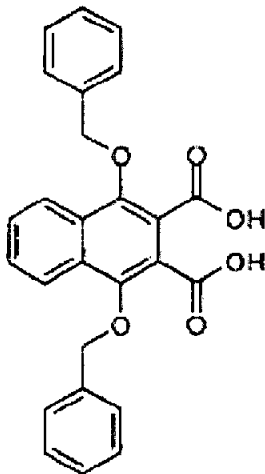
10

15

A una solución agitada de 1,4-dihidroxi-2,3-naftalendicarboxilato de dietilo (3g, 9.87mmol) y carbonato de potasio (3.40g, 24.7mmol) en acetona (100ml), se le agregó bromuro de bencilo (2.95ml, 24.7mmol). La mezcla de reacción se puso en reflujo durante 18 horas bajo una atmósfera de argón. La mezcla resultante se evaporó y la mezcla de reacción se trituró con agua. El sólido de color canela resultante se recogió por filtración y se lavó con agua; después se secó al vacío para dar el compuesto del título (5.23g, 10.8mmol).

LC/MS: t. r.=4.13, [MH]⁺ 485.

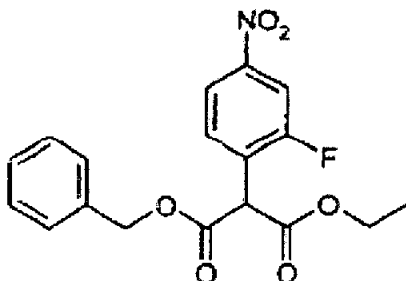
132

DESCRIPCION 2**Acido 1,4-bis[(fenilmetil)oxi]-2,3-naftalendicarboxílico**

Una mezcla de 1,4-bis[(fenilmetil)oxi]-2,3-naftalendicarboxilato de dietilo (4.78g, 9.88mmol), etanol (75ml), y solución acuosa de hidróxido de sodio 2N (75 ml), se puso a reflujo durante 2 horas. La mezcla de reacción se enfrió y se evaporó. Esto se acidificó con HCl (2N) y el sólido cremoso resultante se recogió por filtración y se lavó con agua. Esto se secó al vacío para dar el compuesto del título (3.79g, 8.86mmol).

LC/MS: t. r.=3.15, $[MH]^-$ 427.

133

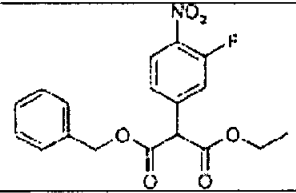
DESCRIPCION 3**Fenilmetil(2-fluoro-4-nitrofenil)propandioato de etilo**

5 A una solución enfriada en un baño de hielo de etil-malonato de
bencilo (2.9g, 12.6mmol) (20ml) en DMF seca (20 ml), se le agregó en
10 porciones hidruro de sodio (504mg, 12.6mmol) y se agitó durante 10 minutos.
A temperatura ambiente, se le agregó 3,4-difluoronitrobenceno (2g, 12.6mmol)
y se agitó bajo argón. Se calentó a 100°C durante 20 horas. La mezcla de
reacción se enfrió y se dividió entre ácido clorhídrico 2N (75 ml) y acetato de
etilo (75 ml). La capa acuosa se extrajo con acetato de etilo (2x 75 ml) y la
15 fase orgánica combinada se evaporó hasta quedar un aceite amarillo. Se
purificó por cromatografía sobre gel de sílice eluyendo con acetato de
etilo/hexano (1:4), para dar el compuesto del título como un aceite amarillo
(3.86g, 10.6mmol).

LC/MS: t. r.=3.40, [MH]⁺ 362.

20 El siguiente compuesto se preparó de manera similar al
fenilmetil-(2-fluoro-4-nitrofenil)propanodioato de etilo, usando los materiales
iniciales adecuados.

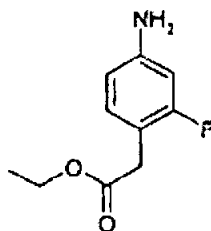
134

	Nombre	LC/MS
	Fenilmetil(3-fluoro-4-nitrofenil)propanodioato de etilo	t. r. = 3.30 [MH] ⁺ 362

5

DESCRIPCION 4**(4-Amino-2-fluorofenil)acetato de etilo**

10



15

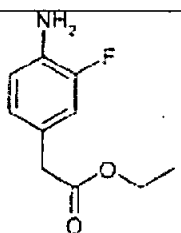
Se disolvió fenilmetil(2-fluoro-4-nitrofenil)propanodioato de etilo (3.86g, 10.6mmol) en etanol, se trató con formiato de amonio (6.7g, 10.6mmol), y se le agregó bajo argón paladio sobre carbono en pasta al 10% (380 mg). La mezcla de reacción se puso a reflujo durante 3 horas, se enfrió y se filtró. Se evaporó y se purificó por cromatografía sobre gel de sílice diluyendo con acetato de etilo/hexano (1:1), para dar el compuesto del título como un aceite amarillo (1.26g).

20

LC/MS: t. r.=2.10, [MH]⁺ 198.

El siguiente compuesto se preparó de manera similar al (4-amino-2-fluorofenil)acetato de etilo, usando los materiales iniciales adecuados.

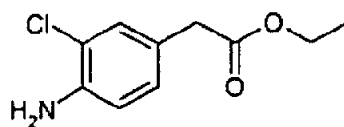
BS

	Nombre	LC/MS
	(4-Amino-3-fluorofenil)acetato de etilo	t. r.=2.20 [MH] ⁺ 198

5

DESCRIPCION 5

(4-Amino-3-clorofenil)acetato de etilo



10

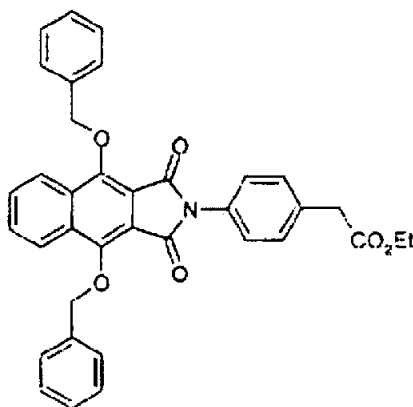
Se disolvió 4-aminofenilacetato de etilo (20g, 112mmol) en cloroformo (300 ml) y se trató con N-clorosuccinimida (14.92 g, 112 mmol); se agitó durante 15 minutos a temperatura ambiente bajo argón. La mezcla de reacción se lavó con agua y salmuera, y se secó sobre sulfato de magnesio. Se evaporó hasta quedar un aceite pardo, que se purificó por cromatografía sobre gel de sílice eluyendo con acetato de etilo (0-45%) en hexano, para dar el compuesto del título como un aceite anaranjado (10.12 g, 47.4 mmol).

15

LC/MS: t. r.= 2.59, [MH]⁺ 214.

DESCRIPCION 6

(4-{1,3-Dioxo-4,9-bis[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo



Una mezcla de ácido 1,4-bis[fenilmetil]oxi-2,3-naftalendicarboxílico (2.0g, 4.67mmol) y (4-aminofenil)acetato de etilo (1.67g, 9.35mmol), se calentó a 120 °C en ácido acético (30ml) durante 2 horas. La mezcla se solidificó al reposar a temperatura ambiente durante la noche. Se le agregó agua y el sólido se recogió por filtración y se lavó con agua. Esto se secó al vacío para dar el compuesto del título (2.65g, 4.64mmol).

LC/MS: t. r.=4.24, [MH]⁺ 572.

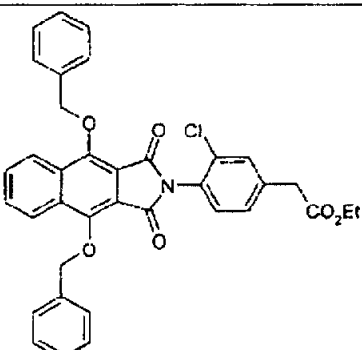
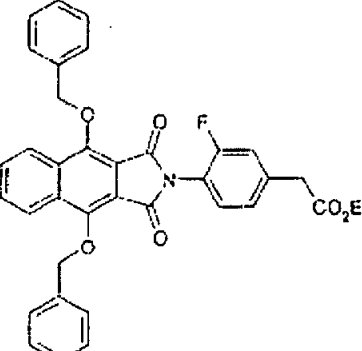
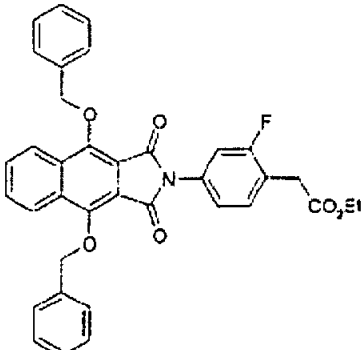
Los siguientes compuestos se prepararon de manera similar al (4-{1,3-dioxo-4,9-bis[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)-acetato de etilo, usando los materiales iniciales adecuados.

137

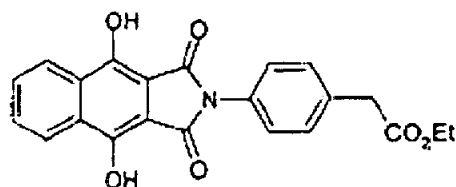
5

10

15

	Nombre	LC/MS
	(3-Cloro-4-{1,3-dioxo-4,9-bis[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo	t. r.=4.15 [MH] ⁺ 606
	(4-{1,3-Dioxo-4,9-bis[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acetato de etilo	t. r. = 4.08 [MH] ⁺ 590
	(4-{1,3-Dioxo-4,9-bis[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}-fluorofenil)acetato de etilo	t. r. = 4.10 [MH] ⁺ 590

138

DESCRIPCION 7**[4-(4,9-Dihidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il)fenil]acetato de etilo**

Se suspendió paladio al 10% sobre carbono (0.265 g) en etanol (250 ml), y a esto se le agregó (4-{1,3-dioxo-4,9-bis[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo (2.65g, 4.64mmol). La reacción se agitó a temperatura ambiente bajo una atmósfera de hidrógeno durante 3 horas. Esto se filtró a través de una almohadilla de celite bajo un manto de argón, y se lavó con diclorometano. El filtrado se evaporó para dar un sólido de color canela (1.52 g, 3.89 mmol).

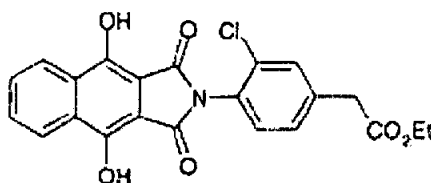
LC/MS: t. r.=3.25, [MH]⁺ 392.

Los siguientes compuestos se prepararon de manera similar al [4-(4,9-dihidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il)fenil]acetato de etilo, usando los materiales iniciales adecuados.

	Nombre	LC/MS
	[4-(4,9-Dihidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il)-3-fluorofenil]acetato de etilo	t. r. = 3.16 [MH] ⁺ 410
	[4-(4,9-Dihidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il)-2-fluorofenil]acetato de etilo	t. r. = 3.24 [MH] ⁺ 410

DESCRIPCION 8

[3-Cloro-4-(4,9-dihidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il)fenil]acetato de etilo



A una solución de (3-cloro-4-{1,3-dioxo-4,9-bis[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo (0.505 g, 0.84 mmol) en DCM (30 ml), enfriada a -78°C bajo una atmósfera de argón, se le agregó tribromuro de boro (0.24 ml, 2.50 mmol), gota a gota. Se agitó a -78°C durante 25 minutos. La mezcla de reacción se inactivó con agua y se calentó a temperatura ambiente. Esto se extrajo dos veces con DCM usando una frita hidrofóbica. La fase orgánica se evaporó hasta quedar un sólido anaranjado. La trituración en caliente en DCM dio como resultado un sólido amarillo que se

740

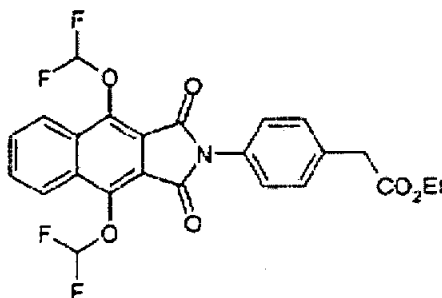
recogió por filtración (0.189 g, 0.44 mmol). El filtrado se purificó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo (0-70%) en hexano, para dar el compuesto de título como un sólido amarillo (0.035 g, 0.082 mmol).

5 LC/MS: t. r. = 3.22, $[MH]^+$ 426.

DESCRIPCION 9

(4-{4,9-bis[(Difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo

10



15

A una solución de [4-(4,9-dihidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il)fenil]acetato de etilo (0.200 g, 0.51 mmol) en dimetilformamida (7 ml), se le agregó carbonato de sodio (0.163 g, 1.53 mmol), seguido por clorodifluoroacetato de sodio (0.233 g, 1.53 mmol). La mezcla se calentó a 100 °C durante 2.5 horas. Se le agregó más carbonato de sodio (0.054 g, 0.51 mmol) y clorodifluoroacetato de sodio (0.078 g, 0.51 mmol), continuando el calentamiento durante una hora; nuevamente se le agregaron las mismas cantidades y el calentamiento se continuó durante 30 minutos. La mezcla se enfrió a temperatura ambiente y se le agregó agua. El

20

sólido pardo resultante se recogió por filtración y se lavó con agua. Esto se purificó por cromatografía sobre gel de sílice eluyendo con acetato de etilo (0-30%) en hexano, para dar el compuesto del título como un sólido blanco (0.032 g, 0.065 mmol).

5 LC/MS: t. r. = 3.61, $[MH]^+$ 492.

Los siguientes compuestos se prepararon de manera similar al (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-fenil)acetato de etilo, usando los materiales iniciales adecuados.

10

15

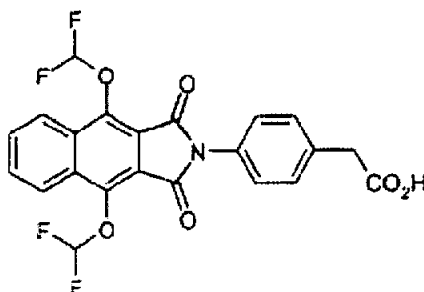
20

	Nombre	LC/MS
	(4-{4,9-bis[(Difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-clorofenil)acetato de etilo	t. r. = 3.64 $[MH]^+$ 526
	(4-{4,9-bis[(Difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acetato de etilo	t. r. = 3.61 $[MH]^+$ 510
	(4-{4,9-bis[(Difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acetato de etilo	t. r. = 3.63 $[MH]^+$ 510

142

EJEMPLO 1

Acido (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acético



Se calentó (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo (0.03g, 0.061mmol) a 100 °C en una mezcla 1:1 de ácido acético : ácido clorhídrico acuoso 2N (4ml), durante 2 horas. La reacción se enfrió a temperatura ambiente. Al agregarle agua, el sólido blanco resultante se recogió por filtración y se lavó con agua. Este se purificó por MDAP para dar el producto deseado (0.017g, 0.037mmol).

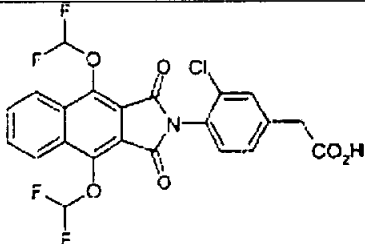
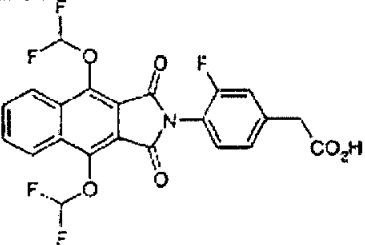
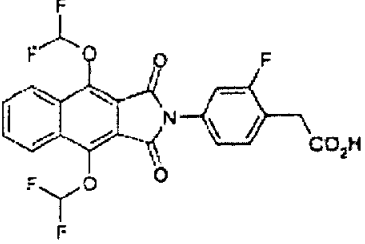
LC/MS: t. r. = 3.28, [MH]⁺ 464.

Los siguientes compuestos se prepararon de manera similar al ácido (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acético, usando los materiales iniciales adecuados.

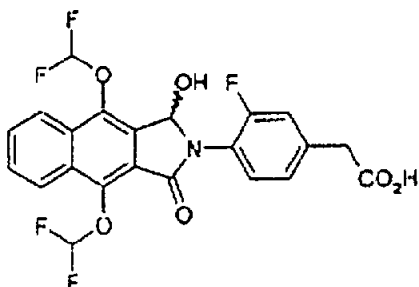
143

5

10

		Nombre	LC/MS
Ejemplo 2		Acido 4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-clorofenil)acético	t. r. = 3.23 [MH] ⁺ 498
Ejemplo 3		Acido 4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético	t. r. = 3.15 [MH] ⁺ 482
Ejemplo 4		Acido 4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acético	t. r. = 3.18 [MH] ⁺ 482

144

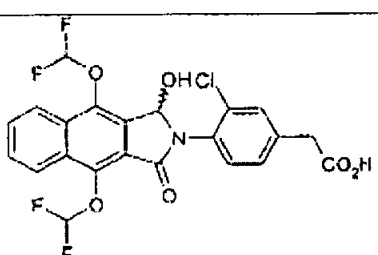
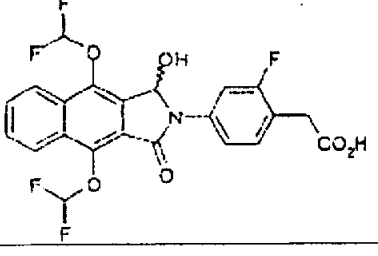
DESCRIPCION 10**Acido (4-{4,9-bis[(difluorometil)oxi]-1-hidroxi-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético**

5
10 A una solución de ácido (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético (0.041 g, 0.085 mmol) en etanol (2 ml) y tetrahidrofurano (4 ml), se le agregó borohidruro de sodio (0.019g, 0.51 mmol). Esto se agitó a 0 °C durante 5 minutos. La mezcla se evaporó y después se inactivó con una solución acuosa saturada de cloruro de amonio hasta que la mezcla alcanzó un pH de 7. Esto se extrajo 2 veces
15 con acetato de etilo, se lavó con salmuera, se secó sobre sulfato de magnesio, y se evaporó, para dar el producto crudo (0.035 g, 0.072 mmol).

LC/MS: t. r. = 2.88, [MH]⁺ 484.

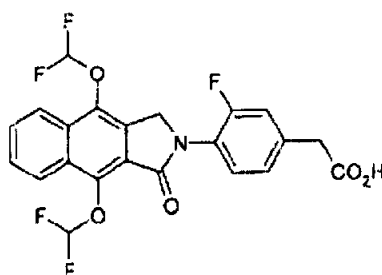
Los siguientes compuestos se prepararon de manera similar al ácido (4-{4,9-bis[(difluorometil)oxi]-1-hidroxi-3-oxo-1,3-dihidro-2H-benzo[f]-
20 isoindol-2-il}-3-fluorofenil)acético, usando los materiales iniciales adecuados.

MS

	Nombre	LC/MS
	Acido (4-{4,9-bis[(difluorometil)oxi]-1-hidroxi-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-clorofenil)acético	t. r. = 2.95 [MH] ⁺ 500
	Acido (4-{4,9-bis[(difluorometil)oxi]-1-hidroxi-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acético	t. r. = 3.03 [MH] ⁺ 484

EJEMPLO 5

Acido(4-{4,9-bis[(difluorometil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético



A una solución de ácido (4-{4,9-bis[(difluorometil)oxi]-1-hidroxi-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético (0.035g, 0.072mmol) en ácido trifluoroacético (2ml) enfriado a 0 °C, se le agregó trietilsilano (0.019ml, 0.110mmol). La agitación se continuó a 0 °C durante 5 minutos y después la mezcla se evaporó. La mezcla cruda se purificó usando

116

MDAP. Las fracciones limpias se evaporaron para dar el compuesto del título (0.015g, 0.033mmol).

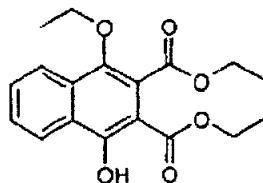
LC/MS: t. r. = 3.15, $[MH]^+$ 468.

Los siguientes compuestos se prepararon de manera similar al ácido 4-{4,9-bis[(difluorometil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético, usando los materiales iniciales adecuados.

		Nombre	LC/MS
Ejemplo 6		Acido 4-{4,9-bis[(difluorometil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-clorofenil)acético	t. r. = 3.21 $[MH]^+$ 484
Ejemplo 7		Acido 4-{4,9-bis[(difluorometil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acético	t. r. = 3.27 $[MH]^+$ 468

DESCRIPCION 11

1-(Etiloxi)-4-hidroxi-2,3-naftalendicarboxilato de dietilo

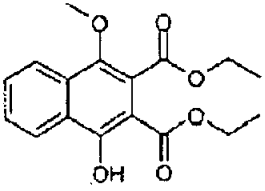
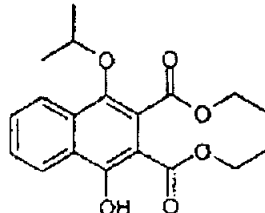
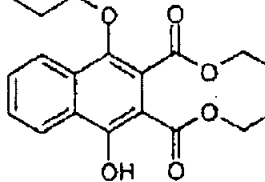


A una solución agitada de 1,4-dihidroxi-2,3-naftalendicarboxilato

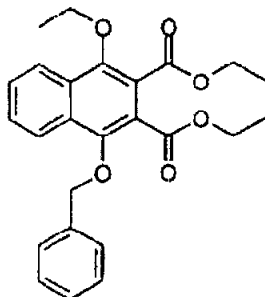
de dietilo (1g, 3.29mmol) y carbonato de potasio (0.454g, 3.29mmol) en acetona (25ml), se le agregó bromoetano (0.359g, 3.29mmol). La mezcla de reacción se puso a reflujo durante 24 horas bajo una atmósfera de argón. La mezcla resultante se evaporó y el residuo se dividió entre acetato de etilo 2x y agua. La parte orgánica combinada se lavó con agua y se secó sobre sulfato de magnesio. El aceite anaranjado se purificó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo (0-10%) en hexano, para dar el compuesto del título como un aceite transparente (0.661 g, 1.99mmol).

LC/MS: t. r. = 3.63, $[MH]^+$ 331.

Los siguientes compuestos se prepararon de manera similar al 1-(etiloxy)-4-hidroxi-2,3-naftalendicarboxilato de dietilo, usando los materiales iniciales adecuados.

	Nombre	LC/MS
	1-Hidroxi-4-(metiloxi)-2,3-naftalendicarboxilato de dietilo	t. r. = 3.50 $[MH]^+$ 317
	1-Hidroxi-4-[(metiletoxi)]-2,3-naftalendicarboxilato de dietilo	t. r. = 3.69 $[MH]^+$ 345
	1-Hidroxi-4-(propiloxi)-2,3-naftalendicarboxilato de dietilo	t. r. = 3.80 $[MH]^+$ 345

148

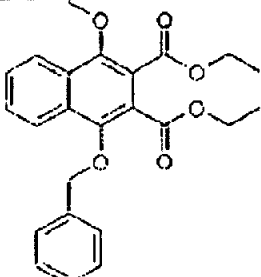
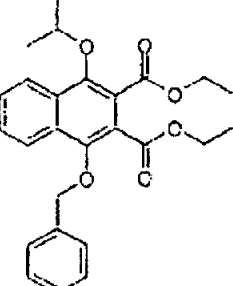
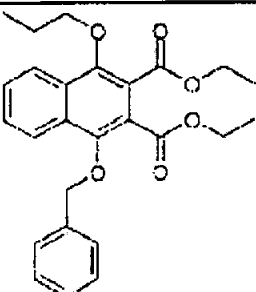
DESCRIPCION 12**1-(Etiloxi)-4-[(fenilmetil)oxi]-2,3-naftalendicarboxilato de dietilo**

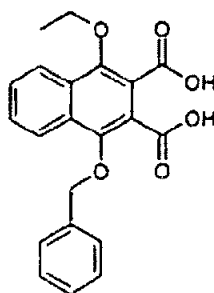
A una solución agitada de 1-(etiloxi)-4-hidroxi-2,3-naftalendicarboxilato de dietilo (2.45g, 7.38mmol) y carbonato potasio (1.53g, 11.1 mmol) en acetona (50ml), se le agregó bromuro de bencilo (1.32ml, 11.1mmol). La mezcla de reacción se puso a reflujo durante una hora bajo una atmósfera de argón. La mezcla resultante se evaporó y el residuo se dividió entre acetato de etilo 2x y salmuera. La fase orgánica combinada se lavó con agua y se secó sobre sulfato de magnesio. El aceite transparente se purificó por cromatografía en gel de sílice, eluyendo con acetato de etilo (0-40%) en hexano, para dar el compuesto del título como un aceite transparente (3.05g, 7.23mmol).

LC/MS: t. r. = 3.77, $[MH]^+$ 423.

Los siguientes compuestos se prepararon de manera similar al 1-(etiloxi)-4-[(fenilmetil)oxi]-2,3-naftalendicarboxilato de dietilo, usando los materiales iniciales adecuados.

mla

	Nombre	LC/MS
	1-(Metiloxi)-4-[(fenilmetil)oxi]-2,3-naftalendicarboxilato de dietilo	t. r. = 3.80 [MH] ⁺ 409
	1-(Metiletoxi)-4-[(fenilmetil)oxi]-2,3-naftalendicarboxilato de dietilo	t. r. = 3.83 [MNH ₄] ⁺ 454
	1-[(Fenilmetil)oxi]-4-(propiloxi)-2,3-naftalendicarboxilato de dietilo	t. r. = 3.98 [MH] ⁺ 436.98

DESCRIPCION 13**Acido 1-(etiloxi)-4-[(fenilmetil)oxi]-2,3-naftalendicarboxílico**

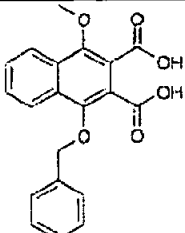
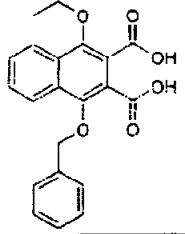
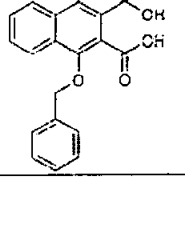
Una mezcla de 1-(etiloxi)-4-[(fenilmetil)oxi]-2,3-

VSD

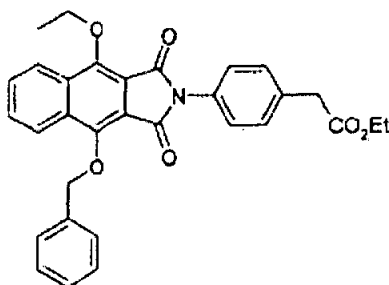
naftalendicarboxilato de dietilo (3.05g, 7.23mmol), etanol (30ml), y solución acuosa de hidróxido de sodio 2N (35ml), se puso a reflujo durante 3 horas. La mezcla de reacción se enfrió y se evaporó. Esto se acidificó con HCl (2N) y se extrajo con acetato de etilo dos veces. La fase orgánica combinada se secó sobre sulfato de magnesio y el disolvente se evaporó, para dar el compuesto del título como un sólido blanco (2.55g, 6.97mmol).

LC/MS: t. r. = 2.76, $[MH]^+$ 365.

Los siguientes compuestos se prepararon de manera similar al ácido 1-(etiloxi)-4-[(fenilmetil)oxi]-2,3-naftalendicarboxílico, usando los materiales iniciales adecuados.

	Nombre	LC/MS
	Acido 1-(metiloxi)-4-[(fenilmetil)oxi]-2,3-naftalendicarboxílico	t. r. = 2.62 $[MH]^+$ 351
	Acido 1-[metiletoxi]-4-[(fenilmetil)oxi]-2,3-naftalendicarboxílico	t. r. = 2.87 $[MH]^+$ 381
	Acido 1-[(fenilmetil)oxi]-4-(propiloxi)-2,3-naftalendicarboxílico	t. r. = 2.95 $[MH]^+$ 379

191

DESCRIPCION 14**(4-{4-(Etiloxi)-1,3-dioxo-9-[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo**

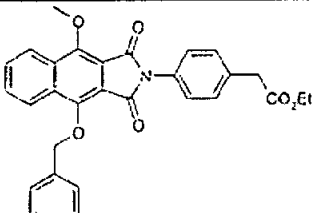
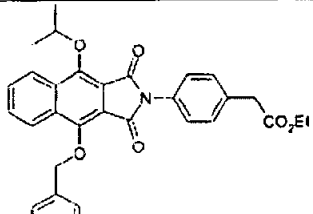
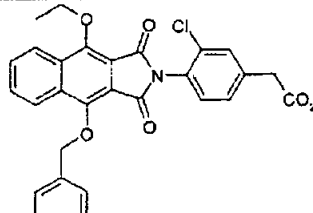
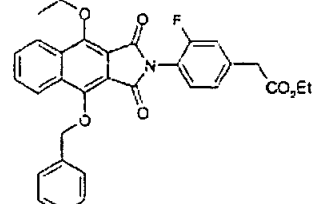
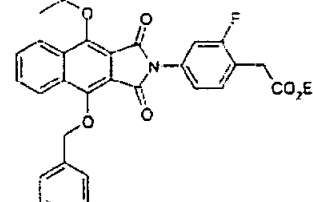
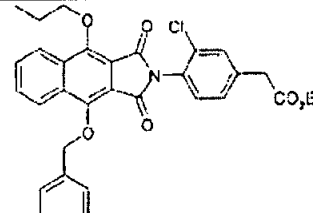
Una mezcla de ácido 1-(etiloxi)-4-[(fenilmetil)oxi]-2,3-naftalendicarboxílico (2.55g, 6.97mmol) y (4-aminofenil)acetato de etilo (2.49g, 13.9mmol) se calentó a 120 °C en ácido acético (20ml) durante 18 horas. La mezcla de reacción se diluyó con salmuera y se extrajo con acetato de etilo dos veces. La fase orgánica combinada se lavó con agua y después se secó sobre sulfato de magnesio, y el disolvente se evaporó para dar un aceite pardo. Este se purificó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo (0-30%) en hexano para dar el compuesto del título como un sólido de color durazno (2.63g, 5.17mmol).

LC/MS: t. r.=3.95, [MH]⁺ 510.

Los siguientes compuestos se prepararon de manera similar al (4-{4-(etiloxi)-1,3-dioxo-9-[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo usando los materiales iniciales adecuados, y en algunas ocasiones se incluyó MDAP (denotado por *).

152

5

	Nombre	LC/MS
	(4-{4-(Metiloxi)-1,3-dioxo-9-[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo	t. r. = 3.94 [MH] ⁺ 496
	(4-{4-[(Metiloxi)-1,3-dioxo-9-[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo	t. r. = 3.96 [MH] ⁺ 524
	(3-Cloro-4-{4-(etiloxi)-1,3-dioxo-9-[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo *	t. r. = 4.04 [MH] ⁺ 544
	(4-{4-(Etiloxi)-1,3-dioxo-9-[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acetato de etilo *	t. r. = 3.95 [MH] ⁺ 528
	(4-{4-(Etiloxi)-1,3-dioxo-9-[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acetato de etilo *	t. r. = 3.96 [MH] ⁺ 528
	{3-Cloro-4-[1,3-dioxo-4-[(fenilmetil)oxi]-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo	t. r. = 4.07 [MH] ⁺ 558

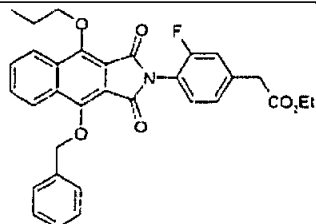
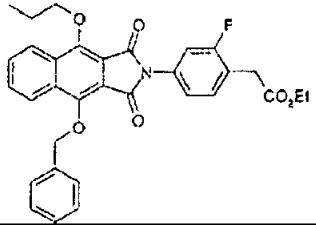
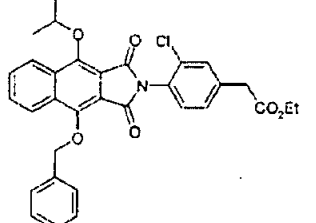
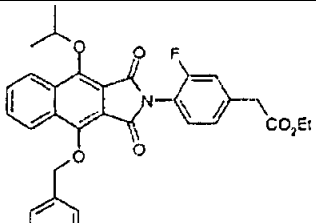
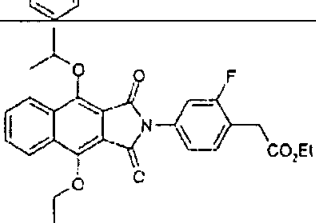
193

5

10

15

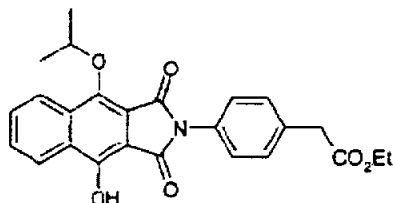
20

	Nombre	LC/MS
	{4-[1,3-Dioxo-4-[(fenilmetil)oxi]-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo	t. r. = 4.11 [MH] ⁺ 542
	{4-[1,3-Dioxo-4-[(fenilmetil)oxi]-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acetato de etilo	t. r. = 4.13 [MH] ⁺ 542
	(3-Cloro-4-{4-[(1-metiletil)oxi]-1,3-dioxo-9-[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo *	t. r. = 4.13 [MH] ⁺ 558
	(3-Fluoro-4-{4-[(1-metiletil)oxi]-1,3-dioxo-9-[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo *	t. r. = 3.98 [MH] ⁺ 542
	(2-Fluoro-4-{4-[(1-metiletil)oxi]-1,3-dioxo-9-[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo *	t. r. = 4.01 [MH] ⁺ 542

15H

DESCRIPCION 15

(4-{4-Hidroxi-9-[metiletoxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo



Se suspendió paladio al 10% sobre carbono (0.365g) en etanol (500ml); a esto se le agregó (4-{4-[metiletoxi]-1,3-dioxo-9-[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo (3.65g, 6.98mmol). La reacción se agitó a temperatura ambiente bajo una atmósfera de hidrógeno durante 3 horas. Esto se filtró a través de una almohadilla de celite bajo un manto de argón, y se lavó con etanol y diclorometano. El filtrado se evaporó para dar un sólido anaranjado (3.05g, 7.04mmol).

LC/MS: t. r. = 3.72, [MH]⁺ 434.

Los siguientes compuestos se prepararon de manera similar al (4-{4-hidroxi-9-[metiletoxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-fenil)acetato de etilo, usando los materiales iniciales adecuados.

159

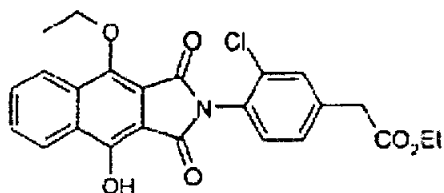
5

10

15

20

	Nombre	LC/MS
	{4-[4-Hidroxi-9-(metiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.51 [MH] ⁺ 406
	{4-[4-(Etiloxi)-9-hidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.56 [MH] ⁺ 420
	{4-[4-(Etiloxi)-hidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo	t. r. = 3.50 [MH] ⁺ 437.99
	{4-[4-(Etiloxi)-9-hidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acetato de etilo	t. r. = 3.63 [MH] ⁺ 438
	{3-Fluoro-4-[4-hidroxi-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.76 [MH] ⁺ 450
	{3-Fluoro-4-[4-hidroxi-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.81 [MH] ⁺ 450
	{2-Fluoro-4-[4-hidroxi-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.69 [MH] ⁺ 450
	(2-Fluoro-4-{4-hidroxi-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.74 [MH] ⁺ 452

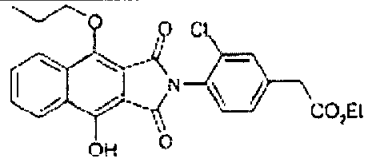
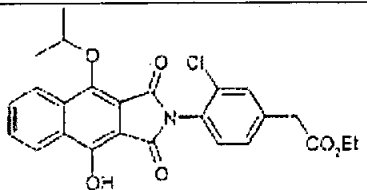
DESCRIPCION 16**{3-Cloro-4-[4-(etiloxi)-9-hidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-****2 il]fenil}acetato de etilo**

A una solución de (3-cloro-4-{4-(etiloxi)-1,3-dioxo-9-
[(fenilmetil)oxi]-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo (1.75g,
3.22mmol) en DCM (40ml), enfriada a -78 °C y bajo una atmósfera de argón,
se le agregó tribromuro de boro (0.31 ml, 3.22mmol), gota a gota. Se agitó a -
78 °C durante 12 minutos. Se hizo una adición más de tribromuro de boro
(0.31 ml, 3.22mmol), gota a gota. La mezcla de reacción se inactivó con agua
y se calentó a temperatura ambiente. Esto se extrajo dos veces con DCM
usando una frita hidrofóbica. La fase orgánica se separó hasta quedar un
sólido amarillo. Este se purificó por cromatografía sobre gel de sílice, eluyendo
con acetato de etilo (0-60%) en hexano, para dar el compuesto del título como
un sólido oleoso anaranjado (0.920g, 2.03mmol).

LC/MS: t. r. = 3.65, [MH]⁺ 454.

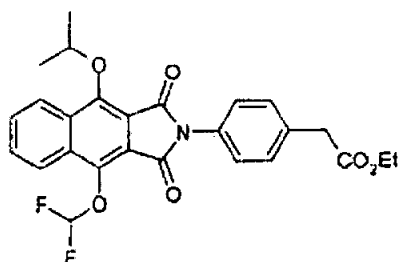
Los siguientes compuestos se prepararon de manera similar al
{3-cloro-4-[4-(etiloxi)-9-hidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-
il]fenil}acetato de etilo, usando los materiales iniciales adecuados.

197

	Nombre	LC/MS
	{3-Chloro-4-[4-hidroxi-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.80 [MH] ⁺ 468
	(3-Chloro-4-[4-hidroxi-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil)acetato de etilo	t. r. = 3.77 [MH] ⁺ 468

DESCRIPCION 17

(4-{4-[(Difluorometil)oxi]-9-[metiletoxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo



A una solución de (4-{4-hidroxi-9-[metiletoxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo (0.25g, 0.577mmol) en dimetilformamida (10ml), se le agregó carbonato de potasio (0.120g, 0.866mmol), seguido por yoduro de potasio (0.048g, 0.289mmol). Se burbujeó cloro(difluoro)metano a través de la solución a 80°C durante 2 horas. El burbujeo se detuvo y el calentamiento se continuó durante 25 horas. La mezcla fría se dividió entre acetato de etilo 2x y salmuera; el extracto orgánico combinado se lavó con agua, se secó sobre sulfato de sodio y se evaporó hasta quedar un aceite amarillo. Este se purificó por cromatografía sobre gel

196

de sílice, eluyendo con acetato de etilo (0-30%) en hexano, para dar el compuesto del título como un sólido de color blanco (0.142g, 0.294mmol).

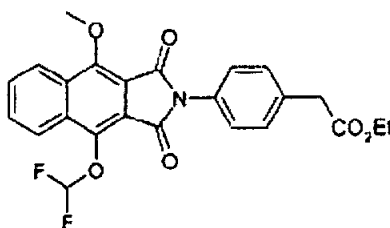
LC/MS: t. r. = 3.82, $[MH]^+$ 484.

5

DESCRIPCION 18

{4-[4-[(Difluorometil)oxi]-9-(metiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo

10



15

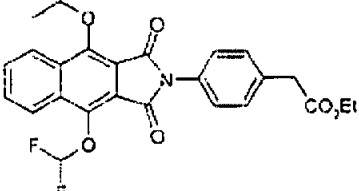
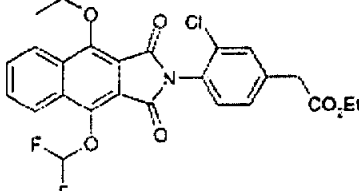
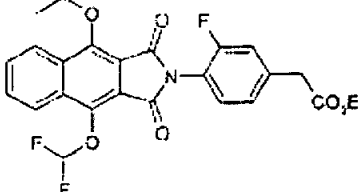
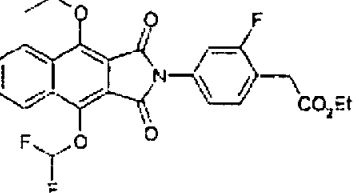
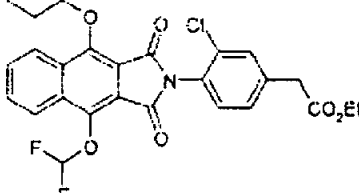
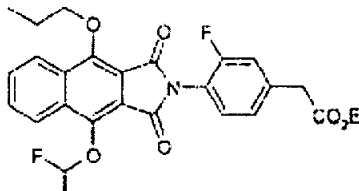
20

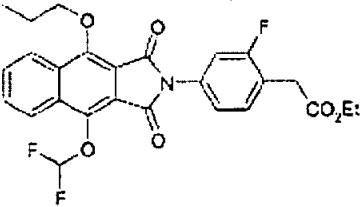
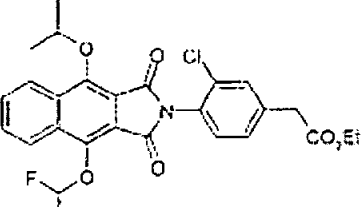
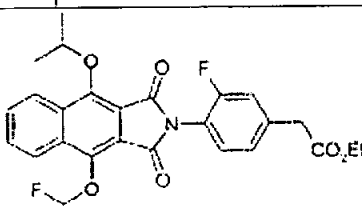
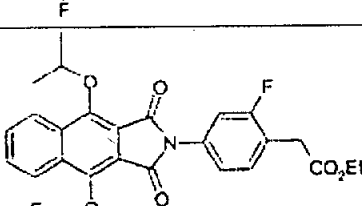
A una solución de {4-[4-hidroxi-9-(metiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo (0.700g, 1.73mmol) en dimetilformamida (25ml) se le agregó carbonato de sodio (0.220g, 2.07mmol), seguido por clorodifluoroacetato de sodio (0.315g, 2.07mmol). La mezcla se calentó 100°C durante 1.5 horas. Después se le agregó carbonato de sodio (0.220g, 2.07mmol) y clorodifluoroacetato de sodio (0.315g, 2.07mmol), continuando el calentamiento durante 2 horas, y nuevamente se le agregaron las mismas cantidades. La mezcla se enfrió a temperatura ambiente y se le agregó agua. El sólido resultante de color beige se recogió por filtración y se lavó con agua. Este se secó al vacío (0.680g, 1.49mmol).

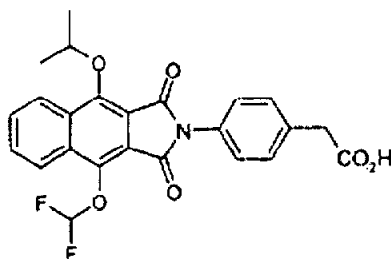
LC/MS: t. r. = 3.62, $[MH]^+$ 456.

Los siguientes compuestos se prepararon de manera similar al

{4-[4-[(difluorometil)oxi]-9-(metiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato, usando los materiales iniciales adecuados.

	Nombre	LC/MS
	[4-[4-[(Difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.77 [MH] ⁺ 470
	[3-Cloro-4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.69 [MH] ⁺ 503.89
	{4-[4-[(Difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo	t. r. = 3.73 [MH] ⁺ 488
	{4-[4-[(Difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acetato de etilo	t. r. = 3.62 [MH] ⁺ 488
	{3-Cloro-4-[4-[(difluorometil)oxi]-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.86 [MH] ⁺ 516
	{4-[4-[(Difluorometil)oxi]-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo	t. r. = 3.83 [MH] ⁺ 502

	Nombre	LC/MS
5	 <chem>CCOC(=O)c1ccc(N2C(=O)c3ccccc3Oc2c2F)c(F)c1</chem>	t. r. = 3.85 [MH] ⁺ 502
10	 <chem>CCOC(=O)c1ccc(N2C(=O)c3ccccc3Oc2c2F)c(Cl)c1</chem>	t. r. = 3.84 [MH] ⁺ 516
15	 <chem>CCOC(=O)c1ccc(N2C(=O)c3ccccc3Oc2c2F)c(F)c1</chem>	t. r. = 3.76 [MH] ⁺ 502
	 <chem>CCOC(=O)c1ccc(N2C(=O)c3ccccc3Oc2c2F)c(F)c1</chem>	t. r. = 3.75 [MH] ⁺ 502

EJEMPLO 8**Acido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acético**

Se calentó (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo (0.14g, 0.289mmol) a 100 °C en una mezcla de 1:1 de ácido acético: ácido clorhídrico acuoso 2N (8ml) durante 1 hora. La reacción se enfrió a temperatura ambiente. Al agregar agua el sólido blanco resultante se recogió por filtración y se lavó con agua. Esto se secó en el horno de vacío para dar el compuesto del título (0.120g, 0.026mmol).

LC/MS: t. r. = 3.36, [MH]⁺ 456.

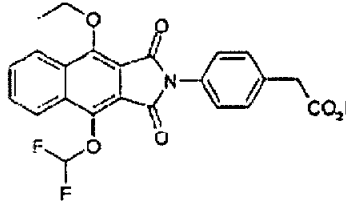
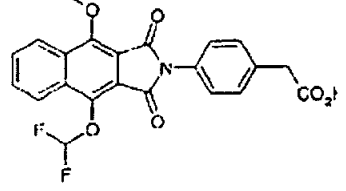
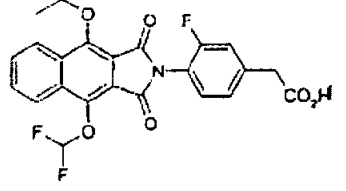
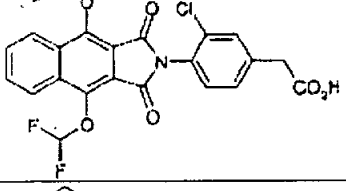
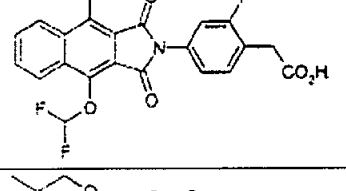
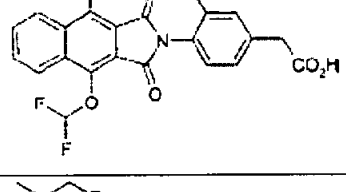
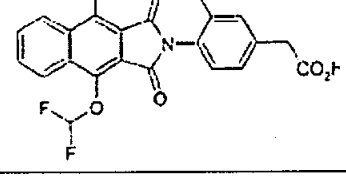
Los siguientes compuestos se prepararon de manera similar al ácido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acético, usando los materiales iniciales adecuados.

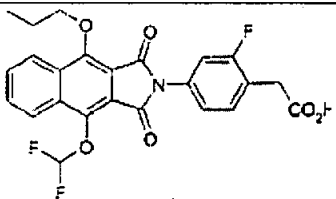
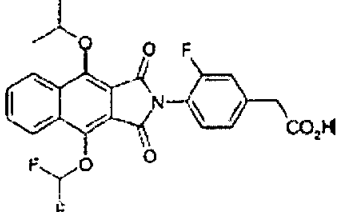
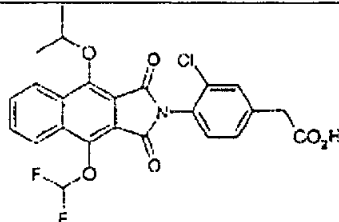
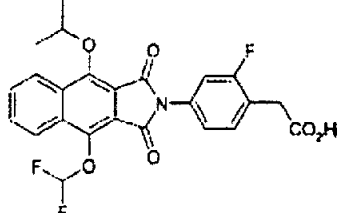
5

10

15

20

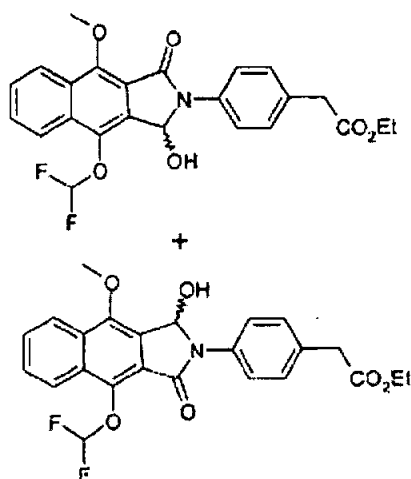
		Nombre	LC/MS
Ejemplo 9		Acido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]}fenil}acético	t. r. = 3.29 [MH] ⁺ 442
Ejemplo 10		Acido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]}fenil}acético	t. r. = 3.14 [MH] ⁺ 428
Ejemplo 11		Acido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético	t. r. = 3.33 [MH] ⁺ 460
Ejemplo 12		Acido {3-cloro-4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]}fenil}acético	t. r. = 3.33 [MH] ⁺ 476
Ejemplo 13		Acido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético	t. r. = 3.25 [MH] ⁺ 460
Ejemplo 14		Acido {4-[4-[(difluorometil)oxi]-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético	t. r. = 3.39 [MH] ⁺ 474
Ejemplo 15		Acido {3-cloro-4-[(difluorometil)oxi]-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]}fenil}acético	t. r. = 3.51 [MH] ⁺ 490

		Nombre	LC/MS
5	Ejemplo 16 	Acido {4-[4-[(Difluorometil)oxi]-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético	t. r. = 3.51 [MH] ⁺ 474
	Ejemplo 17 	Acido {4-[4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético	t. r. = 3.34 [MH] ⁺ 474
10	Ejemplo 18 	Acido (3-cloro-4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acético	t. r. = 3.41 [MH] ⁺ 490
15	Ejemplo 19 	Acido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético	t. r. = 3.36 [MH] ⁺ 474

16d

DESCRIPCION 19

{4-[4-[(Difluorometil)oxi]-1-hidroxi-9-(metiloxi)-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo y {4-[4-[(Difluorometil)oxi]-3-hidroxi-9-(metiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo



A una solución de {4-[4-[(difluorometil)oxi]-9-(metiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo (0.455g, 1.00mmol) en etanol (4ml) y tetrahidrofurano (8ml), se le agregó borohidruro de sodio (0.114g, 3.0mmol) en porciones. La reacción se agitó una hora y después se le agregó una porción más de borohidruro de sodio (0.114g, 3.0mmol), continuando la agitación a temperatura ambiente durante 1 hora. La mezcla se inactivó con una solución acuosa saturada de cloruro de amonio y después se evaporó. Esto se extrajo dos veces con acetato de etilo, se secó sobre sulfato de magnesio y se evaporó, para dar el producto crudo (0.515g, 1.13mmol).

LC/MS: t. r. = 3.21 y 3.26, $[MH]^+$ 457.97.

Los siguientes compuestos se prepararon de manera similar al

165

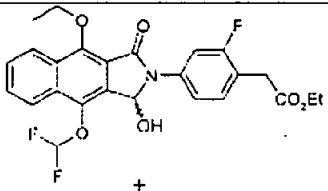
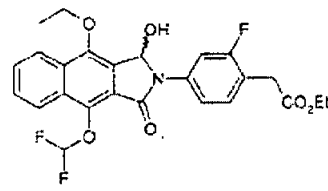
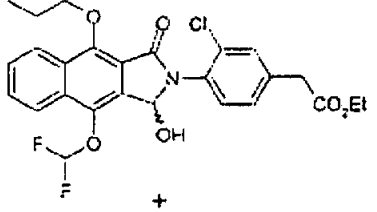
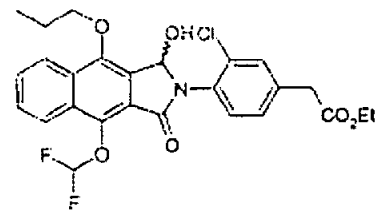
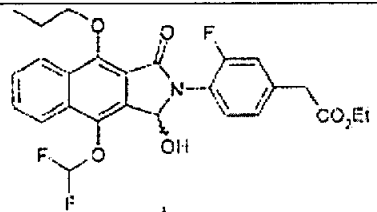
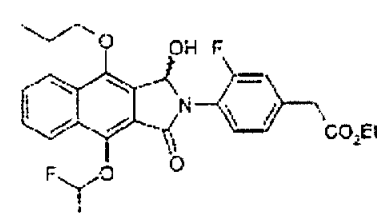
{4-[4-[(difluorometil)oxi]-1-hidroxi-9-(metiloxi)-3-oxo-1,3-dihidro-2H-benzo[f]-isoindol-2-il]fenil}acetato de etilo y {4-[4-[(difluorometil)oxi]-3-hidroxi-9-(metiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo, usando los materiales iniciales adecuados.

5

	Nombre	LC/MS
	{4-[4-[(Difluorometil)oxi]-9-(etiloxi)-1-hidroxi-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo {4-[4-[(Difluorometil)oxi]-9-etiloxi)-3-hidroxi-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo	t. r. = 3.35, 3.38 [MH]⁺ 490
	{3-Cloro-4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-hidroxi-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo {3-Cloro-4-[4-[(difluorometil)oxi]-9-(etiloxi)-3-hidroxi-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.43, 3.47 [MH]⁺ 506

20

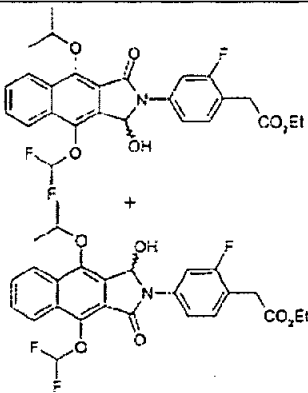
5

	Nombre	LC/MS
5	 	t. r. = 3.43 [MH] ⁺ 490
10	 	t. r. = 3.60 [MH] ⁺ 520
15	 	t. r. = 3.52 [MH] ⁺ 504

20

		Nombre	LC/MS
5		{4-[4-[(Difluorometil)oxi]-1-hidroxi-3-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acetato de etilo {4-[4-[(Difluorometil)oxi]-3-hidroxi-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acetato de etilo	t. r. = 3.64 [MH] ⁺ 504
10		(3-Cloro-4-{4-[(difluorometil)oxi]-1- hidroxi-9-[(1-metiletil)oxi]-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo (3-Cloro-4-{4-[(difluorometil)oxi]-3-hidroxi-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acetato de etilo	t. r. = 3.53 [MH] ⁺ 520
15		(4-{4-[(Difluorometil)oxi]-1-hidroxi-9-[(1-metiletil)oxi]-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acetato de etilo (4-{4-[(Difluorometil)oxi]-3-hidroxi-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acetato de etilo	t. r. = 3.44 [MH] ⁺ 504
20		(4-{4-[(Difluorometil)oxi]-1-hidroxi-9-[(1-metiletil)oxi]-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acetato de etilo (4-{4-[(Difluorometil)oxi]-3-hidroxi-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acetato de etilo	

168

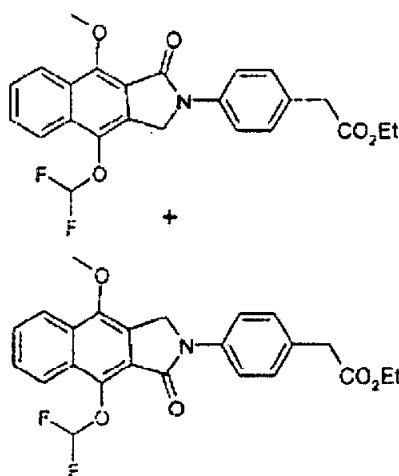
	Nombre	LC/MS
5	 (4-{4-[(Difluorometil)oxi]-1-hidroxi-9-[(1-metiletil)oxi]-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acetato de etilo (4-{4-[(Difluorometil)oxi]-3-hidroxi-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acetato de etilo	t. r. = 3.57 [MH] ⁺ 504

10

DESCRIPCION 20

{4-[4-[(Difluorometil)oxi]-9-(metiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo y {4-[9-[(Difluorometil)oxi]-4-(metiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo

15



20

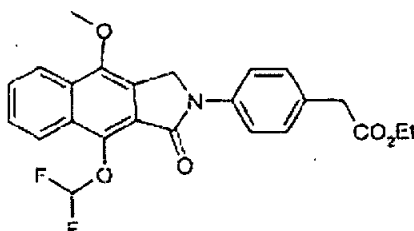
A una solución de {4-[4-[(difluorometil)oxi]-3-hidroxi-9-(metiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo y {4-[4-[(difluorometil)oxi]-1-hidroxi-9-(metiloxi)-3-oxo-1,3-dihidro-2H-benzo[f]isoindol-

2-il]fenil}acetato de etilo (0.457g, 100mmol) en ácido trifluoroacético (5ml), enfriada a 0 °C, se le agregó trietilsilano (0.089ml, 0.561 mmol). La agitación se continuó a 0°C durante 15 minutos y después la mezcla se evaporó. La mezcla cruda se purificó usando cromatografía sobre gel de sílice, eluyendo con acetato de etilo (0-30%) en hexano. Después, los isómeros se separaron usando cromatografía de fluido supercrítico.

{4-[9-[(Difluorometil)oxi]-4-(metiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo (0.036g, 0.082mmol).

LC/MS: t. r. = 3.75, [MH]⁺442.

10

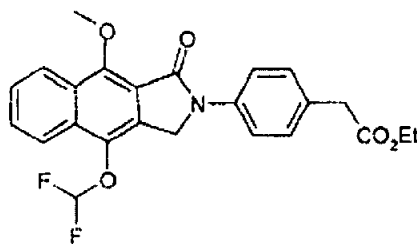


{4-[4-[(Difluorometil)oxi]-9-(metiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo (0.036g, 0.082mmol).

15

LC/MS: t. r. = 3.60, [MH]⁺442.

20

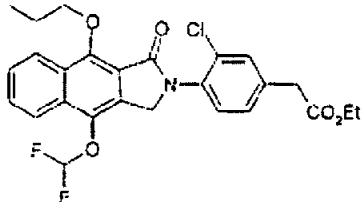
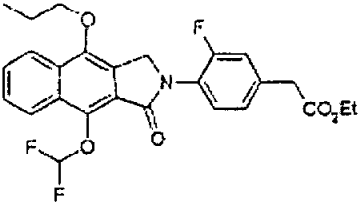
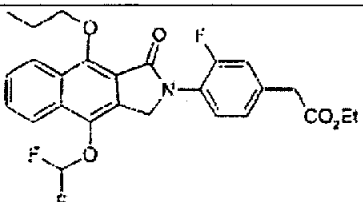
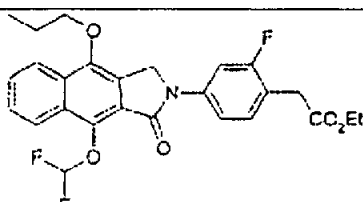
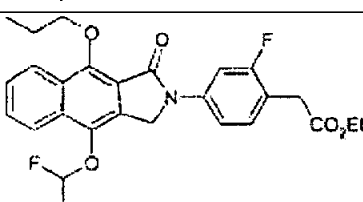
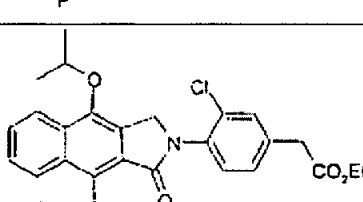


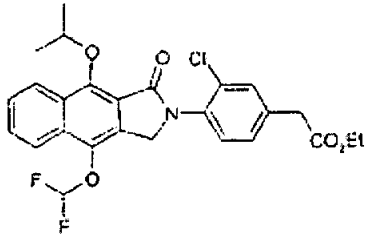
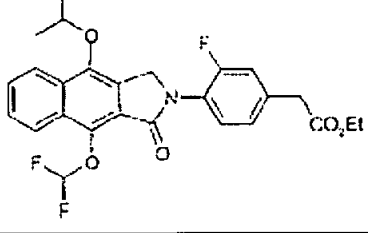
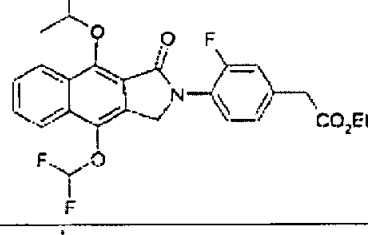
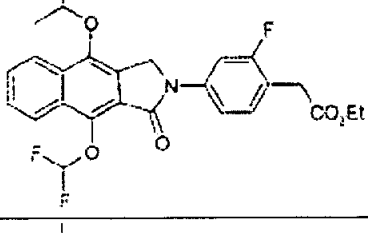
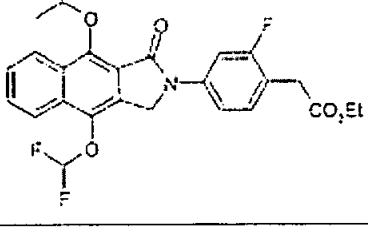
Los siguientes compuestos se prepararon de manera similar al {4-[4-[(difluorometil)oxi]-9-(metiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo y {4-[9-[(difluorometil)oxi]-4-(metiloxi)-1-oxo-1,3-dihidro-

2H-benzo[f]isoindol-2-il]fenil}acetato de etilo, usando los materiales iniciales adecuados; los isómeros se separaron usando cromatografía de líquidos de alto rendimiento o cromatografía de fluido supercrítico.

5		Nombre	LC/MS
		{3-Cloro-4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.69 [MH] ⁺ 490
10		{3-Cloro-4-[9-[(difluorometil)oxi]-4-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.75 [MH] ⁺ 490
		{4-[4-[(Difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo	t. r. = 3.60 [MH] ⁺ 474
15		{4-[9-[(Difluorometil)oxi]-4-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo	t. r. = 3.65 [MH] ⁺ 474
		{4-[4-[(Difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acetato de etilo	t. r. = 3.70 [MH] ⁺ 474
20		{4-[9-[(Difluorometil)oxi]-4-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acetato de etilo	t. r. = 3.73 [MH] ⁺ 474

191

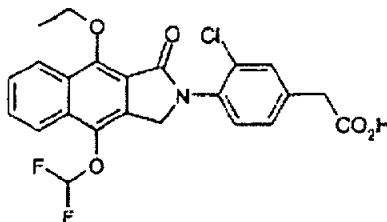
		Nombre	LC/MS
5		{3-Cloro-4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo	t. r. = 3.83 [MH] ⁺ 504
10		{4-[9-[(difluorometil)oxi]-1-oxo-4-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo	t. r. = 3.89 [MH] ⁺ 488
15		{4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo	t. r. = 3.84 [MH] ⁺ 488
20		{4-[9-[(difluorometil)oxi]-1-oxo-4-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acetato de etilo	t. r. = 3.93 [MH] ⁺ 488
		{4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acetato de etilo	t. r. = 3.93 [MH] ⁺ 488
		(3-Cloro-4-{9-[(difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-fenil}acetato de etilo	t. r. = 3.81 [MH] ⁺ 504

		Nombre	LC/MS
5		(3-Cloro-4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acetato de etilo	t. r. = 3.76 [MH] ⁺ 504
		(4-[9-[(Difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil)acetato de etilo	t. r. = 3.77 [MH] ⁺ 488
10		(4-{4-[(Difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acetato de etilo	t. r. = 3.73 [MH] ⁺ 488
15		(4-[9-[(Difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil)acetato de etilo	t. r. = 3.88 [MH] ⁺ 488
		(4-{4-[(Difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil}acetato de etilo	t. r. = 3.91 [MH] ⁺ 488

173

EJEMPLO 20**Acido {3-cloro-4-[4-[(difluorometil)oxi]-9-(etilo)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acético**

5

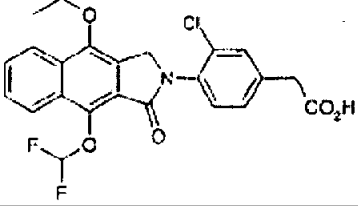
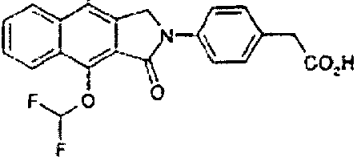
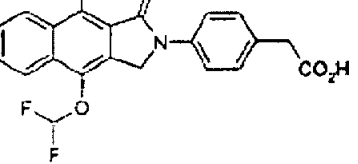
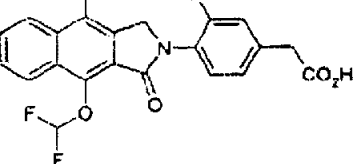
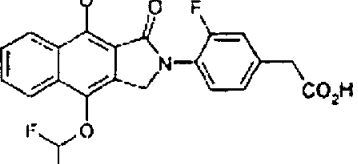
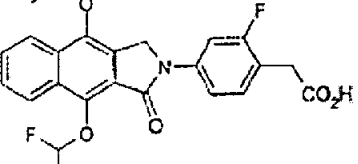


Se calentó {3-cloro-4-[4-[(difluorometil)oxi]-9-(etilo)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acetato de etilo (0.141g, 0.288mmol) a reflujo en una mezcla 1:1 de hidróxido de sodio 2N : etanol (6ml) durante 1.5 horas. La reacción se enfrió a temperatura ambiente. El etanol se evaporó y la mezcla se acidificó con ácido clorhídrico acuoso 2N. El sólido blanco resultante se recogió por filtración, se lavó con agua y se secó al vacío para dar el compuesto del título (0.125g, 0.271 mmol).

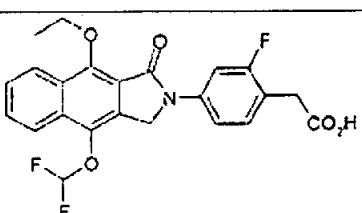
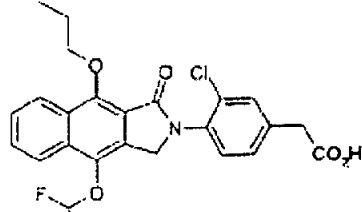
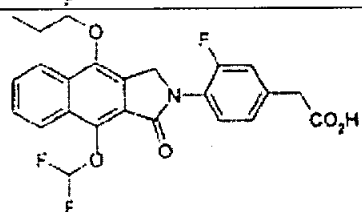
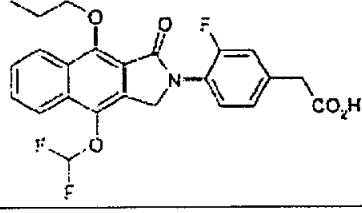
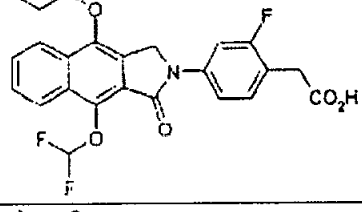
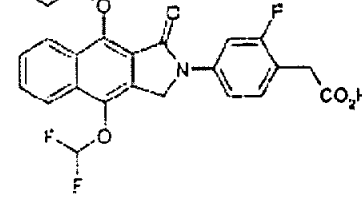
15 LC/MS: t. r. = 3.19, [MH]⁺ 462.

Los siguientes compuestos se prepararon de manera similar al ácido {3-cloro-4-[4-[(difluorometil)oxi]-9-(etilo)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acético, usando los materiales iniciales adecuados. Algunos compuestos se sometieron a un tratamiento acuoso alternativo y extracción con acetato de etilo, seguido por purificación por medio de MDAP (denotado por*), o se purificaron por trituración con éter dietílico (denotado por #).

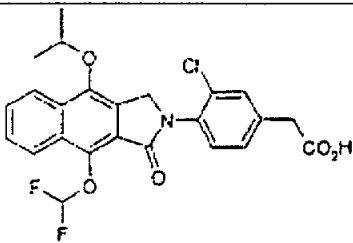
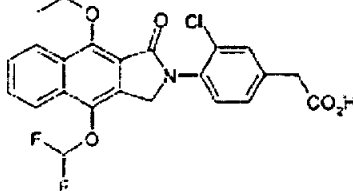
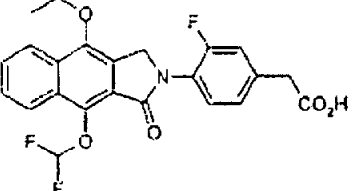
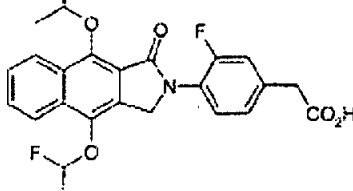
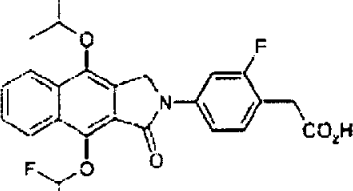
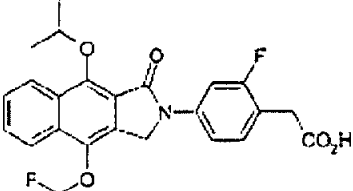
17H

		Nombre	LC/MS
5	Ejemplo 21		t. r. = 3.28 [MH] ⁺ 462
	Ejemplo 22		t. r. = 3.16 [MH] ⁺ 414
10	Ejemplo 23		t. r. = 3.11 [MH] ⁺ 414
	Ejemplo 24		t. r. = 3.20 [MH] ⁺ 446
15	Ejemplo 25		t. r. = 3.10 [MH] ⁺ 446
20	Ejemplo 26		t. r. = 3.31 [MH] ⁺ 446

175

			Nombre	LC/MS
5	Ejemplo 27		Acido 4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético	t. r. = 3.28 [MH] ⁺ 446
	Ejemplo 28		Acido {3-cloro-4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acético	t. r. = 3.38 [MH] ⁺ 476
10	Ejemplo 29		Acido {4-[9-[(difluorometil)oxi]-1-oxo-4-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético	t. r. = 3.42 [MH] ⁺ 460
	Ejemplo 30		Acido {4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético	t. r. = 3.32 [MH] ⁺ 460
15	Ejemplo 31		Acido {4-[9-[(difluorometil)oxi]-1-oxo-4-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético	t. r. = 3.51 [MH] ⁺ 460
20	Ejemplo 32		Acido {4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético	t. r. = 3.46 [MH] ⁺ 460

176

		Nombre	LC/MS
Ejemplo 33		Acido (3-cloro-4-{9-[(difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acético	t. r. = 3.39 [MH] ⁺ 476
Ejemplo 34		Acido (3-cloro-4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acético	t. r. = 3.32 [MH] ⁺ 476
Ejemplo 35		Acido (4-{9-[(difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético	t. r. = 3.32 [MH] ⁺ 460
Ejemplo 36		Acido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético	t. r. = 3.36 [MH] ⁺ 460
Ejemplo 37		Acido (4-{9-[(difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acético	t. r. = 3.44 [MH] ⁺ 460
Ejemplo 38		Acido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acético	t. r. = 3.41 [MH] ⁺ 460

197

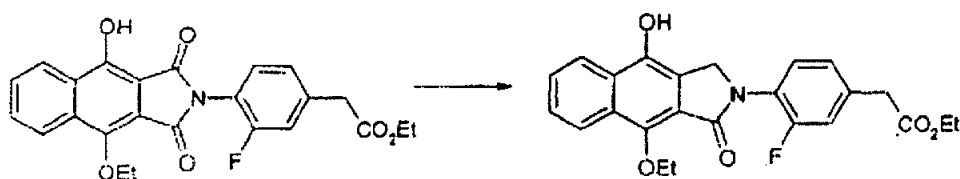
El ácido {4-[4-[(difluorometil)oxi]-9-(etilo)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético [ejemplo 25] también se preparó de manera conveniente usando una metodología regioselectiva, de la siguiente manera:

5

DESCRIPCION 21

{4-[9-(Etiloxi)-4-hidroxi-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo

10



A una solución de {4-[4-(etilo)-9-hidroxi-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo (2.50g, 5.72mmol) en THF (50ml), bajo una atmósfera de argón, se le agregó borohidruro de sodio (0.217g, 5.72mmol), seguido por una solución de complejo de borano-THF (1.0M en THF, 5.72ml, 5.72mmol). Esto se agitó a temperatura ambiente durante 2 horas. Se agregaron a la mezcla de reacción 5.72 mmol adicionales de borohidruro de sodio y complejo de borano-THF, y la agitación se continuó durante 2 horas. Finalmente se hizo una adición más de 2.86 mmol de borohidruro de sodio y complejo de borano-THF, continuando la agitación durante 1.5 horas, hasta que se terminó la reacción. Esta se inactivó con acetato de etilo (100ml) y metanol (3ml), y después se lavó con HCl 2N

128

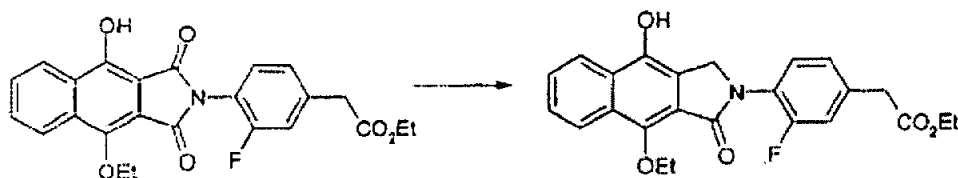
(100ml). La fase acuosa se volvió a extraer con acetato de etilo (200ml). La fase orgánica combinada se lavó con salmuera (200ml), se secó sobre sulfato de magnesio, se filtró y se evaporó, para dar el compuesto del título como un sólido amarillo claro (2.45g, 5.79mmol).

5 LC/MS: t. r. = 3.04, $[MH]^+$ 424.

DESCRIPCION 22

{4-[4-[(Difluorometil)oxi]-9-(etilo)-1-oxo-1,3-dihidro-2H- benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo

10



A una solución de {4-[9-(etilo)-4-hidroxi-1-oxo-1,3-dihidro-2H-
15 benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo (2.40g, 5.67mmol) en DMF (30ml), se le agregó clorodifluoroacetato de sodio (1.72g, 11.34mmol) y carbonato de sodio (1.20g, 11.34mmol). La mezcla se calentó a 100 °C durante 3 horas. Se le agregó más clorodifluoroacetato de sodio (1.72g, 11.34mmol), continuando el calentamiento durante 1.5 horas, y nuevamente
20 se le agregó la misma cantidad y se siguió calentando durante 30 minutos. La mezcla se enfrió a temperatura ambiente y se dividió entre acetato de etilo x2 y agua. La fase orgánica combinada se lavó con agua tres veces y con salmuera. Esto se secó sobre sulfato de magnesio, se filtró y se evaporó,

129

hasta quedar un aceite pardo. Este se purificó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo (5-40%) en hexano, para dar el compuesto del título como un sólido amarillo (0.60g, 1.27mmol).

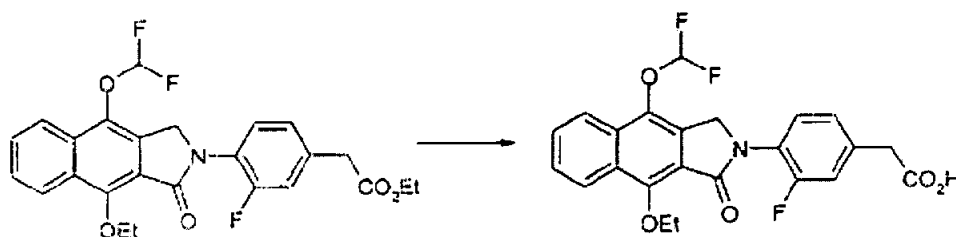
LC/MS: t. r. = 3.49, $[MH]^+$ 474.

5

EJEMPLO 25

Acido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético

10



15

Se calentó {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acetato de etilo (0.60g, 1.27mmol) a 100 °C en una mezcla 1:1 de ácido acético: ácido clorhídrico acuoso 2N (20ml) durante 50 minutos. La reacción se enfrió a temperatura ambiente. Al agregar agua, el sólido blanco resultante se recogió por filtración, se lavó con agua y se secó al vacío para dar el compuesto del título (0.516g, 1.09mmol).

LC/MS: t. r. = 3.13, $[MH]^+$ 446.

20

^1H -RMN (DMSO) δ 8.42 (1H₁ ddd, J=8.4,1.1,0.6Hz), δ 8.12 (1H, d, J=8.5Hz), δ 7.84 (1H, ddd, J=8.2,6.9,1.3Hz), δ 7.74 (1 H, ddd, J=8.4, 6.8, 1.2Hz), δ 7.63 (1H, t, J=8.1 Hz), δ 7.32 (1H, dd, 11.5,1.9Hz), δ 7.22 (1H, dd, 8.1,1.8Hz), δ 7.30 (1H, t, 73.6Hz), δ 5.06 (2H, s), δ 4.50 (2H, q, J=7.0Hz), δ 3.67

180

(2H, s), δ 1.44 (3H, t, 7.0Hz).

Datos biológicos

Se realizaron estudios usando células HEK-293(T) que expresan el receptor prostanoide EP₄ humano recombinante (células HEK-EP₄). Las células se desarrollaron como un cultivo de monocapa en DMEM-F12/F12, que contenía glutamax II (Gibco) y estaba suplementado con suero fetal bovino al 10% y 0.4 mg.ml⁻¹ de G418. Las células HEK-EP₄ se trataron previamente durante 24 horas y 30 minutos antes del experimento con indometacina 10 μ M, y se cosecharon usando Versene que contenía 10 μ M de indometacina. Las células se resuspendieron en amortiguador de prueba (DMEM:F12, 10 μ M de indometacina y 200 μ M de IBMX) a 1 x 10⁶ células por ml, y se incubaron durante 20 minutos a 37°C. Posteriormente se agregaron 50 μ l de las células a 50 μ l de agonista (compuesto de fórmula (I)), y se incubó a 37°C durante 4 minutos antes de detener las reacciones con 100 μ l de triton X-100 al 1%. Se determinaron las concentraciones de AMPc en los lisados celulares usando una prueba de unión de competencia. En esta prueba se midió la capacidad de los lisados celulares para inhibir la unión de ³H-AMPc (Amersham) con la subunidad de unión de la proteína cinasa A, y se calcularon las concentraciones de AMPc partiendo de una curva patrón. Los datos de cada compuesto se expresan como % de la respuesta a una concentración máxima de 10nM del agonista estándar PGE₂. Para cada compuesto se calculó la respuesta máxima y la concentración de compuesto

181

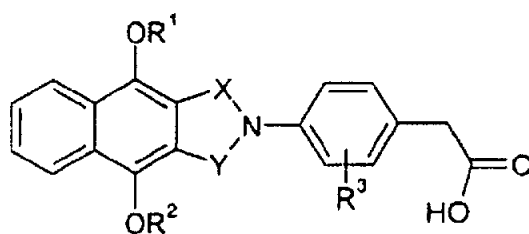
que ocasiona 50% de su respuesta máxima. La actividad intrínseca se expresa con respecto a la respuesta máxima a PGE₂. A menos que se indique de otra manera, los reactivos se compraron a Sigma.

Los compuestos ejemplares de la presente invención se
5 analizaron con la prueba anteriormente mencionada y exhibieron valores de pCE₅₀ de 6.1 o más altos. Algunos compuestos exhibieron valores de pCE₅₀ de 7 o más altos y actividades intrínsecas de 50% o más altas.

182

NOVEDAD DE LA INVENCION**REIVINDICACIONES**

- 5 1.- Un compuesto de fórmula (I), o un derivado farmacéuticamente aceptable del mismo,



10

(I)

- en donde: R¹ y R² representan independientemente alquilo de C₁₋₄ o difluorometilo, siempre que por lo menos uno de R¹ y R² represente difluorometilo; R³ representa H, F, Cl o Br; y X y Y representan
15 independientemente C=O o CH₂, siempre que por lo menos uno de X y Y represente C=O.

- 2.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque uno de R¹ y R² representa alquilo de C₁₋₄ y el otro representa difluorometilo.

- 20 3.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque tanto R¹ como R² representan difluorometilo.

- 4.- El compuesto de fórmula (I) de conformidad con cualquiera

103

de las reivindicaciones 1 a 3, caracterizado además porque tanto X como Y representan C=O.

5 5.- El compuesto de fórmula (I) de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque R³ representa H, F o Cl.

6.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque se selecciona del grupo que consiste en: ácido (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acético; ácido (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-clorofenil)acético; ácido (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)acético; ácido (4-{4,9-bis[(difluorometil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acético; ácido (4-{4,9-bis[(difluorometil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil)-acético; ácido (4-{4,9-bis[(difluorometil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-clorofenil)acético; ácido (4-{4,9-bis[(difluorometil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil)acético; ácido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil)acético; ácido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acético; ácido {4-[4-[(difluorometil)oxi]-9-(metiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]fenil}acético; ácido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético; ácido {3-cloro-4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-

18H

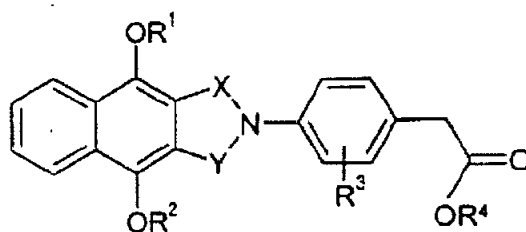
1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético; ácido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético; ácido {4-[4-[(difluorometil)oxi]-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético; ácido {3-cloro-4-[4-[(difluorometil)oxi]-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético; ácido {4-[4-[(difluorometil)oxi]-1,3-dioxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético; ácido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil}acético; ácido (3-cloro-4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético; ácido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1,3-dioxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil}acético; ácido {3-cloro-4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético; ácido {3-cloro-4-[9-[(difluorometil)oxi]-4-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético; ácido {4-[9-[(difluorometil)oxi]-4-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético; ácido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil}acético; ácido {4-[9-[(difluorometil)oxi]-4-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético; ácido {4-[4-[(difluorometil)oxi]-9-(etiloxi)-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético; ácido {3-cloro-4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-

159

il}fenil}acético; ácido {4-[9-[(difluorometil)oxi]-1-oxo-4-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético; ácido {4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-3-fluorofenil}acético; ácido {4-[9-[(difluorometil)oxi]-1-oxo-4-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético; ácido {4-[4-[(difluorometil)oxi]-1-oxo-9-(propiloxi)-1,3-dihidro-2H-benzo[f]isoindol-2-il]-2-fluorofenil}acético; ácido (3-cloro-4-{9-[(difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético; ácido (3-cloro-4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}fenil}acético; ácido (4-{9-[(difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil}acético; ácido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-3-fluorofenil}acético; ácido (4-{9-[(difluorometil)oxi]-4-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil}acético; ácido (4-{4-[(difluorometil)oxi]-9-[(1-metiletil)oxi]-1-oxo-1,3-dihidro-2H-benzo[f]isoindol-2-il}-2-fluorofenil}acético; o un derivado farmacéuticamente aceptable de los mismos.

7.- Un procedimiento para preparar un compuesto de fórmula (I) de la reivindicación 1, en donde uno de X y Y representa C=O y el otro representa CH₂, y R¹, R² y R³ son como se define en la reivindicación 1, dicho procedimiento comprende hacer reaccionar un compuesto de fórmula (II),

186

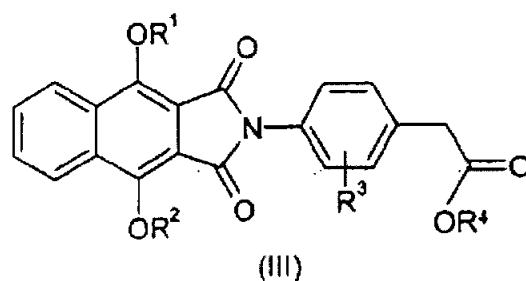


5

(II)

en donde uno de X y Y representa C=O y el otro representa CH₂; R¹, R² y R³ son como se define en la reivindicación 1; y R⁴ representa alquilo de C₁₋₆; con una base adecuada, y opcionalmente formar un derivado farmacéuticamente
 10 aceptable del compuesto así formado, y/o convertir un compuesto de fórmula (I) en otro.

8.- Un procedimiento para preparar un compuesto de fórmula (I) de la reivindicación 1, en donde X y Y representan C=O, y R¹, R² y R³ son como se define en la reivindicación 1, dicho procedimiento comprende agregar
 15 un compuesto de fórmula (III),



20

en donde R¹, R² y R³ son como se define en la reivindicación 1; y R⁴ representa alquilo de C₁₋₆; a un ácido o mezcla de ácidos adecuados, y opcionalmente formar un derivado farmacéuticamente aceptable del compuesto así formado,

18X

y/o convertir un compuesto de fórmula (I) en otro.

9.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque se usa en medicina humana o veterinaria.

5 10.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque se usa en el tratamiento de una condición que es mediada por la acción, o pérdida de acción, de la PGE_2 en los receptores EP_4 .

10 11.- Un método de tratamiento de un sujeto humano o animal que padece una condición mediada por la acción, o pérdida de acción, de la PGE_2 en los receptores EP_4 , que comprende administrar a dicho sujeto una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) de la reivindicación 1.

15 12.- El uso de un compuesto de fórmula (I) de la reivindicación 1, para la fabricación de un medicamento para el tratamiento de una condición mediada por la acción de la PGE_2 en los receptores EP_4 .

13.- Una composición farmacéutica que comprende un compuesto de fórmula (I) de la reivindicación 1, y uno o más vehículos o diluentes aceptables para el mismo.

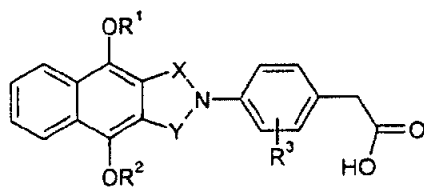
20 14.- La composición farmacéutica de conformidad con la reivindicación 13, caracterizada además porque comprende uno o más agentes terapéuticos adicionales.

178

RESUMEN DE LA INVENCION

Un compuesto de fórmula (I),

5



(I)

o un derivado farmacéuticamente aceptable del mismo, en donde R¹, R², R³, X
10 y Y son como se define en la especificación; un procedimiento para preparar
dichos compuestos; una composición farmacéutica que comprende dichos
compuestos; y el uso de dichos compuestos en medicina.

15

EA

P08/1235F

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:

GLAXOSMITHKLINE
Attn: King, Lawrence
980 Great West Road
Brentford, Middlesex TW8 9GS
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year) 05/06/2007

Applicant's or agent's file reference

LLK/PB61685

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP2007/050991

International filing date
(day/month/year)

01/02/2007

Applicant

GLAXO GROUP LIMITED

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 84 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 20 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/B/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority

 European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Saskia Stark

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ELK/PB61685	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2007/050991	International filing date (day/month/year) 01/02/2007	(Earliest) Priority Date (day/month/year) 03/02/2006
Applicant GLAXO GROUP LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

BENZOISOINDOLE DERIVATIVES FOR THE TREATMENT OF PAIN.

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/050991

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D209/64 C07D209/66 A61K31/4035 A61P25/02

According to International Patent Classification (IPC) or to both national classification and IPO

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/064564 A (GLAXO GROUP LTD.) 22 August 2002 (2002-08-22) page 14, line 5 - page 18, line 5; claims; examples	1-14
Y	WO 02/47669 A (GLAXO GROUP LTD.) 20 June 2002 (2002-06-20) page 1, line 26 - page 2, line 34; claims; example 1	1-14
Y	WO 02/50033 A (GLAXO GROUP LTD.) 27 June 2002 (2002-06-27) page 5, line 25 - page 9, line 5; claims; examples	1-14

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the international search

24 May 2007

Date of mailing of the international search report

05/06/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Helps, Ian

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/050991**Box II. Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11(part)
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III. Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/050991

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02064564	A	22-08-2002	EP 1368312 A1	10-12-2003
			JP 2004520400 T	08-07-2004
			US 2005080257 A1	14-04-2005
			US 2007088068 A1	19-04-2007
WO 0247669	A	20-06-2002	AU 2219102 A	24-06-2002
WO 0250033	A	27-06-2002	AU 1728702 A	01-07-2002
			EP 1343759 A1	17-09-2003
			JP 2004517847 T	17-06-2004
			US 2004087624 A1	06-05-2004
			US 2006252799 A1	09-11-2006

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

*As discussed on phone with
Mrs. Jaber Nangat*
PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2007/050991

International filing date (day/month/year)
01.02.2007

Priority date (day/month/year)
03.02.2006

International Patent Classification (IPC) or both national classification and IPC
INV. C07D209/64 C07D209/66 A61K31/4035 A61P25/02

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523855 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Helps, Ian

Telephone No. +49 89 2399-8209



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/EP2007/050991**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/EP2007/050991**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 11(part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for the whole application or for said claims Nos. 11(part)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/EP2007/050991

149

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Yes: Claims	<u>1-14</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-14</u>
Industrial applicability (IA)	Yes: Claims	<u>1-10, 12-14</u>
	No: Claims	<u>11 see below</u>

2. Citations and explanationssee separate sheet**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2007/050991

V. CITATIONS AND EXPLANATIONS

The following documents are cited in this Written Opinion.

WO-A-02 064564	(A)
WO-A-02 047669	(B)
WO-A-02 050033	(C)

The novel structural feature of the compounds of claim 1 is the presence of at least one difluoromethoxy group attached to the benz[f]isoindole ring at the 4- or 9-position. The dependent claims 2-6, as well as claims 7 and 8 drawn to processes for the preparation of compounds of claim 1, claims 9 and 10 drawn to compounds of claim 1 for use in therapy, claim 11 drawn to therapeutic methods of treatment using compounds of claim 1, claim 12 drawn to the use of compounds of claim 1 for the preparation of medicaments, and claims 13-14 drawn to pharmaceutical compositions containing compounds of claim 1 are novel by consequence. Claims 1 to 14 therefore meet the Novelty requirements of Article 33(2) PCT.

The compounds of the present invention are agonists of the EP4 receptor and are useful for the treatment of disorders such as pain and inflammation. Document (A), which represents the closest prior art, discloses benzo[f]isoindoles which are N-substituted by a 4-carboxymethylphenyl group, and which have alkoxy substituents at the 4- and 9-positions (see examples). These compounds also have EP4 receptor agonist activity. Document (B) describes the use of a compound under the scope of (A) for the treatment of neuropathic pain. The presently claimed compounds differ from the compounds of (A) in that at least one of the alkoxy groups at the 4- or 9-positions is replaced by a difluoromethoxy group. However, it is noted that the claims of document (A) also embrace benzo[f]isoindoles which have a trifluoromethoxy or trifluoroethoxy group at the 4- or 9-position (see definitions of R5 and R8). Since there is only a small structural difference between a difluoromethoxy group and a methoxy group, and that fluoroalkoxy substituents have already been suggested in document (A), the skilled man would have expected that the structural change described above would lead to further compounds with EP4 receptor agonist activity.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No. *19d*PCT/EP2007/050991

Consequently, inventive step (Article 33(3) PCT) cannot be recognised because the problem of making available further EP receptor agonist compounds of the treatment of pain appears to have been solved in an obvious manner. Inventive step for the presently claimed compounds could be recognised if the Applicant could demonstrate an unexpected effect in comparison with the closest prior art compounds from document (A). The applicant is requested to submit further information and argumentation in order to make credible the involvement of inventive step for the presently claimed compounds.

Document (B) also describes benzo[f]isoindole derivatives as EP4 receptor agonists. Since these compounds have a sulfonylaminocarbonyl group linked to the N-phenyl moiety, these compounds are structurally less close than the compounds of (A) or (B).

For the assessment of the present claim 11 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VII. CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION.

It is noted that claim 1 includes "pharmaceutically acceptable derivatives" of compounds of formula (I). This appears to be a non limiting definition because the term "derivative" could embrace any related compound (e.g. esters, amides, carbamates, etc). Claim 1 therefore does not meet the requirements of Article 6 PCT (clarity).

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D209/64 C07D209/66 A61K31/4035 A61P25/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/064564 A (GLAXO GROUP LTD.) 22 August 2002 (2002-08-22) page 14, line 5 - page 18, line 5; claims; examples	1-14
Y	WO 02/47669 A (GLAXO GROUP LTD.) 20 June 2002 (2002-06-20) page 1, line 26 - page 2, line 34; claims; example 1	1-14
Y	WO 02/50033 A (GLAXO GROUP LTD.) 27 June 2002 (2002-06-27) page 5, line 25 - page 9, line 5; claims; examples	1-14

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

24 May 2007

Date of mailing of the international search report

05/06/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Helps, Ian

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/050991

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11(part)
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/050991

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02064564	A	22-08-2002	EP 1368312 A1	10-12-2003
			JP 2004520400 T	08-07-2004
			US 2005080257 A1	14-04-2005
			US 2007088068 A1	19-04-2007
WO 0247669	A	20-06-2002	AU 2219102 A	24-06-2002
WO 0250033	A	27-06-2002	AU 1728702 A	01-07-2002
			EP 1343759 A1	17-09-2003
			JP 2004517847 T	17-06-2004
			US 2004087624 A1	06-05-2004
			US 2006252799 A1	09-11-2006

Handwritten marks:
A large 'X' and the number '202' are written in the top right corner of the page.

203

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-079189- -00000-0000

Fecha: 2008-07-30 16:26:58 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 202

Industria y Comercio
SUPERINTENDENCIA

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
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 Navarrete
Firma Responsable

Fecha 30-07-08

Carrera 13 No. 27-00 Piso 5, 7 y 10
Corrutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@slc.gov.co
www.slc.gov.co
Bogotá, D.C., Colombia

224

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
GLAXO GROUP LIMITED

REFERENCIA	Radicación No.	8 79189
	Solicitud internacional	PCT/EP2007/050991
	Fecha inicio fase nacional	03/09/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	11586

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

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 12 SET. 2008
adpall