

Q.F.



Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

04-42442

21. EXPEDIENTE No.

54. TITULO DERIVADOS HETEROCICLICOS DE GLICAMIDA Y
SU USO MEDICO.

51. CLASIFICACION INTERNACIONAL A61K31/47 // C07D215/06

71. SOLICITANTE SMITHKLINE BEECHAM P.L.C.

DOMICILIO 980 GREAT WEST ROAD BRENTFORD, MIDDLESEX
TW8 9GS, REINO UNIDO.

74. APODERADO CARLOS Z. DIAZTE.

22. BOGOTA, D.C., MAYO 7, 2004.

SS

OLARTE RAISBECK


Industria y Comercio
SUPERINTENDENCIA

04/63
SUPERINDUSTRIA Y COMERCIO
Radicación : 0404242 0000000 Folios: 150
Fecha (REB): 2004-05-07 17:11:13
Trámite : 011 PCT-PATENT 379 FASE NCI 411 PRESENTAR
Dependencia: 2020 DIVISION DE CIENCIAS QUIMICAS

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD PATENTE PCT ENTRADA EN FASE NACIONAL

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☐

Capítulo I.

☒

Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: SMITHKLINE BEECHAM P.L.C.

Dirección: 980 Great West Road, Brentford,
Middlesex TW8 9GS, Reino Unido

Nacionalidad o Domicilio: Reino Unido

Lugar de Constitución: Inglaterra

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual _____

Número _____

**REPRESENTANTE
O APODERADO**

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre A,
Calle 100 No. 8A-37 Piso 10

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual _____

Número 79782747Bta
TP 74.295

**INVENTOR (ES)
(72)**

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

PCT (86)

1

Solicitud Internacional No. PCT/EP02/12505

Fecha Noviembre 8, 2002

Publicación Internacional No. WO 03/042179

Fecha Mayo 22, 2003

2

Título (54) DERIVADOS HETEROCICLICOS DE GLICINAMIDA Y SU USO MEDICO.

Clasificación Internacional (51) C07D 215/06 // A61K31/47 // A61P9/10

Prioridad

SI

☒

NO

☐

(33) País de Origen

GB

(32) Fecha

Noviembre 10, 2001

(31) Número de Solicitud

0127141.0

10

ANEX S

☒ x

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

☐

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

☒ x

Poderes, si fuere el caso.

☐

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

☐

Declaraciones.

☒ x

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

☒ x

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

☐

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

☐

Traducción del examen preliminar internacional efectuado por la IPEA.

☐

De 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

1

FIGURA CARACTERÍSTICA:

2

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES**RICHARD LEONARD ELLIOTT**

New Frontiers Science Park South
Third Avenue Harlow Essex CM19 5AW
Reino Unido.
Nacionalidad: BRITANICA.

DEIRDRE MARY BERNADETTE HICKEY

Gunnels Wood Road
Stevanage
Hertfordshire, SG1 2NY,
Reino Unido
Nacionalidad: IRLANDES

ROBERT JOHN IFE

Gunnels Wood Road
Stevanage
Hertfordshire, SG1 2NY;
Reino Unido
Nacionalidad: BRITANICA.

COLIN ANDREW LEACH

Gunnels Wood Road
Stevanage
Hertfordshire, SG1 2NY,
Reino Unido
Nacionalidad: BRITANICA.

JOHN LIDDLE

Gunnels Wood Road
Stevanage
Hertfordshire, SG1 2NY,
Reino Unido
Nacionalidad: BRITANICA.

IVAN LEO PINTO

Gunnels Wood Road
Stevanage
Hertfordshire, SG1 2NY,

A

Reino Unido
Nacionalidad: BRITANICA.

STEVEN JAMES STANWAY
New Frontiers Science Park South
Third Avenue Harlow Essex CM19 5AW
Reino Unido.
Nacionalidad: BRITANICA.

STEPHEN ALLAN SMITH
Gunnels Wood Road
Stevanage
Hertfordshire, SG1 2NY,
Reino Unido
Nacionalidad: BRITANICA.

5

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04042442 C0000000 Folios: 158
Fecha (VCD): 2004-05-07 17:11:13
Tramite : 011 PCT-PATENT 379 FASE INCI 411 PRESENTA
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 33,177
FECHA : ABRIL 27 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	22152651	27/04/2004	2,830,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
		TOTAL :	\$ 422,000.00

SOM: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE :  _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

**APOSTILLA EN PODER DE REPRESENTACIÓN DE
SMITHKLINE BEECHAM P.L.C.**

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 certificando que Peter John Giddings es apoderado de Smithkline Beecham p.l.c. 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 el Reino Unido de Gran Bretaña e Irlanda del Norte exteriores y de la Mancomunidad
8. No. G229471
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.

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

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

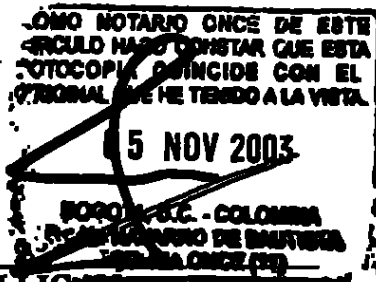
C E R T I F I C O:

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 "SMITHKLINE BEECHAM p.l.c.", Sociedad legalmente constituida y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número 2337959, con domicilio social en 980 Great West Road, Brentford, Middlesex TW8 9GS, Inglaterra;

QUE el citado Señor Don PETER JOHN GIDDINGS está debida y suficientemente autorizado para firmar documentos de esta clase, en virtud del Poder otorgado en su favor por la referida Sociedad fechado el 30 de enero de 2003, copia del cual he tenido a la vista;

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 Londres, el día de hoy trece de agosto del año dos mil tres.



JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



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

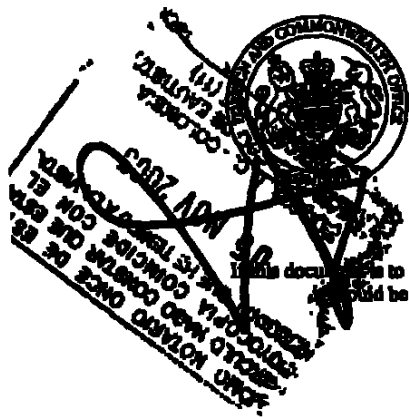
UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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
Certified/Attesté
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' **G229471**
9. Stamp:
timbre:
10. Signature: J. Garbarrak

J. Garbarrak

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

This document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
and 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-65 Piso 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

SmithKline Beecham p.l.c.

El suscrito,

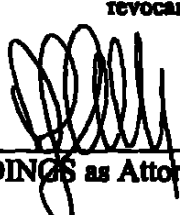
domiciliado en

980 Great West Road, Brentford, Middlesex TW8 9GS, GB

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.

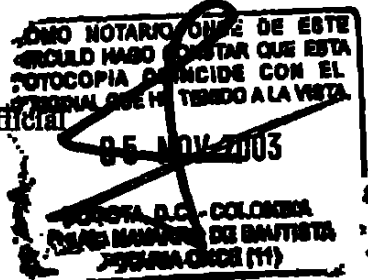
por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, 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



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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 May 2003 (22.05.2003)

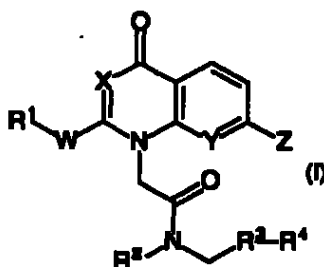
(10) International Publication Number
WO 03/042179 A1

PCT

- (51) International Patent Classification⁷: C07D 215/06, A61K 31/47, A61P 9/10
- (21) International Application Number: PCT/EP02/12505
- (22) International Filing Date:
8 November 2002 (08.11.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0127141.0 10 November 2001 (10.11.2001) GB
- (71) Applicant (for all designated States except US):
SMITHKLINE BEECHAM P.L.C. (GB/GB); 90
Great West Road, Brentford, Middlesex TW8 9GS (GB).
- (72) Inventors, and
(73) Inventors/Applicants (for US only): ELLIOTT, Richard,
Leonard (GB/GB); GlaxoSmithKline, Gunnels Wood
Road, Stevenage, Hertfordshire SG1 2NY (GB). HACKETT,
Deirdre, Mary, Bernadette (IE/GB); GlaxoSmithKline,
Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY
(GB). IFE, Robert, John (GB/GB); GlaxoSmithKline,
Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY
(GB). LEACH, Colin, Andrew (GB/GB); GlaxoSmithK-
line, Gunnels Wood Road, Stevenage, Hertfordshire SG1
2NY (GB). LIDDLE, John (GB/GB); GlaxoSmithKline,
Gunnels Wood Road, Stevenage, Hertfordshire SG1
2NY (GB). PINTO, Ivan, Leo (GB/GB); GlaxoSmithK-
line, Gunnels Wood Road, Stevenage, Hertfordshire
- SG1 2NY (GB). STANWAY, Steven, James (GB/GB);
GlaxoSmithKline, Gunnels Wood Road, Stevenage,
Hertfordshire SG1 2NY (GB). SMITH, Stephen, Allan
(GB/GB); GlaxoSmithKline, Gunnels Wood Road, Stev-
enage, Hertfordshire SG1 2NY (GB).
- (74) Agents: HACKETT, Ruth, Elizabeth; Corporate Intel-
lectual Property, GlaxoSmithKline, 940 Great West Road,
Brentford, Middlesex TW8 9GS (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GR, GU,
HN, HR, HU, ID, IL, IN, IS, JP, KR, KG, KP, KZ, LC,
LK, LU, LS, LT, LV, MA, MD, MG, MK, MN, MW,
MX, MY, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
European patent (AM, AZ, BY, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NI, SN, TD, TO).
- Published
with international search report
- 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.

(94) Title: HETEROCYCLIC DERIVATIVES OF GLYCINAMIDE AND THEIR MEDICAL USE

(57) Abstract: Compounds of the formula (I) are inhibitors of the enzyme
Lp-PLA₂ and are of use in therapy, in particular for treating atherosclerosis.



WO 03/042179 A1

HETEROCYCLIC DERIVATIVES OF GLYCINAMIDE AND THEIR MEDICAL USE

5 The present invention relates to certain novel compounds, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy, in particular in the treatment of atherosclerosis.

10 WO 95/00649 (SmithKline Beecham plc) describes the phospholipase A₂ enzyme Lipoprotein Associated Phospholipase A₂ (Lp-PLA₂), the sequence, isolation and purification thereof, isolated nucleic acids encoding the enzyme, and recombinant host cells transformed with DNA encoding the enzyme. Suggested therapeutic uses for inhibitors of the enzyme included atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. A subsequent publication from the same group further describes this enzyme (Tew D *et al*, 15 *Arterioscler Thromb Vas Biol* 1996;16:591-9) wherein it is referred to as LDL-PLA₂. A later patent application (WO 95/09921, Icos Corporation) and a related publication in *Nature* (Tjoelker *et al*, vol 374, 6 April 1995, 549) describe the enzyme PAF-AH which has essentially the same sequence as Lp-PLA₂ and suggest that it may have potential as a therapeutic protein for regulating pathological inflammatory events.

20 It has been shown that Lp-PLA₂ is responsible for the conversion of phosphatidylcholine to lysophosphatidylcholine, during the conversion of low density lipoprotein (LDL) to its oxidised form. The enzyme is known to hydrolyse the sn-2 ester of the oxidised phosphatidylcholine to give lysophosphatidylcholine and an oxidatively modified fatty acid. Both products of Lp-PLA₂ action are biologically active with 25 lysophosphatidylcholine, in particular having several pro-atherogenic activities ascribed to it including monocyte chemotaxis and induction of endothelial dysfunction, both of which facilitate monocyte-derived macrophage accumulation within the artery wall. Inhibition of the Lp-PLA₂ enzyme would therefore be expected to stop the build up of these macrophage enriched lesions (by inhibition of the formation of 30 lysophosphatidylcholine and oxidised free fatty acids) and so be useful in the treatment of atherosclerosis.

35 The increased lysophosphatidylcholine content of oxidatively modified LDL is also thought to be responsible for the endothelial dysfunction observed in patients with atherosclerosis. Inhibitors of Lp-PLA₂ could therefore prove beneficial in the treatment of this phenomenon. An Lp-PLA₂ inhibitor could also find utility in other disease states that exhibit endothelial dysfunction including diabetes, hypertension, angina pectoris and after ischaemia and reperfusion.

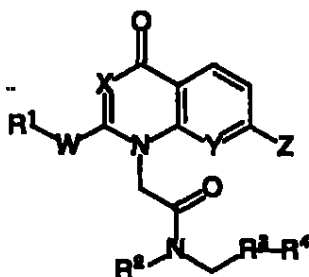
40 In addition, Lp-PLA₂ inhibitors may also have a general application in any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA₂. Examples of such disorders include psoriasis.

Furthermore, Lp-PLA₂ inhibitors may also have a general application in any disorder that involves lipid oxidation in conjunction with Lp-PLA₂ activity to produce the two injurious products, lysophosphatidylcholine and oxidatively modified fatty acids. Such conditions include the aforementioned conditions atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, ischaemia, reperfusion injury and acute and chronic inflammation.

Patent applications WO 96/12963, WO 96/13484, WO 96/19451, WO 97/02242, WO 97/217675, WO 97/217676, WO 96/41098, and WO 97/41099 (SmithKline Beecham plc) disclose *inter alia* various series of 4-thionyl/sulfinyl/sulfonyl azetidione compounds which are inhibitors of the enzyme Lp-PLA₂. These are irreversible, acylating inhibitors (Tew *et al.*, Biochemistry, 37, 10087, 1998).

A further class of compounds has now been identified which are non-acylating inhibitors of the enzyme Lp-PLA₂. Thus, WO 99/24420, WO 00/10980, WO 00/66566, WO 00/66567 and WO 00/68208 (SmithKline Beecham plc) disclose a class of pyrimidone compounds. We have now found that the pyrimidone ring, optionally replaced by a pyridone ring, may be fused to a substituted benzo or pyrido ring to give compounds having good activity as inhibitors of the enzyme Lp-PLA₂.

Accordingly, the present invention provides a compound of formula (I):



25

(I)

in which:

R¹ is an aryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₆₎alkyl, C₍₁₋₆₎alkoxy, C₍₁₋₆₎alkylthio, hydroxy, halogen, CN, mono to perfluoro-C₍₁₋₄₎alkyl, mono to perfluoro-C₍₁₋₄₎alkoxyaryl, and arylC₍₁₋₄₎alkyl;

R² is hydrogen, C₍₁₋₆₎alkyl which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR⁵, COR⁵, carboxy, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, mono- or di-(hydroxyc₍₁₋₆₎alkyl)amino and N-hydroxyc₍₁₋₆₎alkyl-N-C₍₁₋₆₎alkylamino; or

R² is Het-C₍₀₋₄₎alkyl in which Het is a 5- to 7- membered heterocyclyl ring comprising N and optionally O or S, and in which N may be substituted by COR⁵,

COOR⁵, CONR⁷R⁸, or C₍₁₋₆₎alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR⁵, COR⁵, carboxy, COOR⁵, CONR⁷R⁸ or NR⁷R⁸, for instance, piperidin-4-yl, pyrrolidin-3-yl;

5 R³ is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₆₎alkyl, C₍₁₋₆₎alkoxy, C₍₁₋₆₎alkylthio, arylC₍₁₋₆₎alkoxy, hydroxy, halogen, CN, COR⁵, carboxy, COOR⁵, NR⁵COR⁶, CONR⁷R⁸, SO₂NR⁷R⁸, NR⁵SO₂R⁶, NR⁷R⁸, mono to perfluoro-C₍₁₋₄₎alkyl and mono to perfluoro-C₍₁₋₄₎alkoxy;

10 R⁴ is an aryl or a heteroaryl ring which is further optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₆₎alkyl, C₍₁₋₆₎alkoxy, C₍₁₋₆₎alkylthio, C₍₁₋₆₎alkylsulfonyl, arylC₍₁₋₆₎alkoxy, hydroxy, halogen, CN, COR⁵, carboxy, COOR⁵, CONR⁷R⁸, NR⁵COR⁶, SO₂NR⁷R⁸, NR⁵SO₂R⁶, NR⁷R⁸, mono to perfluoro-C₍₁₋₄₎alkyl and mono to perfluoro-C₍₁₋₄₎alkoxy, or C₍₅₋₁₀₎alkyl;

15 W is a C₍₂₋₄₎alkylene group, optionally substituted by 1, 2 or 3 substituents selected from methyl and ethyl, CH=CH, (CH₂)_nS or (CH₂)_nO where n is 1, 2 or 3;

X and Y are independently CH or N;

Z is NO₂, NR⁵R⁹, OR⁹, SR⁹, SOR⁹, SO₂R⁹ or R¹⁰;

R⁵ and R⁶ are independently hydrogen or C₍₁₋₁₂₎alkyl, for instance C₍₁₋₄₎alkyl (e.g. methyl, ethyl or t-butyl);

20 R⁷ and R⁸ which may be the same or different is each selected from hydrogen, or C₍₁₋₁₂₎alkyl, or R⁷ and R⁸ together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and optionally substituted by one or two substituents selected from hydroxy, oxo, C₍₁₋₄₎alkyl, C₍₁₋₄₎alkylcarboxy, aryl, e.g. phenyl, or aralkyl, e.g. benzyl, for instance morpholine or piperazine;

25 R⁹ is hydrogen or C₍₁₋₆₎alkyl optionally substituted by 1, 2 or 3 substituents which may be the same or different selected from hydroxy, halogen, OR⁵, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, aryl, heteroaryl and a 5- to 7-membered heterocyclyl ring, which aryl or heteroaryl is optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₆₎alkyl, C₍₁₋₆₎alkoxy, C₍₁₋₆₎alkylthio, arylC₍₁₋₆₎alkoxy, hydroxy, halogen, CN, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, SO₂NR⁷R⁸, NR⁵SO₂R⁶, mono to perfluoroC₍₁₋₄₎alkyl and mono to perfluoroC₍₁₋₄₎alkoxy, and which 5- to 7-membered heterocyclyl ring is optionally substituted by COR⁵, COOR⁵, CONR⁷R⁸, or C₍₁₋₆₎alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR⁵, COR⁵, carboxy, COOR⁵, CONR⁷R⁸ or NR⁷R⁸, for instance, piperidin-4-yl, pyrrolidin-3-yl; and

30 R¹⁰ is C₍₁₋₆₎alkyl optionally substituted by 1, 2 or 3 substituents which may be the same or different selected from hydroxy, halogen, OR⁵, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, aryl, heteroaryl and a 5- to 7-membered heterocyclyl ring, which aryl or heteroaryl is optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₆₎alkyl, C₍₁₋₆₎alkoxy, C₍₁₋₆₎alkylthio, arylC₍₁₋₆₎alkoxy, hydroxy, halogen, CN, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, SO₂NR⁷R⁸, NR⁵SO₂R⁶, mono to perfluoroC₍₁₋₄₎alkyl and mono to perfluoroC₍₁₋₄₎alkoxy, and

which 5- to 7-membered heterocyclyl ring is optionally substituted by COR⁵, COOR⁵, CONR⁷R⁸, or C₍₁₋₆₎alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR⁵, COR⁵, carboxy, COOR⁵, CONR⁷R⁸ or NR⁷R⁸, for instance, piperidin-4-yl, pyrrolidin-3-yl; or

- 5 R¹⁰ is a 5- to 7-membered heterocyclic ring optionally substituted by COR⁵, COOR⁵, CONR⁷R⁸, or C₍₁₋₆₎alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR⁵, COR⁵, carboxy, COOR⁵, CONR⁷R⁸ or NR⁷R⁸, for instance, piperidin-4-yl, pyrrolidin-3-yl;

with the proviso that Z is not amino and that the compound of formula (I) is not:

- 10 *N*-(2-diethylaminoethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-7-trifluoromethyl-4-oxo-4*H*-quinazolin-1-yl]-*N*-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide;
N-(2-diethylaminoethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-7-methyl-4-oxo-4*H*-quinazolin-1-yl]-*N*-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide;
N-(1-ethylpiperidin-4-yl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-7-methyl-4-oxo-4*H*-
 15 [1,8]naphthyridin-1-yl]-*N*-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide;
N-(2-diethylaminoethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-7-methyl-4-oxo-4*H*-[1,8]naphthyridin-1-yl]-*N*-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide;
N-(1-methylpiperidin-4-yl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-7-methyl-4-oxo-4*H*-
 [1,8]naphthyridin-1-yl]-*N*-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide;
 20 *N*-(1-isopropylpiperidin-4-yl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-7-methyl-4-oxo-4*H*-[1,8]naphthyridin-1-yl]-*N*-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide; or
N-(1-(2-methoxyethyl)piperidin-4-yl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-7-methyl-4-oxo-4*H*-[1,8]naphthyridin-1-yl]-*N*-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide.

- 25 In one aspect the aryl group of R¹ may be phenyl or naphthyl. Preferably, R¹ is phenyl optionally substituted by halogen, C₍₁₋₆₎alkyl, trifluoromethyl, C₍₁₋₆₎alkoxy, preferably, from 1 to 3 fluoro, more preferably, 2,3-difluoro.

- In another aspect R² may be hydrogen, methyl, ethyl, isopropyl, 2-(diethylamino)ethyl, 2-(piperidin-1-yl)ethyl, 2-(pyrrolidin-1-yl)ethyl, 1-(2-methoxyethyl)piperidin-4-yl, 1-methylpiperidin-4-yl, 1-ethyl-piperidin-4-yl or 1-ethyl-pyrrolidin-2-ylmethyl. Preferably
 30 R² is methyl, ethyl, isopropyl or 1-ethyl-piperidin-4-yl especially methyl or ethyl.

In another aspect R³ may be phenyl or pyridyl. Preferably, R³ is phenyl.

- 35 In another aspect R⁴ may be phenyl optionally substituted by halogen, or trifluoromethyl, preferably at the 4-position, or ethyl. Preferably, R⁴ is phenyl substituted by trifluoromethyl at the 4-position.

- 40 Preferably, R³ and R⁴ together form a 4-(phenyl)phenyl or a 2-(phenyl)pyridinyl substituent in which the remote phenyl ring may be optionally substituted by halogen or trifluoromethyl, preferably at the 4-position.

Preferably W is $(CH_2)_nS$ or $CH_{(2-4)}$ alkylene e.g. $C_{(2-3)}$ alkylene, most preferably W is $(CH_2)_2$ or CH_2S .

In another aspect X may be CH.

5

In another aspect Y may be CH.

In another aspect Z may be NO_2 , OR^9 or R^{10} .

10 In another aspect Z may be:

NO_2 ;

NR^5R^9 , OR^9 , SR^9 , SOR^9 or SO_2R^9 where R^9 is as hereinbefore defined; or

R^{10} where R^{10} is $C_{(2-6)}$ alkyl, or $C_{(1-6)}$ alkyl substituted by 1, 2 or 3 substituents

which may be the same or different selected from hydroxy, OR^5 , COR^5 , $COOR^5$,

15 $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , aryl, heteroaryl and a 5- to 7-membered heterocyclyl

ring, which aryl or heteroaryl is optionally substituted by 1, 2, 3 or 4 substituents which

may be the same or different selected from $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxy, $C_{(1-6)}$ alkylthio,

aryl $C_{(1-6)}$ alkoxy, hydroxy, halogen, CN, COR^5 , $COOR^5$, $CONR^7R^8$, NR^7R^8 ,

NR^5COR^6 , $SO_2NR^7R^8$, $NR^5SO_2R^6$, mono to perfluoro $C_{(1-4)}$ alkyl and mono to

20 perfluoro $C_{(1-4)}$ alkoxy, and which 5- to 7-membered heterocyclyl ring is optionally

substituted by COR^5 , $COOR^5$, $CONR^7R^8$, or $C_{(1-6)}$ alkyl optionally substituted by 1, 2

or 3 substituents selected from hydroxy, halogen, OR^5 , COR^5 , carboxy, $COOR^5$,

$CONR^7R^8$ or NR^7R^8 , for instance, piperidin-4-yl, pyrrolidin-3-yl, or R^{10} is a 5- to 7-

membered heterocyclic ring optionally substituted by COR^5 , $COOR^5$, $CONR^7R^8$, or

25 $C_{(1-6)}$ alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxy,

halogen, OR^5 , COR^5 , carboxy, $COOR^5$, $CONR^7R^8$ or NR^7R^8 , for instance, piperidin-4-

yl, pyrrolidin-3-yl.

In another aspect Z may be:

30

NO_2 ;

SOR^9 , SO_2R^9 or NR^5R^9 where R^9 is $C_{(1-6)}$ alkyl;

OR^9 , SR^9 , SOR^9 , SO_2R^9 or NR^5R^9 where R^9 is hydrogen or mono to perfluoro-

$C_{(1-6)}$ alkyl;

OR^9 , SR^9 , SOR^9 , SO_2R^9 or NR^5R^9 where R^9 is $C_{(1-6)}$ alkyl substituted by 1, 2

35 or 3 substituents which may be the same or different selected from hydroxy, OR^5 , COR^5 ,

$COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , aryl, heteroaryl and a 5- to 7-membered

heterocyclyl ring, which aryl or heteroaryl is optionally substituted by 1, 2, 3 or 4

substituents which may be the same or different selected from $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxy,

$C_{(1-6)}$ alkylthio, aryl $C_{(1-6)}$ alkoxy, hydroxy, halogen, CN, COR^5 , $COOR^5$, $CONR^7R^8$,

40 NR^7R^8 , NR^5COR^6 , $SO_2NR^7R^8$, $NR^5SO_2R^6$, mono to perfluoro $C_{(1-4)}$ alkyl and mono

to perfluoro $C_{(1-4)}$ alkoxy, and which 5- to 7-membered heterocyclyl ring is optionally

substituted by COR^5 , $COOR^5$, $CONR^7R^8$, or $C_{(1-6)}$ alkyl optionally substituted by 1, 2

or 3 substituents selected from hydroxy, halogen, OR⁵, COR⁵, carboxy, COOR⁵, CONR⁷R⁸ or NR⁷R⁸, for instance, piperidin-4-yl, pyrrolidin-3-yl; or

R¹⁰ where R¹⁰ is C₍₁₋₆₎alkyl substituted by 1, 2 or 3 substituents which may be the same or different selected from hydroxy, OR⁵, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, aryl, heteroaryl and a 5- to 7-membered heterocyclyl ring, which aryl or heteroaryl is optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₆₎alkyl, C₍₁₋₆₎alkoxy, C₍₁₋₆₎alkylthio, arylC₍₁₋₆₎alkoxy, hydroxy, halogen, CN, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, SO₂NR⁷R⁸, NR⁵SO₂R⁶, mono to perfluoroC₍₁₋₄₎alkyl and mono to perfluoroC₍₁₋₄₎alkoxy, and which 5- to 7-membered heterocyclyl ring is optionally substituted by COR⁵, COOR⁵, CONR⁷R⁸, or C₍₁₋₆₎alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR⁵, COR⁵, carboxy, COOR⁵, CONR⁷R⁸ or NR⁷R⁸, for instance, piperidin-4-yl, pyrrolidin-3-yl, or R¹⁰ is a 5- to 7-membered heterocyclic ring optionally substituted by COR⁵, COOR⁵, CONR⁷R⁸, or C₍₁₋₆₎alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR⁵, COR⁵, carboxy, COOR⁵, CONR⁷R⁸ or NR⁷R⁸, for instance, piperidin-4-yl, pyrrolidin-3-yl; with the proviso that when X is CH, Z is not C₍₁₋₃₎alkoxyC₍₁₋₃₎alkyl.

In another aspect Z may be hydroxy, nitro, mono or di-N-C₍₁₋₆₎alkylaminoC₍₁₋₆₎alkyl, mono or di-N-C₍₁₋₆₎alkylaminoC₍₁₋₆₎alkoxy, carboxyC₍₁₋₆₎alkoxy or an ester thereof, or arylC₍₁₋₆₎alkoxy, arylC₍₁₋₆₎alkyl, heteroarylC₍₁₋₆₎alkoxy, heteroarylC₍₁₋₆₎alkyl, 5- to 7-membered heterocyclylC₍₁₋₆₎alkoxy optionally substituted by C₍₁₋₆₎alkyl, or 5- to 7-membered heterocyclylC₍₁₋₆₎alkyl optionally substituted by C₍₁₋₆₎alkyl.

When Z includes an aryl, heteroaryl or heterocyclyl ring, said ring is preferably selected from benzyl, pyridinyl isoxazolyl, piperidinyl, pyrrolidinyl and morpholino, particularly piperidinyl and morpholino.

In another aspect Z may be 3-(diethylamino)propyl, 3-(dimethylamino)propoxy, nitro, 2-(dimethylamino)ethoxy, 2-(diethylamino)ethoxy, 2-(piperidin-1-yl)ethoxy, 3-(piperidin-1-yl)propoxy, OCH₂CO₂^tBu, (pyridin-2-yl)methoxy, (5-methylisoxazol-3-yl)methoxy, (1-methylpyrrolidin-2-yl)methoxy, benzyloxy, hydroxy, OCH₂CO₂H, dimethylaminomethyl, diethylaminomethyl, (pyrrolidin-1-yl)methyl, (piperidin-1-yl)methyl, 2-dimethylaminoethyl, 2-diethylaminoethyl, 2-(pyrrolidin-1-yl)ethyl, 3-diethylaminopropyl, 3-(pyrrolidin-1-yl)propyl, 3-(piperidin-1-yl)propyl or 3-(4-morpholino)propyl, particularly 3-(piperidin-1-yl)propyl or 3-(4-morpholino)propyl.

It will be appreciated that compounds of the present invention may comprise one or more chiral centres so that one or more stereoisomers may be formed.

The present invention encompasses all stereoisomers of the compounds of formula (I) including geometric isomers and optical isomers (eg. diastereoisomers and enantiomers)

whether as individual stereoisomers isolated such as to be substantially free of the other stereoisomers (i.e. pure) or as mixtures thereof including racemic modifications. An individual stereoisomer isolated such as to be substantially free of other stereoisomer (i.e. pure) will preferably be isolated such that less than 10% preferably less than 1% especially less than 0.1% of the other stereoisomers is present.

Certain compounds of formula (I) may exist in one of several tautomeric forms. It will be understood that the present invention encompasses all tautomers of the compounds of formula (I) whether as individual tautomers or as mixtures thereof.

10

It will be appreciated that in some instances, compounds of the present invention may include a basic function such as an amino group as a substituent. Such basic functions may be used to form acid addition salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhous, *J. Pharm. Sci.*, 1977, 66, 1-19. Such salts may be formed from inorganic and organic acids. Representative examples thereof include maleic, fumaric, benzoic, ascorbic, pantoic, succinic, bis-methylenesalicylic, methanesulfonic, ethanesulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, taurocholic acid, benzenesulfonic, p-toluenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

20

It will be appreciated that in some instances, compounds of the present invention may include a carboxy group as a substituent. Such carboxy groups may be used to form salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhous, *J. Pharm. Sci.*, 1977, 66, 1-19. Preferred salts include alkali metal salts such as the sodium and potassium salts.

25

When used herein, the term "alkyl" and similar terms such as "alkoxy" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, t-butyl, n-pentyl and n-hexyl.

30

When used herein, the term "aryl" refers to, unless otherwise defined, a mono- or bicyclic aromatic ring system containing up to 10 carbon atoms in the ring system, for instance phenyl or naphthyl.

35

When used herein, the term "heteroaryl" refers to a mono- or bicyclic heteroaromatic ring system comprising up to four, preferably 1 or 2, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring.

40

When used herein, the term "heterocyclyl" refers to, unless otherwise defined, a single or fused non-aromatic ring comprising up to four heteroatoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted with up to three substituents.

Suitably the heterocyclic ring comprises from 5 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring.

- 5 When used herein, the terms "halogen" and "halo" include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

It is to be understood that the present invention covers all combinations of substituent groups referred to hereinabove.

10

Representative compounds of formula (I) are:

- N-Methyl-2-(2-(2-(2,3-difluorophenyl)ethyl)-7-(3-dimethylaminoprop-1-yl)-4-oxo-4H-quinolin-1-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(3-(dimethylamino)propoxy)-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 15 N-Methyl-2-(2-(2-(2,3-difluorophenyl)ethyl)-7-nitro-4-oxo-4H-quinolin-1-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-(2-dimethylaminoethoxy)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 20 2-(7-(2-Diethylaminoethoxy)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(2-(piperidin-1-yl)ethoxy)-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(3-(piperidin-1-yl)propoxy)-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 25 tert. Butyl 2-(2-(2-(2,3-difluorophenyl)ethyl)-1-(N-(4-(4-trifluoromethylphenyl)benzyl)-N-methyl-aminocarbonylmethyl)-4-oxo-4H-quinolin-7-yloxy)acetate;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(pyridin-2-ylmethoxy)-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide hydrochloride;
 30 2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-(5-methylisoxazol-3-ylmethoxy)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-(1-methylpiperidin-2-ylmethoxy)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-Benzylloxy-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide;
 35 2-(7-Benzylloxy-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4-quinolin-1-yl)-N-(1-ethylpiperidin-4-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-hydroxy-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide;
 40 2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-hydroxy-4-oxo-4H-quinolin-1-yl)-N-(1-ethylpiperidin-4-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-1-(N-(4-(4-trifluoromethylphenyl)benzyl)-N-methyl-aminocarbonylmethyl)-4-oxo-4H-quinolin-7-yloxy)acetic acid
 2-(7-(Dimethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 45 2-(7-(Diethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;

- 2-(7-(Diethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(Diethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-isopropyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 5 2-(7-(Pyrrolidin-1-yl)methyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(Piperidin-1-yl)methyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(2-Dimethylaminoethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 10 2-(7-(2-Diethylaminoethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(2-(Pyrrolidin-1-yl)ethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 15 2-(7-(3-Diethylaminopropyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(3-(Pyrrolidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 20 2-(7-(3-(Piperidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(3-(Piperidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-isopropyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(Diethylaminomethyl)-2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate; and
 25 2-(7-(3-(4-Morpholino)propyl)-2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide hydrochloride.

Preferred compounds are:

- 30 2-(7-(3-(Piperidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate; and
 2-(7-(3-(4-Morpholino)propyl)-2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide hydrochloride.

- 35 Preferred salts are the bitartrate and hydrochloride salts.

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

19

When some of the compounds of this invention are allowed to crystallise or are re-crystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly,
5 some of the compounds of this invention may be crystallised or re-crystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates 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
10 of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of formula (I).

Compounds of the present invention are inhibitors of the enzyme lipoprotein associated phospholipase A₂ (Lp-PLA₂) and as such are expected to be of use in therapy, in
15 particular in the treatment of atherosclerosis. In a further aspect therefore the present invention provides a compound of formula (I) for use in therapy.

The compounds of formula (I) are inhibitors of lysophosphatidylcholine production by Lp-PLA₂ and may therefore also have a general application in any disorder that involves
20 endothelial dysfunction, for example atherosclerosis, diabetes, hypertension, angina pectoris and after ischaemia and reperfusion. In addition, compounds of formula (I) may have a general application in any disorder that involves lipid oxidation in conjunction with enzyme activity, for example in addition to conditions such as atherosclerosis and diabetes, other conditions such as rheumatoid arthritis, stroke, inflammatory conditions of
25 the brain such as Alzheimer's Disease, myocardial infarction, ischaemia, reperfusion injury, sepsis, and acute and chronic inflammation.

Further applications include any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA₂. Examples of such disorders
30 include psoriasis.

Accordingly, in a further aspect, the present invention provides for a method of treating a disease state associated with activity of the enzyme Lp-PLA₂ which method involves
35 treating a patient in need thereof with a therapeutically effective amount of an inhibitor of the enzyme. The disease state may be associated with the increased involvement of monocytes, macrophages or lymphocytes; with the formation of lysophosphatidylcholine and oxidised free fatty acids; with lipid oxidation in conjunction with Lp PLA₂ activity; or with endothelial dysfunction.

40 Compounds of the present invention may also be of use in treating the above mentioned disease states in combination with an anti-hyperlipidaemic, anti-atherosclerotic, anti-diabetic, anti-anginal, anti-inflammatory, or anti-hypertension agent or an agent for lowering Lp(a). Examples of the above include cholesterol synthesis inhibitors such as

statins, anti-oxidants such as probucol, insulin sensitisers, calcium channel antagonists, and anti-inflammatory drugs such as NSAIDs. Examples of agents for lowering Lp(a) include the aminophosphonates described in WO 97/02037, WO 98/28310, WO 98/28311 and WO 98/28312 (Symphar SA and SmithKline Beecham).

5

A preferred combination therapy will be the use of a compound of the present invention and a statin. The statins are a well known class of cholesterol lowering agents and include atorvastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, lovastatin and ZD 4522 (also referred to as S-4522, rosuvastatin, Astra Zeneca). The two agents may be
10 administered at substantially the same time or at different times, according to the discretion of the physician.

A further preferred combination therapy will be the use of a compound of the present invention and an anti-diabetic agent or an insulin sensitiser, as coronary heart disease is a
15 major cause of death for diabetics. Within this class, preferred compounds for use with a compound of the present invention include the PPARgamma activators, for instance GI262570 (GlaxoSmithKline) and the glitazone class of compounds such as rosiglitazone (Avandia, GlaxoSmithKline), troglitazone and pioglitazone.

20 In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier, optionally with one or more other therapeutic compounds such as a statin or an anti-diabetic.

25

Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository, particularly for oral administration.

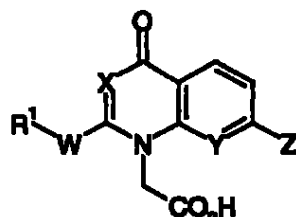
Compounds of formula (I) which are active when given orally can be formulated as
30 liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent. A composition in the form
35 of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose. A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin
40 capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, allicates or oils and the dispersion or suspension then filled into a soft gelatin capsule. Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a

sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilized and then reconstituted with a suitable solvent just prior to administration. A typical suppository formulation comprises a compound of formula (I) which is active

- 5 when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.
- Preferably the composition is in unit dose form such as a tablet or capsule. Each dosage unit for oral administration contains preferably from 1 to 500 mg (and for parenteral
- 10 administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I). The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I), the compound being administered
- 15 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

According to a first process A, a compound of formula (I) may be prepared by reacting an acid compound of formula (II):

20



(II)

- 25 in which W, X, Y, Z and R¹ are as hereinbefore defined, with an amine compound of formula (III):



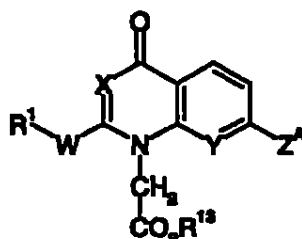
(III)

- 30 in which R², R³ and R⁴ are as hereinbefore defined; under amide forming conditions.

Suitable amide forming conditions are well known in the art and include treating the acid of formula (II) with the amine of formula (III) in the presence of a coupling agent such as 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (DEC) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) in an aprotic solvent such as dichloromethane or dimethylformamide (DMF).

35

A compound of formula (II) may be readily prepared from a corresponding ester of formula (IV):



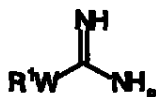
(IV)

5 in which W, X, Y and R¹ are as hereinbefore defined, Z^A is Z as hereinbefore defined or a group convertible to Z, and R¹³ is C₍₁₋₆₎alkyl, for example ethyl or t-butyl, by treating with a de-esterifying agent, for instance, for t-butyl, trifluoroacetic acid.

10 It will be appreciated that removal of R¹³ may be carried out as a separate step, so that an acid of formula (II), or a salt thereof, for example the sodium salt, is isolated or, alternatively, that the acid of formula (II), or a salt thereof, is formed from the intermediate ester (IV) as a preliminary first step, prior to reaction with an amine of formula (III).

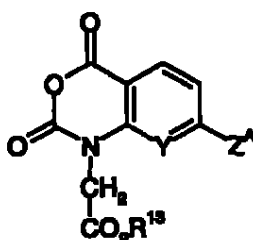
15 Thus, according to another process B a compound of formula (I) can be prepared by (a) treating a compound of formula (IV) with a deesterifying agent to form a compound of formula (II) or a salt thereof; and (b) treating said compound of formula (II) or salt thereof with an amine compound of formula (III) under amide forming conditions.

20 When X is N and Y is CH, the ester of formula (IV) may be readily prepared by reacting an amidine of formula (V):



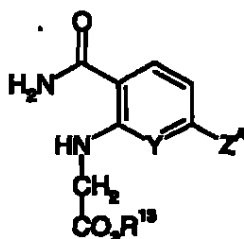
(V)

25 in which R¹ and W are as hereinbefore defined, preferably as a salt thereof, for instance the hydrochloride salt, with a compound of formula (VI):



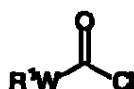
(VI)

- in which Z^A is Z as hereinbefore defined or a group convertible to Z, and R^{13} is as hereinbefore defined, for example ethyl, under standard pyrimidone ring forming conditions, in the presence of a base such as pyridine, to give an intermediate ester (IV) which can then be converted into a compound of formula (II), for instance by treatment with aqueous sodium hydroxide.
- 10 Alternatively, when X is N and Y is CH, the pyrimidone ring may be formed by reacting a compound of formula (VII):



(VII)

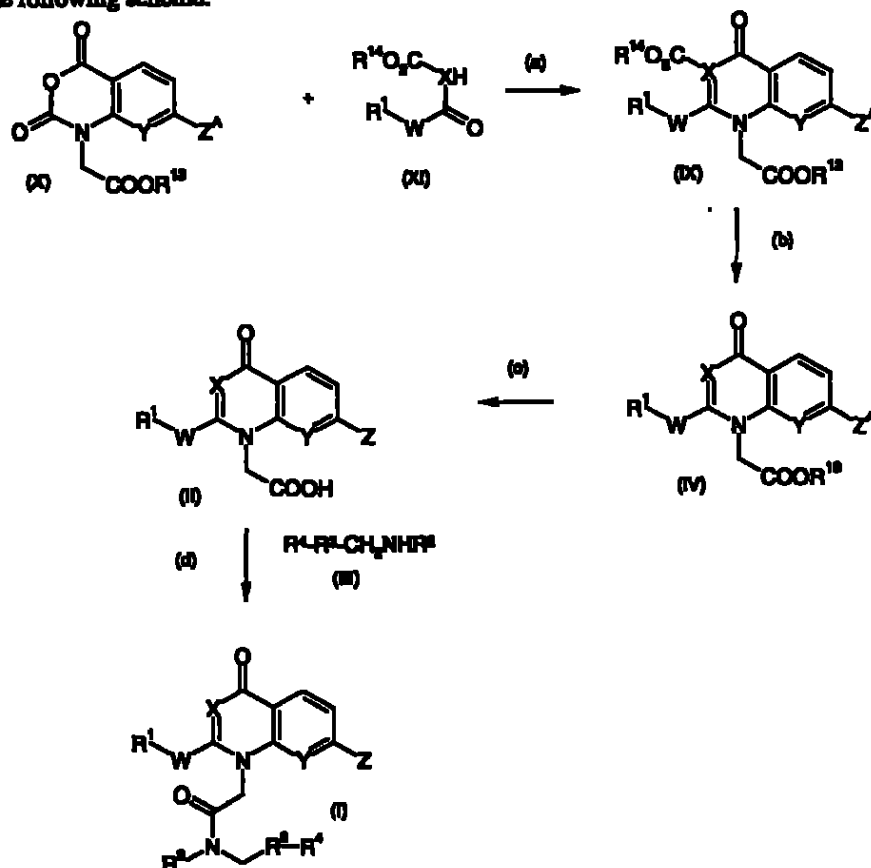
- 15 in which Z^A is Z as hereinbefore defined or a group convertible to Z, and R^{13} is as hereinbefore defined, for example ethyl, with an acyl chloride compound of the formula (VIII):



(VIII)

- 20 in which R^1 and W are as hereinbefore defined;
under standard pyrimidone ring forming conditions, in a solvent such as benzene, or via a two step procedure by treatment with pyridine, followed by a suitable base e.g. NaH in DMF, followed by treatment of the intermediate so formed with an acid e.g. p-toluene sulfonic acid in refluxing toluene; to give an intermediate ester (IV) which can then be converted into a compound of formula (II), for instance by treatment with aqueous sodium hydroxide.
- 25

When X and Y are CH, the overall synthesis of compounds of formula (I) is illustrated in the following scheme:

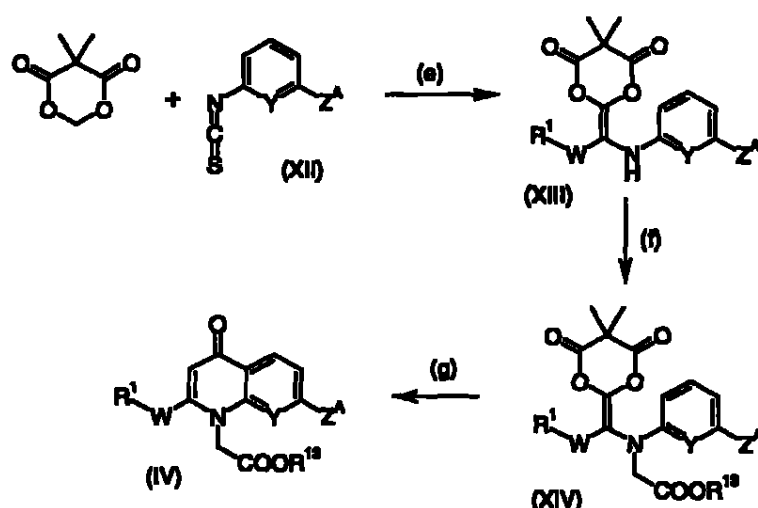


5

Referring to the scheme, the key intermediate (IV) may be synthesised by removing the 3-ester group from intermediate (IX) wherein R¹⁴ is C₍₁₋₆₎alkyl, for example by heating in diphenyl ether where R¹⁴ is ^tBu (step b). Intermediate (IX) is formed from the 2,6-dioxo-1,3-oxazine (X) and ester (XI) by treatment with a base, for example 1,8-diazabicyclo[5.4.0]undec-7-ene in tetrahydrofuran or NaH in DMF.

10

Alternatively where W is S and X and Y are CH, the synthesis of intermediate (IV) is illustrated in the following scheme:



Referring to the scheme, the key intermediate (IV) may be synthesised by acid catalysed cyclisation of intermediate (XIV), for example by heating with trifluoromethanesulfonic acid in dichloromethane. Intermediate (XIV) is formed by alkylation of intermediate (XIII) with a compound of formula (XV):



in which L is a leaving group, for example chloro or bromo, in the presence of a base such as potassium tert-butoxide, in a solvent such as N-methylpyrrolidone. Intermediate (XIII) is formed by reaction of Meldrum's acid with a compound of formula (XII) in the presence of a base such as N,N-diisopropylethylamine in a solvent such as N-methylpyrrolidone, immediately followed by treatment with an alkylating agent for formula (XVI):



for example 2,3-difluorobenzyl bromide.

Conversion of Z^A to Z typically arises if a protecting group, or a group which can take part in subsequent reactions such as coupling reactions, is needed during the above reactions or during the preparation of the reactants. The conversion of Z^A to Z may be carried out at different stages in the synthesis of the compounds of formula (I) depending on the nature of Z, including as a final step.

Z^A may be, for example, a protected hydroxy group. Suitable protecting groups are those well known in the art which may be removed under conventional conditions and without disrupting the remainder of the molecule. A comprehensive discussion of the ways in

which groups may be protected and methods for cleaving the resulting protected derivatives is given in for example *Protective Groups in Organic Chemistry*, T.W. Greene and P.G.M. Wuts, (Wiley-Interscience, New York, 2nd edition, 1991). Particularly suitable hydroxy protecting groups include benzyl.

5

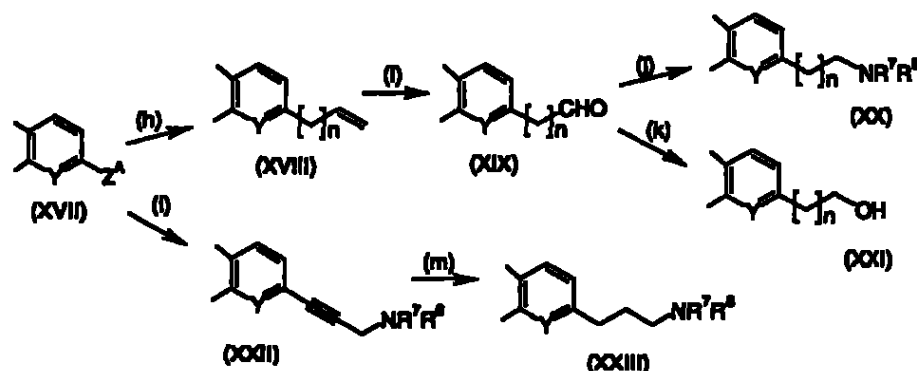
Thus, according to another process C, a compound of formula (I) may be prepared by subjecting a protected derivative of a compound of formula (I) to reaction to remove the protecting group or groups present, constituting a further aspect of the present invention.

10

Z^A may also be a group such as halo, for example chloro, bromo or iodo, which can be converted to Z at different stages in the synthesis of the compounds of formula (I), including as a final step using one of the general methods for functional group transformation described in the literature provided that the method chosen is compatible with the other functional groups in the molecule. Functional group transformations are well known in the art and are described in for instance *Comprehensive Organic Functional Group Transformations*, eds. A.R. Katritzky, O. Meth-Cohn and C.W. Rees (Elsevier Science Ltd., Oxford, 1995), *Comprehensive Organic Chemistry*, eds. D. Barton and W.D. Ollis (Pergamon Press, Oxford, 1979), and *Comprehensive Organic Transformations*, R.C. Larock (VCH Publishers Inc., New York, 1989). Some representative examples of transformations based on intermediates where Z^A is halo are shown in the following scheme (part structures shown):

15

20



25

Thus an intermediate with part-structure (XVII), in which Z^A is bromo or iodo, can undergo palladium-catalysed coupling with vinyl stannanes to form (XVIII) where $n=0$, or with allyl stannanes to form (XVIII) where $n=1$ (step h). Oxidative cleavage of the terminal alkene group of (XVIII), for example by oxidation with cerium tetroxide followed by treatment with sodium periodate (step i), forms an aldehyde of part structure (XIX). For the case where $n=2$, coupling of (XVII) with allyl alcohol gives (XIX) directly. Such compounds, in which Z^A is $(CH_2)_nCHO$, in turn represent versatile intermediates. For example, reductive amination with an amine of formula NHR^7R^8 and a reducing agent such as sodium triacetoxyborohydride forms (XX), in which Z is

30

$(CH_2)_{n+1}NR^7R^8$; or reduction by standard means forms alcohols (XXI). In a further example, longer chain substituents can conveniently be formed by palladium-catalysed coupling of alkynes to (XVII), in which Z^A is bromo or iodo (step i), and subsequent reduction (step m).

5

Thus, according to another process D, a compound of formula (I) may be prepared from a compound of formula (I) in which Z^A is a group convertible to Z by functional group transformation, constituting another aspect of the present invention.

10

It will further be appreciated that compounds of formula (I) may also be prepared from other compounds of formula (I) using conventional interconversion procedures (process E), constituting yet a further aspect of the present invention.

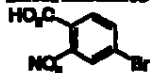
The following Examples illustrate the invention.

15

Examples

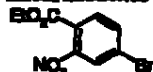
The structure and purity of the intermediates and examples was confirmed by ¹H-NMR and (in nearly all cases) mass spectroscopy, even where not explicitly indicated below.

5 Intermediate A1 — 4-Bromo-2-nitrobenzoic acid.



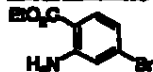
Potassium permanganate (29.6g, 187mmol) was added in portions over 8h to a refluxing solution of 4-bromo-2-nitrotoluene (10.1g, 46.75mmol) in pyridine (80ml) and water (70ml). The suspension was filtered whilst hot and the resultant yellow solution was evaporated to about 1/4 volume. Sodium hydroxide (2M, 20ml) was added and the solution extracted with diethyl ether (to remove any 4-bromo-2-nitrotoluene that remained). The solution was acidified with hydrochloric acid (conc.) and the resultant solid collected and dried under reduced pressure to afford the title compound (5.72g, 50%). ¹H NMR (d₆-DMSO) δ 7.79 (1H, d), 7.98 (1H, dd), 8.23 (1H, d).

15 Intermediate A2 — Ethyl 4-bromo-2-nitrobenzoate



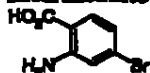
A solution of intermediate A1 (6.9g, 28.05mmol) and sulphuric acid (conc., 10ml) in ethanol (80ml) was heated to reflux for 18h. After cooling the solvent was evaporated. The residue was dissolved in diethyl ether and washed with water, saturated sodium bicarbonate, dried (MgSO₄) and the solvent evaporated to afford the title compound (7.09g, 92%). ¹H NMR (CDCl₃) δ 1.35 (3H, t), 4.39 (2H, q), 7.65 (1H, d), 7.78 (1H, dd), 8.00 (1H, d).

25 Intermediate A3 — Ethyl 2-amino-4-bromobenzoate.



A mixture of intermediate A2 (7.09g, 25.9mmol) and iron (14.5g, 259mmol) in 10% aqueous ethanol (250ml) was heated to reflux for 6h. The mixture was filtered through celite and the resultant solution evaporated. The crude mixture was purified by chromatography (plug of silica gel) in dichloromethane to afford the title compound (4.53g, 72%). ¹H NMR (CDCl₃) δ 1.37 (3H, t), 4.32 (2H, q), 5.77 (2H, br s), 6.73 (1H, dd), 6.83 (1H, d), 7.71 (1H, d).

Intermediate A4 — 2-Amino-4-bromobenzoic acid hydrochloride.

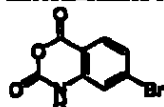


Sodium hydroxide (2M, 28ml) was added to a stirred solution of intermediate A3 (4.53g, 18.6mmol) in dioxan (150ml) and water (22ml) and the resultant solution heated at 75°C

for 4h. After cooling the solvent was evaporated and the residue suspended in water. The mixture was acidified (conc. HCl) and the resultant solid collected and dried to afford the title compound (4.29g, 89%). ¹H NMR (d₆-DMSO) δ 6.64 (1H, dd), 6.97 (1H, d), 7.59 (1H, d).

5

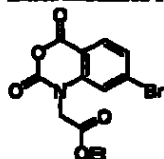
Intermediate A5 — 7-Bromo-1 *H*-benzo[*d*][1,3]oxazine-2,4-dione.



10

Phosgene (20% in toluene, 12.9ml) was added dropwise to a stirred solution of intermediate A4 (3.15g, 12.5mmol) in dioxan (30ml), stirring was continued for 18h. The solvent was evaporated to afford the title compound (2.96g, 98%). ¹H NMR (d₆-DMSO) δ 7.33 (1H, d), 7.42 (1H, dd), 7.83 (1H, d), 11.87 (1H, s); ¹³C NMR (d₆-DMSO) 109.7, 117.6, 126.4, 130.1, 130.7, 142.4, 146.7 and 159.2.

Intermediate A6 — Ethyl (7-bromo-2,4-dioxo-4 *H*-benzo[*d*][1,3]oxazin-1-yl)acetate.

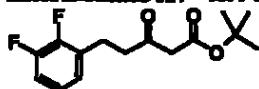


15

Ethyl bromoacetate (4ml, 36.1mmol) was added dropwise to a stirred solution of intermediate A5 (8.74g, 36.1mmol) and diisopropylethylamine (7.5ml, 43.3mmol) in *N*-methyl-2-pyrrolidinone (50ml) at 0°C. Stirring was continued at room temperature for 18h. The solution was diluted with water (150ml) and the resultant solid collected and dried (MgSO₄) to afford the title compound (10g, 85%). ¹H NMR (d₆-DMSO) δ 1.23 (3H, t), 4.20 (2H, q), 4.91 (2H, s), 7.41 (1H, dd), 7.81 (1H, d), 7.94 (1H, d).

20

Intermediate A7 - *tert*-Butyl 5-(2,3-difluorophenyl)-3-oxopentanoate



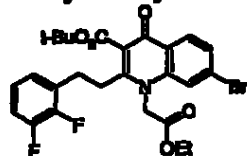
25

To an ice cooled stirring suspension of sodium hydride (1.96 g, 49.1 mmol, 60% dispersion in oil) in dry tetrahydrofuran (100 ml) was added dropwise under an argon atmosphere *tert*-butylacetoacetate (7.4 ml, 44.6 mmol). After a further 15 min, *n*-butyllithium (18.7 ml, 46.8 mmol, 2.5M in hexanes) was added dropwise maintaining the reaction temperature below 10°C. 2,3-Difluorobenzyl bromide (11.08 g, 53.5 mmol) was added dropwise 20 min later, then the mixture allowed to warm to ambient temperature. After a further 15 min the reaction mixture was poured onto a mixture of water (150 ml) and glacial acetic acid (10 ml), extracted 3 times with ethyl acetate and the combined extracts washed with saturated sodium hydrogen carbonate then brine, dried (MgSO₄) and evaporated to a yellow oil. Chromatography (fine silica, ethyl acetate-light petrol) gave

30

the title compound as a yellow oil, yield 9.05 g (71%). ¹H NMR (CDCl₃) δ 1.45 (9H, s), 2.84-2.91 (2H, m), 2.95-3.00 (2H, m), 3.35 (2H, s), 6.92-7.04 (3H, m).

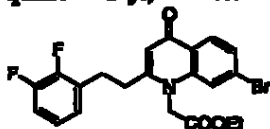
5 **Intermediate A8** — *tert*-butyl (7-bromo-2-(2-(2,3-difluorophenyl)ethyl)-1-ethoxycarbonyl-4-oxo-4*H*-quinolin-1-yl)-3-carboxylate.



10 1,8-Diazabicyclo[5.4.0]undec-7-ene (9.1ml, 61mmol) was added dropwise to a stirred solution of intermediate A6 (10g, 30.5mmol) and intermediate A7 (9.52g, 33.5mmol) in tetrahydrofuran (100ml) at 0°C. Stirring was continued at room temperature for 18h. The solution was diluted with ethyl acetate, washed with saturated sodium bicarbonate, dried (MgSO₄) and the solvent evaporated. The residue was purified by chromatography (petrol / ethyl acetate) to afford the title compound (9.3g, 55%). ¹H NMR (CDCl₃) δ 1.33 (3H, t), 1.62 (9H, s), 2.97 (2H, m), 3.07 (2H, m), 4.34 (2H, q), 4.94 (2H, br s), 7.00-7.12 (3H, m), 7.42 (1H, d), 7.49 (1H, dd), 8.29 (1H, d).

15

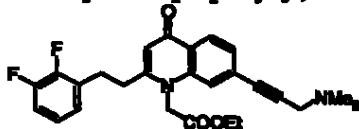
Intermediate A9 — Ethyl (7-bromo-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4*H*-quinolin-1-yl)acetate.



20 Intermediate A8 (9.3g, 16.9mmol) in diphenyl ether (30ml) was heated to reflux for 15min. After cooling petrol was added and the resultant solid collected by filtration. The crude product was purified by chromatography (silica gel, petrol / ethyl acetate) to afford the title compound (2.8g, 37%). ¹H NMR (CDCl₃) δ 1.31 (3H, t), 2.91 (2H, m), 3.05 (2H, m), 4.32 (2H, q), 4.86 (2H, s), 6.25 (1H, s), 6.93-7.14 (3H, m), 7.42 (1H, d), 7.49 (1H, dd), 8.29 (1H, d); MS (APCI+) found (M+1) = 450; C₂₁H₁₈⁷⁹BrNO₃ requires 449.

25

Intermediate A10 — Ethyl (2-(2-(2,3-difluorophenyl)ethyl)-7-(3-dimethylaminoprop-1-ynyl)-4-oxo-4*H*-quinolin-1-yl)acetate.



30 A mixture of Intermediate A9 (0.43g, 0.96mmol), 3-dimethylaminopropyne (0.41ml, 3.8mmol), bis(triphenylphosphine)palladium(II) chloride (0.07g) and copper(I) iodide (0.04g) in 1,2-dimethoxyethane (5ml) and triethylamine (5ml) was heated to 75°C for 2h. After cooling, the solvent was evaporated and the residue suspended in dichloromethane and washed with saturated sodium bicarbonate, dried (MgSO₄) and the solvent

evaporated. The crude product was purified by chromatography (NH₃ / MeOH / CH₂Cl₂) to afford the title compound (390mg, 90%). ¹H NMR (CDCl₃) δ 1.30 (3H, t), 2.39 (6H, s), 2.92 (2H, m), 3.05 (2H, m), 3.49 (2H, s), 4.30 (2H, q), 4.88 (1H, s), 6.25 (1H, s), 6.93-7.10 (3H, m), 7.32 (1H, d), 7.42 (1H, dd), 8.35 (1H, d); MS (APCI+) found (M+1) = 453; C₂₆H₂₆F₂O₃N₂ requires 452.

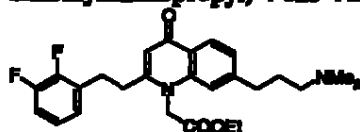
5

The following intermediates were prepared by the method of intermediate A10.

No.	Precursor	Structure	Name
A90	A9		Ethyl (7-(3-diethylaminoprop-1-ynyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
A91	A9		Ethyl (7-(3-(pyrrolidin-1-yl)prop-1-ynyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
A92	A9		Ethyl (7-(3-(piperidin-1-yl)prop-1-ynyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate

Intermediate A11 — Ethyl (2-(2-(2,3-difluorophenyl)ethyl)-7-(3-dimethylaminopropyl)-4-oxo-4H-quinolin-1-yl)acetate.

10



A mixture of intermediate A10 (0.39g, 0.86mmol) and Pd/C (40mg) in ethanol was hydrogenated at room temperature and pressure until the reaction was complete by HPLC. The catalyst was filtered off and the solvent evaporated to afford the title compound (0.29g, 73%). ¹H NMR (CDCl₃) δ 1.28 (3H, t), 1.83 (2H, m), 2.24 (6H, s), 2.31 (2H, t), 2.78 (2H, t), 2.92 (2H, m), 3.05 (2H, m), 4.28 (2H, q), 4.90 (2H, s), 6.25 (1H, s), 6.96-7.11 (4H, m), 7.23 (1H, dd), 8.34 (1H, d); MS (APCI+) found (M+1) = 457; C₂₆H₃₀F₂N₂O₃ requires 456.

15

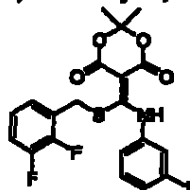
The following intermediates were prepared by the method of intermediate A11.

No.	Precursor	Structure	Name
A100	A90		Ethyl (7-(3-diethylaminopropyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate

32

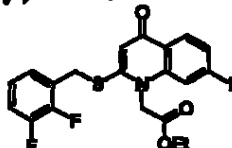
A101	A91		Ethyl (7-(3-(pyrrolidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
A102	A92		Ethyl (7-(3-(piperidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate

Intermediates A12 — 5-((2,3-difluorobenzylthio)-(3-iodophenylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione.



- 5 To a solution of Meldrum's acid (13.4g, 93mmol) in *N*-methylpyrrolidinone (50ml), cooled to 15°C, was added *N,N*-diisopropylethylamine (15ml, 86mmol). The mixture was stirred at 15°C for 1h, then a solution of 3-iodophenylisothiocyanate (20.9g, 80mmol) in *N*-methylpyrrolidinone (90ml) was added. The mixture was stirred at room temperature for 16h, then cooled to 10°C. 2,3-Difluorobenzyl bromide (16.5g, 80 mmol)
- 10 was added over 20 minutes. The reaction mixture was stirred at room temperature for 3h, then poured into a mixture of EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organic phases washed twice with water, then brine, dried (Na₂SO₄) and evaporated. The residual oil was stirred with Et₂O, the resulting solid was collected by filtration to give the title compound (36g). ¹H NMR (CDCl₃) δ 1.77 (6H, s), 4.07 (2H, s), 6.9-7.2 (4H, m), 7.2-7.3 (1H, br.), 7.6-7.75 (2H, br.), 12.8 (1H, s); MS (APCI-) found (M-1) = 530; C₂₀H₁₆F₂INO₄S requires 531.
- 15

Intermediate A13 — Ethyl (7-iodo-2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl)acetate.

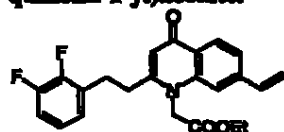


- 20 To a solution intermediate A12 (20g, 38mmol) in NMP (50ml) was added potassium *tert*-butoxide (4.54g, 40mmol). The mixture was stirred at room temperature for 1h, then ethyl bromoacetate (4.6ml, 40mmol) was added. The mixture was stirred at 70°C for 8h. EtOAc was added to the cooled reaction mixture which was washed with water, then
- 25 brine, and evaporated. The residual oil was stirred with Et₂O, the resulting solid was collected by filtration to give a solid (13.6g). To a solution of this solid (9.6g) in CH₂Cl₂ (80ml) at reflux was added trifluoromethanesulfonic acid (1.72ml) portionwise over 90

53

minutes. After a further 2h at reflux, the reaction mixture was cooled and poured into a mixture of saturated sodium bicarbonate and CH₂Cl₂. The organic phase was washed with water, dried (Na₂SO₄) and evaporated. Chromatography (silica gel, MeOH/CH₂Cl₂) gave ethyl 2-(2-(2,3-difluorophenyl)ethyl)-5-iodo-4-oxo-4H-quinolin-1-yl)acetate (2.05g) as the earlier eluting isomer followed by ethyl 2-(2,3-difluorobenzylthio)-7-iodo-4-oxo-4H-quinolin-1-yl)acetate (title compound) (1.1g). ¹H NMR (CDCl₃) δ 1.31 (3H, t), 4.28 (2H, s), 4.30 (2H, q), 5.08 (2H, br s), 6.40 (1H, s), 7.02-7.19 (3H, m), 7.56 (1H, s), 7.69 (1H, d), 8.08 (1H, d); MS (APCI+) found (M+1) = 516; C₂₀H₁₆F₂INO₃S requires 515.

10 Intermediate A110 — Ethyl (7-vinyl-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate.

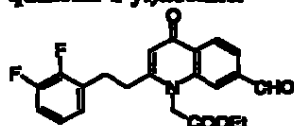


A mixture of intermediate A9 (0.6g, 1.33mmol), tributyl(vinyl)tin (1.0ml, 3.42mmol) and bis(triphenylphosphine)palladium(II) chloride (0.1g) in NMP (8ml) was stirred at 100°C for 1h. After cooling the mixture was diluted with ethyl acetate, washed with water then brine, dried (MgSO₄) and evaporated. Chromatography (silica gel, MeOH/CH₂Cl₂), then crystallization (EtOAc) gave the title compound as a light grey solid (0.357g, 67%). ¹H NMR (CDCl₃) δ 1.29 (3H, t), 2.92-2.97 (2H, m), 3.03-3.09 (2H, m), 4.30 (2H, q), 4.91 (2H, s), 5.45 (1H, d), 5.90 (1H, d), 6.26 (1H, s), 6.80 (1H, dd), 6.96-7.11 (3H, m), 7.18 (1H, s), 7.50 (1H, d), 8.39 (1H, d); MS (APCI+) found (M+1) = 398; C₂₀H₁₈F₂NO₃ requires 397.

The following intermediates were prepared by the method of intermediate A110.

No.	Precursor	Structure	Name
A111	A9		Ethyl (7-allyl-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
A112	A13		Ethyl (2-(2,3-difluorobenzylthio)-7-vinyl-4-oxo-4H-quinolin-1-yl)acetate

25 Intermediate A120 — Ethyl (7-formyl-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate.



To a solution of intermediate A110 (0.549g, 1.38 mmol) in a mixture of acetone, water and *tert*-butanol (30ml, 4:2:1 ratio) was added 4-methylmorpholine *N*-oxide (0.336g, 2.87

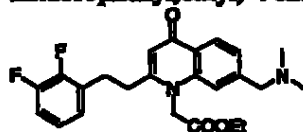
34

mmol) and osmium tetroxide (2.5 wt % solution in *tert*-butanol, 0.34ml). The reaction mixture was stirred at room temperature for 5h. A solution of sodium metabisulfite (10 wt % in water, 17ml) was added and the mixture stirred for 1h. Water (100 ml) and a mixture of CH₂Cl₂ and MeOH (150 ml, 9:1) were added. The aqueous layer was extracted with three further portions of CH₂Cl₂ and MeOH (9:1). The organic extracts were combined and evaporated to give a product which was suspended in THF (21ml) and a solution of sodium periodate (0.535g, 2.5mmol) in water (7 ml) added. The mixture was stirred at room temperature for 1h. Water and EtOAc were added, then the organic phase was washed with brine, dried (Na₂SO₄) and evaporated to give the title compound (0.522g, 95%). ¹H NMR (CDCl₃) δ 1.32 (3H, t), 2.95-2.99 (2H, m), 3.05-3.10 (2H, m), 4.32 (2H, q), 5.00 (2H, s), 6.33 (1H, s), 6.96-7.13 (3H, m), 7.81 (1H, s), 7.86 (1H, d), 8.61 (1H, d), 10.15 (1H, s); MS (APCI+) found (M+1) = 400; C₂₂H₁₉F₂N₂O₄ requires 399.

The following intermediates were prepared by the method of intermediate A120.

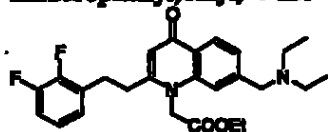
No.	Precursor	Structure	Name
A121	A111		Ethyl (7-formylmethyl-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4 H-quinolin-1-yl)acetate
A122	A112		Ethyl (2-(2,3-difluorobenzylthio)-7-formyl-4-oxo-4 H-quinolin-1-yl)acetate

Intermediate A130 — Ethyl (7-dimethylaminomethyl-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4 H-quinolin-1-yl)acetate.



A mixture of intermediate A120 (0.07g, 0.175mmol), dimethylamine hydrochloride (0.041g, 0.525mmol), sodium triacetoxyborohydride (0.074g, 0.35mmol) and acetic acid (0.01ml) in DMF (1ml) and THF (3ml) was stirred at room temperature for 16h then evaporated under reduced pressure. The residue was stirred with EtOAc and aqueous potassium carbonate. The organic phase was washed with water, then brine, dried (K₂CO₃) and evaporated. Chromatography (silica, CH₂Cl₂/MeOH/NH₃) gave the title compound (0.0644g, 86%). ¹H NMR (CDCl₃) δ 1.29 (3H, t), 2.25 (6H, s), 2.91-2.96 (2H, m), 3.01-3.07 (2H, m), 3.54 (2H, s), 4.28 (2H, q), 4.94 (2H, s), 6.25 (1H, s), 6.95-7.11 (3H, m), 7.28 (1H, s), 7.32 (1H, d), 8.38 (1H, d); MS (APCI+) found (M+1) = 429; C₂₄H₂₅F₂N₂O₃ requires 428.

Intermediate A131 — Ethyl (7-(diethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate.



- To a mixture of intermediate A120 (0.2g, 0.5mmol), acetic acid (0.03ml) and diethylamine (0.155ml, 1.5mmol) in CH_2Cl_2 (15ml) was added sodium triacetoxyborohydride (0.212g, 1.0mmol) portionwise over 10 minutes. After stirring at room temperature for 16h, saturated sodium bicarbonate was added. The organic phase was washed with water, dried (K_2CO_3) and evaporated. Chromatography (silica, $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$) gave the title compound (0.2g, 87%). ^1H NMR (CDCl_3) δ 1.04 (6H, t), 1.29 (3H, t), 2.53 (4H, q), 2.91-2.96 (2H, m), 3.03-3.08 (2H, m), 3.68 (2H, s), 4.28 (2H, q), 4.93 (2H, s), 6.25 (1H, s), 6.96-7.11 (3H, m), 7.32 (1H, d), 7.37 (1H, s), 8.36 (1H, d); MS (APCI+) found ($M+1$) = 457; $\text{C}_{26}\text{H}_{30}\text{F}_2\text{N}_2\text{O}_3$ requires 456.

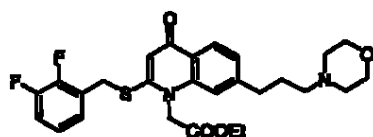
The following intermediates were prepared by the method of intermediate A131.

No.	Precursor	Structure	Name
A132	A120		Ethyl (7-(pyrrolidin-1-ylmethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
A133	A120		Ethyl (7-(piperidin-1-ylmethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
A134	A121		Ethyl (7-(2-dimethylaminoethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
A135	A121		Ethyl (7-(2-diethylaminoethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
A136	A121		Ethyl (7-(2-(pyrrolidin-1-yl)ethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
A137	A122		Ethyl (2-(2,3-difluorobenzylthio)-7-dimethylaminomethyl-4-oxo-4H-quinolin-1-yl)acetate.

15

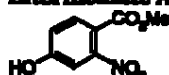
Intermediate A140 — Ethyl (2-(2,3-difluorobenzylthio)-7-(3-morpholinopropyl)-4-oxo-4H-quinolin-1-yl)acetate

36



- a) To a solution of intermediates A13 (0.4g, 0.78mmol) in DMF (20ml) was added sodium bicarbonate (0.125g, 1.5mmol), benzyltriethylammonium chloride (0.18g, 0.79mmol), palladium acetate (0.04g, 0.15mmol) and allyl alcohol (0.1ml, 1.5mmol). The mixture was stirred at 50°C for 2h. Further quantities of allyl alcohol (0.1ml) and palladium acetate (0.04g) were added, and the mixture was stirred for 2h at 50°C, then 16h at room temperature. EtOAc was added and the mixture washed with water, then brine, dried (Na_2SO_4) and evaporated to an oil (0.3g). This was dissolved in dichloromethane (25ml) and morpholine (0.2ml, 2.3mmol) and acetic acid (0.03ml) added. To this solution was added sodium triacetoxyborohydride (0.2g, 0.95mmol) portionwise over 4h. After stirring at room temperature for 16h, the reaction mixture was washed successively with saturated sodium bicarbonate, water, brine, then dried (K_2CO_3) and evaporated. Chromatography (silica, EtOAc/MeOH/ NH_3) gave the title compound (0.14g, 40%). ^1H NMR (CDCl_3) δ 1.28 (3H, t), 1.85 (2H, quintet), 2.35 (2H, t), 2.42 (4H, br t), 2.77 (2H, t), 3.72 (4H, t), 4.27 (2H, q), 4.28 (2H, s), 5.12 (2H, br s), 6.42 (1H, s), 6.98 (1H, s), 7.01-7.16 (3H, m), 7.23 (1H, d), 8.31 (1H, d); MS (APCI+) found ($M+1$) = 517; $\text{C}_{20}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_5\text{S}$ requires 516.

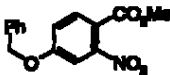
Intermediate A15 -- Methyl 4-Hydroxy-2-nitrobenzoate



- To a suspension of 4-amino-2-nitrobenzoic acid in 20% sulphuric acid (200ml) at 5-6°C in an ice-bath was added a solution of sodium nitrite (0.5g) in water (1.5ml) dropwise ensuring that the temperature remained $\leq 6^\circ\text{C}$. On completion of the addition, a brown homogeneous solution was obtained which was held at 5°C for 20min. This solution was added dropwise to 40% sulphuric acid at 130°C and held at that temperature for 30min after the addition was complete. The red solution was cooled, extracted with ethyl acetate and the combined organic layers were washed with water and brine and dried over MgSO_4 . The solvent was removed under reduced pressure to give a red brown solid (0.58g). A portion of this solid (0.10g) was mixed with methanol (5ml) containing conc. sulphuric acid (1 drop) and heated to reflux for 2 days. The solution was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with further water and brine and dried over MgSO_4 . The solvent was removed under reduced pressure and the residue chromatographed on silica gel eluting with ethyl acetate. This gave the title compound as a yellow solid (0.063g). ^1H NMR (CDCl_3) δ 3.78 (3H, m), 7.11 (1H, dd), 7.24 (1H, d), 7.78 (1H, d), 11.2 (1H, s); MS (APCI-) found ($M-1$) = 196; $\text{C}_8\text{H}_7\text{NO}_5$ requires 197.

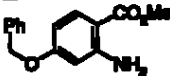
Intermediate A16 -- Methyl 4-benzyloxy-2-nitrobenzoate

3M



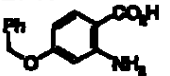
To a mixture of intermediate A15 (7.0g), triphenylphosphine (11.2g) and benzyl alcohol (3.68ml) in dry THF under argon in an ice bath was added diethylazodicarboxylate (7.42g). The dark red-brown solution so formed was stirred at room temperature overnight and the solvent removed under reduced pressure. The residue was taken up in ethyl acetate, washed with water and brine, dried over MgSO₄ and decolourising charcoal and evaporated under reduced pressure to a brown oil. This material was chromatographed on silica gel to give the title compound (6.17g). ¹H NMR (CDCl₃) δ 3.87 (3H, m), 5.15 (2H, s), 7.16 (1H, dd), 7.33 (1H, d), 7.3-7.5 (5H, m), 7.77 (1H, d).

Intermediate A17 ~ Methyl 2-amino-4-benzoyloxybenzoate



To a mixture of intermediate A16 (6.16g) and iron powder (17.96g) in 10% aqueous ethanol (200ml) was added concentrated hydrochloric acid (1ml) and the mixture refluxed for 2h and cooled to room temperature. The mixture was filtered through kieselguhr and the filtrate evaporated under reduced pressure to a black solid. This material was chromatographed on silica using dichloromethane as eluent to give the title compound as a pale yellow solid (2.81g). ¹H NMR (CDCl₃) δ 3.83 (3H, m), 5.05 (2H, s), 5.76 (2H, br s), 6.18 (1H, d), 6.31 (1H, dd), 7.25-7.5 (5H, m), 7.79 (1H, d).

Intermediate A18 ~ 2-Amino-4-benzoyloxybenzoic acid



To a solution of intermediate A17 (2.8g) in methanol (30ml) was added sodium hydroxide (1.3g) in water (30ml) and the mixture was heated to reflux for 5h. The mixture was concentrated and diluted with water then acidified with 5M hydrochloric acid. The mixture was stirred for 15min, the solid filtered off and dried to give the title compound (2.4g). ¹H NMR (d₆-DMSO) δ 5.06 (2H, s), 6.18 (1H, dd), 6.32 (1H, d), 7.2-7.5 (5H, m), 7.62 (1H, d).

The following intermediates were prepared by the method of intermediate A5.

No.	Precursor	Structure	Name
A21	4-Nitroanthranilic acid		7-Nitro-1 <i>H</i> -benzo[d][1,3] oxazine-2,4-dione
A22	Int. 18		7-Benzoyloxy-1 <i>H</i> -benzo[d][1,3] oxazine-2,4-dione

36

The following intermediates were prepared by the method of intermediate A6.

No.	Precursor	Structure	Name
A31	Int. A21		Ethyl (7-nitro-2,4-dioxo-4 H-benzo[d][1,3]oxazin-1-yl) acetate
A32	Int. A22		Ethyl (7-benzyloxy-2,4-dioxo-4 H-benzo[d][1,3]oxazin-1-yl) acetate

5 The following intermediates were prepared by the method of intermediate A8.

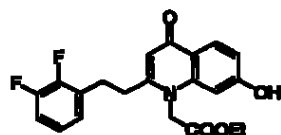
No.	Precursor	Structure	Name
A41	Int. A31		tert-butyl (7-Nitro-2-(2-(2,3-difluorophenyl)ethyl)-1-ethoxycarbonyl-4-oxo 4-H quinolin-1-yl)-3-carboxylate.
A42	Int. A32		tert-butyl (7-Benzyloxy-2-(2-(2,3-difluorophenyl)ethyl)-1-ethoxycarbonyl-4-oxo 4-H quinolin-1-yl)-3-carboxylate.

The following intermediate was prepared by the method of intermediate A9.

No.	Precursor	Structure	Name
A51	Int. A41		Ethyl (7-nitro-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4 H-quinolin-1-yl) acetate
A52	Int. A42		Ethyl (7-benzyloxy-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4 H-quinolin-1-yl) acetate

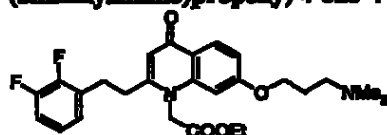
10

Intermediate A61 – Ethyl (2-(2-(2,3-difluorophenyl)ethyl)-7-hydroxy-4-oxo-4 H-quinolin-1-yl) acetate



- To a solution of intermediate A52 (0.235g) in dimethylformamide (DMF) (5ml) was added 10% Pd/C containing 55% water (0.23g) and the mixture hydrogenated at room temperature and pressure for 0.5h. The mixture was filtered through kieselguhr and the kieselguhr washed with further DMF. The filtrate was evaporated under reduced pressure to give the title compound as a pale yellow solid (0.192g). ¹H NMR (d₆-DMSO) δ 1.22 (3H, t), 2.98 (4H, br s), 4.21 (2H, q), 5.09 (2H, br s), 5.89 (1H, d), 6.70 (1H, d), 6.83 (1H, m), 7.05-7.4 (3H, m), 7.98 (1H, d), 10.35 (1H, s).

- 10 Intermediate A71 - Ethyl (2-(2-(2,3-difluorophenyl)ethyl)-7-(3-(dimethylamino)propoxy)-4-oxo-4H-quinolin-1-yl) acetate



- To a solution of intermediate A61 (0.25g) in dry dimethylformamide (4ml) at room temperature under argon was added triphenylphosphine (0.508g) and 3-dimethylaminopropan-1-ol (0.1g) in dry DMF (2ml). Diethylazodicarboxylate (0.337g) in dry DMF (2ml) was added over 15min. The dark orange/red mixture was held at room temperature for 21h and evaporated under reduced pressure. The residue was partitioned between dichloromethane and water. The aqueous layer was extracted with further dichloromethane and the combined organic extracts washed with water and brine and dried over MgSO₄. Evaporation under reduced pressure and chromatography on silica gel using dichloromethane:methanol as eluent gave a gum that was triturated with diethyl ether and hexane (1:1) to give the title compound as an orange solid (0.179g). ¹H NMR (CDCl₃) δ 1.29 (3H, t), 2.00 (2H, dt), 2.28 (6H, m), 2.48 (2H, t), 2.85-3.15 (4H, m), 4.11 (2H, t), 4.29 (2H, q), 4.85 (2H, s), 6.21 (1H, s), 6.64 (1H, d), 6.9-7.2 (4H, m), 8.35 (1H, d); MS (APCI+) found (M+1) = 473; C₂₈H₃₀F₂N₂O₄ requires 472.

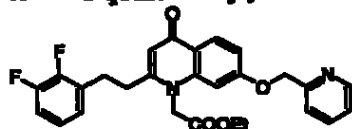
The following intermediates were prepared by the method of intermediate A71 from intermediate A61.

No.	Structure	Name
A72		Ethyl (2-(2-(2,3-difluorophenyl)ethyl)-7-(2-(dimethylamino)ethoxy)-4-oxo-4H-quinolin-1-yl) acetate

40

A73		Ethyl 7-(2-(2-diethylaminoethoxy)-2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl acetate
A74		Ethyl 2-(2-(2,3-difluorophenyl)ethyl)-7-(2-(piperidin-1-yl)ethoxy)-4-oxo-4H-quinolin-1-yl acetate
A75		Ethyl 2-(2-(2,3-difluorophenyl)ethyl)-7-(3-(piperidin-1-yl)propoxy)-4-oxo-4H-quinolin-1-yl acetate
A76		tert. Butyl 2-(2-(2-(2,3-difluorophenyl)-ethyl))-1-(ethoxycarbonylmethyl)-4-oxo-4H-quinolin-7-yloxy)acetate

Intermediate A85 - Ethyl 2-(2-(2,3-difluorophenyl)ethyl)-7-(pyridin-2-ylmethoxy)-4-oxo-4H-quinolin-1-yl acetate

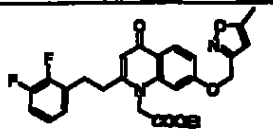
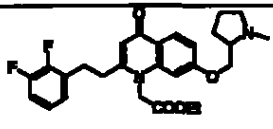


- 5 To a suspension of intermediate A61 (0.2g) in dry DMF (4ml) under argon was added sodium hydride (0.025g) at room temperature to form a brown solution. The mixture was stirred at room temperature for 15min and 2-(bromomethyl)pyridine hydrobromide (0.157g) added. After stirring at room temperature for 1.5h, the mixture was evaporated under reduced pressure and partitioned between dichloromethane and dilute brine. The aqueous layer was extracted with further dichloromethane and the combined organic extracts washed with water and brine and dried over $MgSO_4$. Evaporation under reduced pressure followed by trituration (1:1 diethyl ether-hexane) of the residue so formed gave the title compound as a yellow solid (0.186g). ^1H NMR ($CDCl_3$) δ 1.29 (3H, t), 2.8-3.0 (2H, m), 3.0-3.1 (2H, m), 4.26 (2H, q), 4.82 (2H, br s), 5.29 (2H, s), 6.21 (1H, s), 6.78 (1H, d), 6.9-7.15 (4H, m), 7.27 (1H, m), 7.51 (1H, d), 7.74 (1H, dt), 8.37 (1H, d), 8.63 (1H, m); MS (APCI+) found $(M+1) = 749$; $C_{27}H_{26}F_2N_2O_4$ requires 748.
- 10
- 15

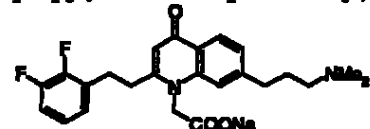
The following intermediates were prepared by the method of intermediate A85.

No.	Precursor	Structure	Name
-----	-----------	-----------	------

41

A86	Int. A61		Ethyl (2-(2-(2,3-difluorophenyl)-ethyl)-7-(5-methyloxazol-3-yl-methoxy)-4-oxo-4 H-quinolin-1-yl) acetate
A87	Int. A61 4-bromomethyl piperidine.HBr		Ethyl (2-(2-(2,3-difluorophenyl)-ethyl)-7-(1-methylpiperidin-2-yl-methoxy)-4-oxo-4 H-quinolin-1-yl) acetate

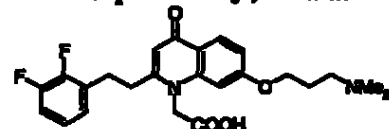
Intermediate B1 — Sodium (2-(2-(2,3-difluorophenyl)ethyl)-7-(3-dimethylamino-propyl)-4-oxo-4 H-quinolin-1-yl)acetate.



- 5 A solution of intermediate A11 (0.29g, 0.64mmol) and sodium hydroxide (0.03g, 0.7mmol) in dioxan (8ml) and water (3ml) was stirred at room temperature for 3h. The solvent was evaporated to give the title compound (0.3g, 100%). ¹H NMR (d₆-DMSO) δ 1.74 (2H, m), 2.13 (6H, s), 2.20 (2H, t), 2.69 (2H, t), 2.96 (2H, m), 3.05 (2H, m), 4.50 (2H, s), 5.87 (1H, s), 7.10-7.35 (5H, m), 8.03 (1H, d).

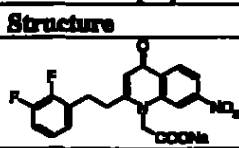
10

Intermediate B2 - (2-(2-(2,3-difluorophenyl)ethyl)-7-(3-(dimethylamino)propoxy)-4-oxo-4 H-quinolin-1-yl)acetic acid hydrochloride



- 15 To a stirred solution of intermediate A71 (0.161g) in methanol (5ml) was added 0.5M sodium hydroxide (1.37ml). After 3h, the mixture was evaporated under reduced pressure, water added and the solution acidified (2M hydrochloric acid) to pH 1 and the precipitate so formed centrifuged to give the title compound (0.137g). ¹H NMR (d₆-DMSO) δ 2.1-2.3 (2H, br), 2.79 (6H, s), 3.03 (4H, br s), 3.15-3.3 (2H, br), 4.1-4.3 (2H, br), 5.20 (2H, br s), 6.08 (1H, br s), 6.9-7.4 (5H, m), 8.11 (1H, d); MS (APCI-) found (M-1) = 443; C₂₄H₂₆F₂N₂O₄ requires 444.
- 20

The following intermediate was prepared by the method of Intermediate B1.

No.	Precursor	Structure	Name
B3	Int. A51		Sodium (7-nitro-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4 H-quinolin-1-yl) acetate

B20	Int. A130		Sodium (7-(dimethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
B21	Int. A131		Sodium (7-(diethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
B22	Int. A132		Sodium (7-((pyrrolidin-1-yl)methyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
B23	Int. A133		Sodium (7-((piperidin-1-yl)methyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
B24	Int. A134		Sodium (7-(2-dimethylaminoethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
B25	Int. A135		Sodium (7-(2-diethylaminoethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
B26	Int. A136		Sodium (7-(2-(pyrrolidin-1-yl)ethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
B27	Int. A100		Sodium (7-(3-diethylaminopropyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
B28	Int. A101		Sodium (7-(3-(pyrrolidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
B29	Int. A102		Sodium (7-(3-(piperidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate
B30	Int. A137		Sodium (7-(diethylaminomethyl)-2-(2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl)acetate
B31	Int. A140		Sodium (7-(3-(4-morpholino)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetate

43

The following intermediates were prepared by the method of intermediate B2.

No.	Precursor	Structure	Name
B10	Int. A72		(2-(2-(2,3-Difluorophenyl)ethyl)-7-(2-dimethylaminoethoxy)-4-oxo-4H-quinolin-1-yl)acetic acid
B11	Int. A73		(7-(2-Diethylaminoethoxy)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetic acid
B12	Int. A74		(2-(2-(2,3-Difluorophenyl)ethyl)-7-(2-(piperidin-1-yl)ethoxy)-4-oxo-4H-quinolin-1-yl)acetic acid
B13	Int. A75		(2-(2-(2,3-Difluorophenyl)ethyl)-7-(3-(piperidin-1-yl)propoxy)-4-oxo-4H-quinolin-1-yl)acetic acid
B14	Int. A76		(7-(tert. Butoxycarbonylmethoxy)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetic acid
B15	Int. A85		(2-(2-(2,3-Difluorophenyl)ethyl)-7-(pyridin-2-ylmethoxy)-4-oxo-4H-quinolin-1-yl)acetic acid
B16	Int. A86		(2-(2-(2,3-Difluorophenyl)ethyl)-7-(5-methylisoxazol-3-ylmethoxy)-4-oxo-4H-quinolin-1-yl)acetic acid
B17	Int. A87		(2-(2-(2,3-Difluorophenyl)ethyl)-7-(1-methylpyrrolidin-2-ylmethoxy)-4-oxo-4H-quinolin-1-yl)acetic acid
B18	Int. A52		(7-Benzoyloxy-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)acetic acid

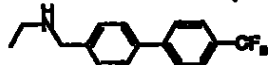
The following amines are known in the literature.

5

No.	Reference	Structure	Name
C1	WO00/66567		4-(4-Trifluoromethylphenyl)-N-methylbenzylamine

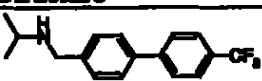
C2	WO01/60805		<i>N</i> -(1-Ethyl-piperidin-4-yl)-4-(4-trifluoromethyl-phenyl)benzylamine
----	------------	---	--

Intermediate C3 - 4-(4-Trifluoromethylphenyl)-*N*-ethylbenzylamine

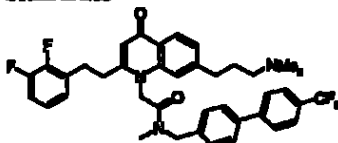


- To a solution of 4-(4-trifluoromethylphenyl)benzaldehyde (5.0g, 20mmol) in CH_2Cl_2 (100ml) was added a solution of ethylamine in THF (2M, 20ml, 40mmol). 4Å molecular sieves (15g) were added and the mixture stirred gently for 16h. The mixture was filtered through celite and the filtrate evaporated. The residue was dissolved in ethanol (200ml), and sodium borohydride (1.13g, 30mmol) was added portionwise over 10 minutes. The mixture was stirred at room temperature for 1h, then concentrated. CH_2Cl_2 and water were added, the organic phase was washed with water, dried (K_2CO_3) and evaporated to give the title compound as a white solid. (4.9g, 88%). ^1H NMR (CDCl_3) δ 1.16 (3H, t), 2.72 (2H, q), 3.85 (2H, s), 7.43 (2H, d), 7.56 (2H, d), 7.68 (4H, s); MS (APCI+) found ($M+1$) = 280; $\text{C}_{16}\text{H}_{16}\text{F}_3\text{N}$ requires 279.

- The following intermediate was prepared by the method of intermediate C3.

No.	Structure	Name
C4		4-(4-Trifluoromethylphenyl)- <i>N</i> -isopropylbenzylamine

Example 1 — *N*-Methyl-2-(2-(2-(2,3-difluorophenyl)ethyl)-7-(3-dimethylamino-prop-1-yl)-4-oxo-4H-quinolin-1-yl)-*N*-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate

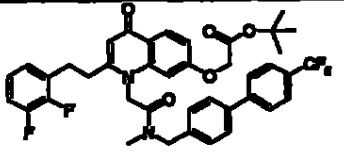
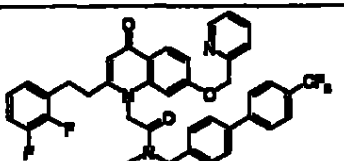
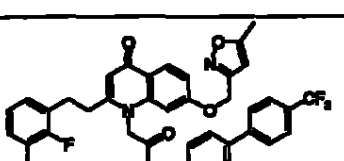
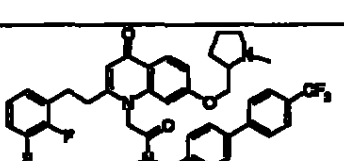
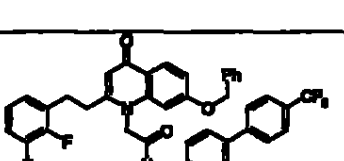
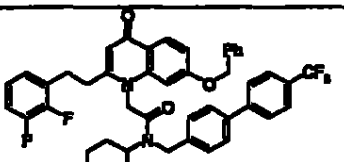
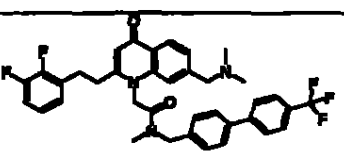


- O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (0.187g, 0.6mmol) was added to a mixture of intermediate B1 (0.195g, 0.43mmol), amine C1 (0.115g, 0.43mmol) and diisopropylethylamine (0.18ml, 1.04mmol) in dimethylformamide (10ml) and the resultant solution stirred for 2h. The solvent was evaporated and the residue diluted with dichloromethane (30ml) and washed successively with saturated ammonium chloride and saturated sodium bicarbonate. The organic layer was dried (K_2CO_3) and the solvent evaporated. The residue was purified by flash chromatography (NH_3 / MeOH / CH_2Cl_2). The amine (0.18g, 0.267mmol) was dissolved in methanol (10ml) and tartaric acid (0.04g, 0.267mmol) added. After stirring for 15min the solvent was evaporated and the residue triturated from diethyl ether to afford the title compound (0.215g). ^1H NMR (d_6 -DMSO) δ 1.81 (2H, m), 2.19 (6H, 2x s), 2.27 (2H, m), 2.65 (6H, m), 3.2 (3H, 2x s), 4.12 (2H s), 4.63, 4.81 (2H, 2x s), 5.29, 5.39 (2H, 2x br s).

5.99 (1H, 2x s), 7.03-7.88 (13H, m), 8.07 (1H, 2x d); MS (APCI+) found (M+1) = 676; C₃₉H₂₈F₉N₃O₂ requires 675.

The following examples were prepared by the method of example 1 using either the
 5 parent acid or its sodium salt.

Ex.	Precursors	Structure	Name
2	Int. B2 Amine C1		2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(3-(dimethylamino)propoxy)-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
3	Int. B3 Amine C1		N-Methyl-2-(2-(2-(2,3-difluorophenyl)ethyl)-7-nitro-4-oxo-4H-quinolin-1-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide
4	Int. B10 Amine C1		2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-(2-dimethylaminoethoxy)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
5	Int. B11 Amine C1		2-(7-(2-Diethylaminoethoxy)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
6	Int. B12 Amine C1		2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(2-(piperidin-1-yl)ethoxy)-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
7	Int. B13 Amine C1		2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(3-(piperidin-1-yl)propoxy)-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate

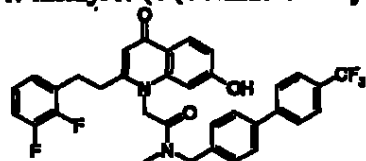
8	Int. B14 Amine C1		<i>tert.</i> Butyl 2-(2-(2-(2,3-difluorophenyl)ethyl))-1-(N-(4-(4-trifluoromethylphenyl)benzyl)-N-methyl-aminocarbonylmethyl)-4-oxo-4H-quinolin-7-yl)oxy)acetate
9	Int. B15 Amine C1		2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(pyridin-2-ylmethoxy)-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide hydrochloride
10	Int. B16 Amine C1		2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-(5-methylisoxazol-3-ylmethoxy)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide
11	Int. B17 Amine C1		2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-(1-methylpyrrolidin-2-ylmethoxy)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
12	Int. B18 Amine C1		2-(7-Benzyloxy-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide
13	Int. B18 Amine C2		2-(7-Benzyloxy-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4-quinolin-1-yl)-N-(1-ethylpiperidin-4-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
20	Int. B20 Amine C1		2-(7-(Dimethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate

42

21	Int. B21 Amine C1		2-(7-(Diethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
22	Int. B21 Amine C3		2-(7-(Diethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
23	Int. B21 Amine C4		2-(7-(Diethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-isopropyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
24	Int. B22 Amine C3		2-(7-((Pyrrolidin-1-yl)methyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
25	Int. B23 Amine C3		2-(7-((Piperidin-1-yl)methyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
26	Int. B24 Amine C1		2-(7-(2-Dimethylaminoethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
27	Int. B25 Amine C1		2-(7-(2-Diethylaminoethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate

28	Int. B26 Amine C1		2-(7-(2-(Pyrrolidin-1-yl)ethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
29	Int. B27 Amine C1		2-(7-(3-Diethylaminopropyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
30	Int. B28 Amine C1		2-(7-(3-(Pyrrolidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
31	Int. B29 Amine C3		2-(7-(3-(Piperidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
32	Int. B29 Amine C4		2-(7-(3-(Piperidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-isopropyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
33	Int. B30 Amine C1		2-(7-(Diethylaminomethyl)-2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate
34	Int. B31 Amine C1		2-(7-(3-(4-Morpholino)propyl)-2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide hydrochloride

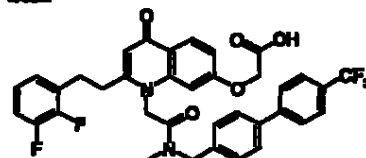
Example 15 - 2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-hydroxy-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide



- 5 To a solution of example 12 (0.382g) in dimethylformamide (DMF) (30ml) was added 10% Pd/C (paste containing 54% water) and the mixture hydrogenated at room temperature for 2.5h. The mixture was diluted with further DMF (70ml), warmed to dissolve any precipitated product and filtered through Celite and a small plug of fine silica gel. The solvent was removed under reduced pressure and the residue triturated with diethyl ether and dried to give the title compound (0.242g). ¹H NMR (d₆-DMSO) δ 2.75-3.1 (4H, m), 3.21 + 3.31 (3H, 2x s), 4.6 + 4.87 (2H, 2xbr s), 5.18 + 5.26 (2H, 2xbr s), 5.89 + 5.91 (1H, 2xs), 6.55-6.9 (2H, m), 7.05-7.5 (5H, m), 7.55-7.75 (2H, m), 7.75-7.90 (4H, m), 7.9-8.05 (1H,m), 10.23 + 10.28 (1H, 2xs).
- 10
- 15 The following example was prepared by the method of Example 15 but using ethanol as solvent.

Ex.	Precursor	Structure	Name
16	Ex. 13		2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-hydroxy-4-oxo-4H-quinolin-1-yl)-N-(1-ethylpiperidin-4-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate

Example 17 - 2-(2-(2-(2,3-Difluorophenyl)ethyl)-1-(N-(4-(4-trifluoromethylphenyl)benzyl)-N-methyl-aminocarbonylmethyl)-4-oxo-4H-quinolin-7-yloxy)acetic acid



- 20 To a solution of example 8 (0.135g) in dichloromethane (3ml) was added trifluoroacetic acid (0.5ml) and the solution stirred for 66h at room temperature. The solvent was removed under reduced pressure and the residue triturated with diethyl ether to give the title compound (0.115g). ¹H NMR (d₆-DMSO) δ 2.8-3.1 + 3.22 (7H, m + s), 4.63 + 4.75-5.0 (4H, br s + m), 5.2-5.5 (2H, m), 6.01 + 6.04 (1H 2xs), 6.8-7.6 (7H, 2x s), 7.55-7.95
- 25

50

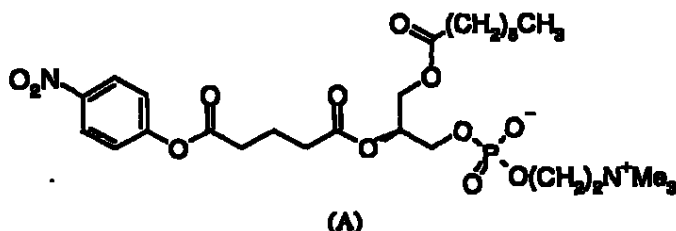
WO 03/042179

PCT/EP02/12505

(6H, m), 8.05-8.2 (1H, m); MS (APCI-) found (M-1) = 663 (weak); $C_{26}H_{29}F_3N_3O_3$ requires 664.

Biological Data**1. Screen for Lp-PLA₂ inhibition.**

- 5 Enzyme activity was determined by measuring the rate of turnover of the artificial substrate (A) at 37 °C in 50mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid) buffer containing 150mM NaCl, pH 7.4.



10

Assays were performed in 96 well titre plates.

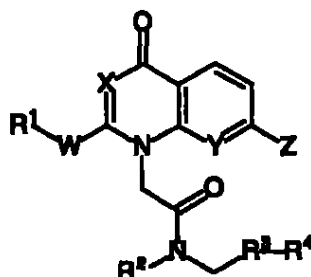
- Recombinant Lp-PLA₂ was purified to homogeneity from baculovirus infected Sf9 cells, using a zinc chelating column, blue sepharose affinity chromatography and an anion exchange column. Following purification and ultrafiltration, the enzyme was stored at 6mg/ml at 4 °C. Assay plates of compound or vehicle plus buffer were set up using automated robotics to a volume of 170µl. The reaction was initiated by the addition of 20µl of 10x substrate (A) to give a final substrate concentration of 20µM and 10 µl of diluted enzyme to an approximate final 0.1nM Lp-PLA₂.
- 20 The reaction was followed at 405 nm and 37 °C for 20 minutes using a plate reader with automatic mixing. The rate of reaction was measured as the rate of change of absorbance.

Results

- 25 The compounds described in the Examples were tested as described above and had IC₅₀ values in the range <0.1 to 100 nM.

Claims

1. A compound of formula (I):



5

(I)

in which:

R^1 is an aryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxy, $C_{(1-6)}$ alkylthio, hydroxy, halogen, CN, mono to perfluoro- $C_{(1-4)}$ alkyl, mono to perfluoro- $C_{(1-4)}$ alkoxyaryl, and aryl- $C_{(1-4)}$ alkyl;

R^2 is hydrogen, $C_{(1-6)}$ alkyl which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR^5 , COR^5 , carboxy, $COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , mono- or di-(hydroxy- $C_{(1-6)}$ alkyl)amino and N-hydroxy- $C_{(1-6)}$ alkyl-N- $C_{(1-6)}$ alkylamino; or

R^2 is Het- $C_{(0-4)}$ alkyl in which Het is a 5- to 7- membered heterocycliyl ring comprising N and optionally O or S, and in which N may be substituted by COR^5 , $COOR^5$, $CONR^7R^8$, or $C_{(1-6)}$ alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR^5 , COR^5 , carboxy, $COOR^5$, $CONR^7R^8$ or NR^7R^8 , for instance, piperidin-4-yl, pyrrolidin-3-yl;

R^3 is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxy, $C_{(1-6)}$ alkylthio, aryl- $C_{(1-6)}$ alkoxy, hydroxy, halogen, CN, COR^5 , carboxy, $COOR^5$, NR^5COR^6 , $CONR^7R^8$, $SO_2NR^7R^8$, $NR^5SO_2R^6$, NR^7R^8 , mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy;

R^4 is an aryl or a heteroaryl ring which is further optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxy, $C_{(1-6)}$ alkylthio, $C_{(1-6)}$ alkylsulfonyl, aryl- $C_{(1-6)}$ alkoxy, hydroxy, halogen, CN, COR^5 , carboxy, $COOR^5$, $CONR^7R^8$, NR^5COR^6 , $SO_2NR^7R^8$, $NR^5SO_2R^6$, NR^7R^8 , mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy, or $C_{(5-10)}$ alkyl;

W is a $C_{(2-4)}$ alkylene group, optionally substituted by 1, 2 or 3 substituents selected from methyl and ethyl, $CH=CH$, $(CH_2)_nS$ or $(CH_2)_nO$ where n is 1, 2 or 3;

X and Y are independently CH or N;

Z is NO_2 , NR^5R^9 , OR^9 , SR^9 , SOR^9 , SO_2R^9 or R^{10} ;

R^5 and R^6 are independently hydrogen or $C_{(1-12)}$ alkyl, for instance $C_{(1-4)}$ alkyl (e.g. methyl, ethyl or t-butyl);

R^7 and R^8 which may be the same or different is each selected from hydrogen, or $C(1-12)$ alkyl, or R^7 and R^8 together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and optionally substituted by one or two substituents selected from hydroxy, oxo, $C(1-4)$ alkyl, $C(1-4)$ alkylcarboxy, aryl, e.g. phenyl, or aralkyl, e.g. benzyl, for instance morpholine or piperazine;

R^9 is hydrogen or $C(1-6)$ alkyl optionally substituted by 1, 2 or 3 substituents which may be the same or different selected from hydroxy, halogen, OR^5 , COR^5 , $COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , aryl, heteroaryl and a 5- to 7-membered heterocyclyl ring, which aryl or heteroaryl is optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C(1-6)$ alkyl, $C(1-6)$ alkoxy, $C(1-6)$ alkylthio, aryl $C(1-6)$ alkoxy, hydroxy, halogen, CN, COR^5 , $COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , $SO_2NR^7R^8$, $NR^5SO_2R^6$, mono to perfluoro $C(1-4)$ alkyl and mono to perfluoro $C(1-4)$ alkoxy, and which 5- to 7-membered heterocyclyl ring is optionally substituted by COR^5 , $COOR^5$, $CONR^7R^8$, or $C(1-6)$ alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR^5 , COR^5 , carboxy, $COOR^5$, $CONR^7R^8$ or NR^7R^8 , for instance, piperidin-4-yl, pyrrolidin-3-yl; and

R^{10} is $C(1-6)$ alkyl optionally substituted by 1, 2 or 3 substituents which may be the same or different selected from hydroxy, halogen, OR^5 , COR^5 , $COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , aryl, heteroaryl and a 5- to 7-membered heterocyclyl ring, which aryl or heteroaryl is optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C(1-6)$ alkyl, $C(1-6)$ alkoxy, $C(1-6)$ alkylthio, aryl $C(1-6)$ alkoxy, hydroxy, halogen, CN, COR^5 , $COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , $SO_2NR^7R^8$, $NR^5SO_2R^6$, mono to perfluoro $C(1-4)$ alkyl and mono to perfluoro $C(1-4)$ alkoxy, and which 5- to 7-membered heterocyclyl ring is optionally substituted by COR^5 , $COOR^5$, $CONR^7R^8$, or $C(1-6)$ alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR^5 , COR^5 , carboxy, $COOR^5$, $CONR^7R^8$ or NR^7R^8 , for instance, piperidin-4-yl, pyrrolidin-3-yl; or

R^{10} is a 5- to 7-membered heterocyclic ring optionally substituted by COR^5 , $COOR^5$, $CONR^7R^8$, or $C(1-6)$ alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxy, halogen, OR^5 , COR^5 , carboxy, $COOR^5$, $CONR^7R^8$ or NR^7R^8 , for instance, piperidin-4-yl, pyrrolidin-3-yl; and pharmaceutically acceptable salts thereof

with the provisos that Z is not amino and that the compound of formula (I) is not:
 N -(2-diethylaminoethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-7-trifluoromethyl-4-oxo-4H-quinazolin-1-yl]- N -(4'-trifluoromethyl-biphenyl-4-ylmethyl)acetamide;
 N -(2-diethylaminoethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-7-methyl-4-oxo-4H-quinazolin-1-yl]- N -(4'-trifluoromethyl-biphenyl-4-ylmethyl)acetamide;
 N -(1-ethylpiperidin-4-yl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-7-methyl-4-oxo-4H-[1,8]naphthyridin-1-yl]- N -(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide;
 N -(2-diethylaminoethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-7-methyl-4-oxo-4H-[1,8]naphthyridin-1-yl]- N -(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide;

SA

N-(1-methylpiperidin-4-yl)-2-[2-(2,3-difluorophenyl)ethyl]-7-methyl-4-oxo-4*H*-[1,8]naphthyridin-1-yl]-*N*-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide;
N-(1-isopropylpiperidin-4-yl)-2-[2-(2,3-difluorophenyl)ethyl]-7-methyl-4-oxo-4*H*-[1,8]naphthyridin-1-yl]-*N*-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide; or
 5 *N*-(1-(2-methoxyethyl)piperidin-4-yl)-2-[2-(2,3-difluorophenyl)ethyl]-7-methyl-4-oxo-4*H*-[1,8]naphthyridin-1-yl]-*N*-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide.

2. A compound according to claim 1 wherein R^1 is phenyl optionally substituted by halogen, C_{1-6} alkyl, trifluoromethyl or C_{1-6} alkoxy.

10 3. A compound according to claim 1 or claim 2 wherein R^2 is hydrogen, methyl, ethyl, isopropyl, 2-(diethylamino)ethyl, 2-(piperidin-1-yl)ethyl, 2-(pyrrolidin-1-yl)ethyl, 1-(2-methoxyethyl)piperidin-4-yl, 1-methylpiperidin-4-yl, 1-ethyl-piperidin-4-yl or 1-ethyl-pyrrolidin-2-ylmethyl.

15 4. A compound according to any of claims 1 to 3 wherein R^3 is phenyl.

5. A compound according to any of claims 1 to 4 wherein R^4 is phenyl optionally substituted by halogen, trifluoromethyl or ethyl.

20 6. A compound according to any of claims 1 to 5 wherein W is $(CH_2)_nS$ or CH_2 -alkylene.

7. A compound according to any of claims 1 to 6 wherein Z is NO_2 , OR^5 or R^{10} .

25 8. A compound according to claim 7 wherein Z is hydroxy, nitro, mono or di-*N*- C_{1-6} alkylamino C_{1-6} alkyl, mono or di-*N*- C_{1-6} alkylamino C_{1-6} alkoxy, carboxy C_{1-6} alkoxy or an ester thereof, or aryl C_{1-6} alkoxy, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkoxy, heteroaryl C_{1-6} alkyl, 5- to 7-membered heterocyclyl C_{1-6} alkoxy optionally substituted by C_{1-6} alkyl, or 5- to 7-membered heterocyclyl C_{1-6} alkyl optionally substituted by C_{1-6} alkyl.

9. A compound according to claim 7 or claim 8 wherein when Z includes an aryl, heteroaryl or heterocyclyl ring, said ring is selected from benzyl, pyridinyl, isoxazolyl, piperidinyl, pyrrolidinyl and morpholino.

10. *N*-Methyl-2-(2-(2,3-difluorophenyl)ethyl)-7-(3-dimethylaminoprop-1-yl)-4-oxo-4*H*-quinolin-1-yl)-*N*-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(3-(dimethylamino)propoxy)-4*H*-quinolin-1-yl)-*N*-methyl-*N*-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 40 *N*-Methyl-2-(2-(2,3-difluorophenyl)ethyl)-7-nitro-4-oxo-4*H*-quinolin-1-yl)-*N*-(4-(4-trifluoromethylphenyl)benzyl)acetamide;
 2-(2-(2,3-Difluorophenyl)ethyl)-7-(2-dimethylaminoethoxy)-4-oxo-4*H*-quinolin-1-yl)-*N*-methyl-*N*-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;

55

- 2-(7-(2-Diethylaminoethoxy)-2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(2-(piperidin-1-yl)ethoxy)-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 5 2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(3-(piperidin-1-yl)propoxy)-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 tert. Butyl 2-(2-(2-(2,3-difluorophenyl)ethyl))-1-(N-(4-(4-trifluoromethylphenyl)benzyl)-N-methyl-aminocarbonylmethyl)-4-oxo-4H-quinolin-7-yloxy)acetate;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-7-(pyridin-2-ylmethoxy)-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide hydrochloride;
 10 2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-(5-methylisoxazol-3-ylmethoxy)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-(1-methylpyrrolidin-2-ylmethoxy)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 15 2-(7-Benzyl-oxy-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide;
 2-(7-Benzyl-oxy-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4-quinolin-1-yl)-N-(1-ethyl-piperidin-4-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(2-(2-(2,3-Difluorophenyl)ethyl)-7-hydroxy-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide;
 20 2-(2-(2-(2,3-Difluoro-phenyl)-ethyl)-7-hydroxy-4-oxo-4H-quinolin-1-yl)-N-(1-ethyl-piperidin-4-yl)-N-(4-(4-trifluoro-methyl-phenyl)benzyl)-acetamide bitartrate;
 2-(2-(2-(2,3-Difluorophenyl)ethyl))-1-(N-(4-(4-trifluoromethylphenyl)benzyl)-N-methyl-aminocarbonylmethyl)-4-oxo-4H-quinolin-7-yloxy)acetic acid
 25 2-(7-(Dimethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(Diethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(Diethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 30 2-(7-(Diethylaminomethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-isopropyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(Pyrrolidin-1-yl)methyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 35 2-(7-(Piperidin-1-yl)methyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(2-Dimethylaminoethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(2-Diethylaminoethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 40 2-(7-(2-(Pyrrolidin-1-yl)ethyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 2-(7-(3-Diethylaminopropyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
 45 2-(7-(3-(Pyrrolidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;

2-(7-(3-(Piperidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-
N-ethyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
2-(7-(3-(Piperidin-1-yl)propyl)-2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl)-
N-isopropyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate;
5 2-(7-(Diethylaminomethyl)-2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl)-N-
methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide bitartrate; and
2-(7-(3-(4-Morpholino)propyl)-2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl)-N-
methyl-N-(4-(4-trifluoromethylphenyl)benzyl)acetamide hydrochloride.

10

11. A pharmaceutical composition comprising a compound of formula (I) as claimed
in any of claims 1 to 10 and a pharmaceutically acceptable carrier.

15

12. A compound of formula (I) as claimed in any of claims 1 to 10 for use in therapy.

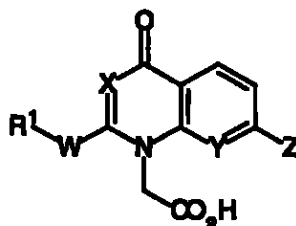
13. The use of a compound of formula (I) as claimed in any of claims 1 to 10 for the
manufacture of a medicament for treating atherosclerosis.

20

14. A method of treating a disease state associated with activity of the enzyme Lp-
PLA₂ which method involves treating a patient in need thereof with a therapeutically
effective amount of a compound of formula (I) as claimed in any of claims 1 to 10.

25

15. A process for preparing a compound of formula (I) as defined in claim 1 which
process comprises reacting an acid compound of formula (II):



(II)

in which W, X, Y, Z and R¹ are as hereinbefore defined,
with an amine compound of formula (III):

30



(III)

in which R², R³ and R⁴ are as hereinbefore defined; under amide forming conditions.

35

DERIVADOS HETEROCICLICOS DE GLICINAMIDA Y SU USO MEDICO

MEMORIA DESCRIPTIVA

5 La presente invención se relaciona con ciertos compuestos
novedosos, procedimientos para su preparación, intermediarios útiles en su
preparación, composiciones farmacéuticas que los contienen y su uso en
terapia, en particular en el tratamiento de la aterosclerosis.

 La WO 95/00649 (SmithKline Beecham plc) describe la enzima
10 fosfolipasa A2 Fosfolipasa Asociada con la Lipoproteína A2 (Lp-PLA₂), la
secuencia, aislamiento y purificación de la misma, ácidos nucleicos aislados
que codifican la enzima y las células hospederas recombinantes
transformadas con ADN que codifica la enzima. Los usos terapéuticos
sugeridos para los inhibidores de la enzima incluyen la aterosclerosis,
15 diabetes, artritis reumatoide, apoplejía, infarto al miocardio, lesión por
reperfusión e inflamación aguda y crónica. Una publicación posterior del
mismo grupo, describe adicionalmente esta enzima (Tew D *et al*, *Arterioscler*
Thromb Vas Biol 1996:16; 591-9), en donde ésta se refiere como LDL-PLA₂.
Una solicitud de patente posterior (WO 95/09921, Icos Corporation), y una
20 publicación relacionada en *Nature* (Tjoelker *et al*, vol 374, 6 de Abril de 1995,
549), describe la enzima PAF-AH, la cual tiene esencialmente la misma
secuencia que la Lp-PLA₂ y sugiere que ésta puede tener un potencial como

una proteína terapéutica para la regulación de los eventos inflamatorios patológicos.

Se ha mostrado que la Lp-PLA₂ es responsable de la conversión de la fosfatidilcolina a lisofosfatidilcolina, durante la conversión de la lipoproteína de baja densidad (LDL) a su forma oxidada. Se sabe que la enzima hidroliza el éster sn-2 de la fosfatidilcolina oxidada para proporcionar la lisofosfatidilcolina y un ácido graso modificado oxidativamente. Ambos productos de la acción de la Lp-PLA₂ son biológicamente activos con la lisofosfatidilcolina, en particular, tienen varias actividades proaterogénicas atribuidas a ésta que incluyen la quimiotaxis monocítica e inducción de la disfunción endotelial, ambas de las cuales facilitan la acumulación del macrófago derivado del monocito dentro de la pared arterial. Se esperaría, por lo tanto, que la inhibición de la enzima Lp-PLA₂ detendría la acumulación de estas lesiones enriquecidas con macrófagos (mediante la inhibición de la formación de lisofosfatidilcolina y los ácidos grasos libres oxidados), y son útiles en el tratamiento de la aterosclerosis.

También se piensa que el aumento del contenido de lisofosfatidilcolina de la LDL modificada oxidativamente, es el responsable de la disfunción endotelial observada en pacientes con aterosclerosis. Los inhibidores de la Lp-PLA₂, por lo tanto, podrían probar ser benéficos en el tratamiento de este fenómeno. Un inhibidor de la Lp-PLA₂, podría también encontrar utilidad en otros estados de enfermedad que exhiben disfunción

endotelial, incluyendo diabetes, hipertensión, angina pectoris y después de isquemia y perfusión.

Además, los inhibidores de la Lp-PLA₂ también pueden tener una aplicación general en cualquier trastorno que involucre monocitos, macrófagos o linfocitos activados, así como todos aquellos tipos de células que expresan la Lp-PLA₂. Los ejemplos de tales trastornos incluyen la psoriasis.

Además, los inhibidores de la Lp-PLA₂ también pueden tener una aplicación general en cualquier trastorno que involucre la oxidación lipídica en conjunto con la actividad de la Lp-PLA₂ para producir los dos productos perjudiciales, la lisofosfatidilcolina y los ácidos grasos modificados oxidativamente. Tales condiciones incluyen las condiciones de aterosclerosis, diabetes, artritis reumatoide, apoplejía, infarto al miocardio, isquemia, lesión por perfusión e inflamación aguda y crónica mencionadas anteriormente.

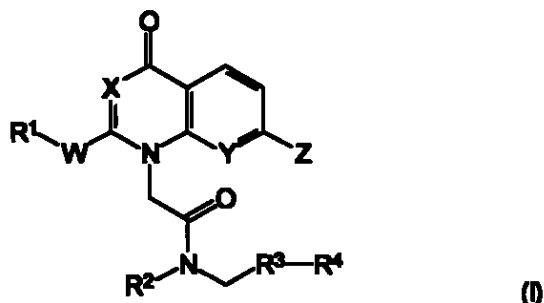
Las solicitudes de patente WO 96/12963, WO 96/13484, WO 96/19451, WO 97/02242, WO 97/217675, WO 97/217676, WO 96/41098 y WO 97/41099 (SmithKline Beecham plc), describen *inter alia*, varias series de compuestos de acetidinon 4-tionilo/sulfinilo/sulfonilo, los cuales son inhibidores de la enzima Lp-PLA₂. Estos son inhibidores acilantes, irreversibles (Tew *et al*, Biochemistry, 37, 10087, 1998).

Una clase adicional de compuestos se ha identificado ahora, los cuales son inhibidores no acilantes de la enzima Lp-PLA₂. Así, la WO 99/24420, WO 00/10980, WO 00/66566, WO 00/66567 y la WO 00/68208 (SmithKline Beecham plc), describen una clase de compuestos de pirimidona.

Hemos encontrado ahora que el anillo de pirimidona, opcionalmente reemplazado por un anillo de piridona, puede ser fusionado a un anillo benzo o pirido para proporcionar los compuestos que tienen buena actividad como inhibidores de la enzima Lp-PLA₂.

5 En consecuencia, la presente invención proporciona un compuesto de fórmula (I):

10



en la cual:

R¹ es un grupo arilo, sustituido opcionalmente por 1, 2, 3 ó 4 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de alquilo de C₍₁₋₈₎, alcoxi de C₍₁₋₈₎, alquiltio de C₍₁₋₈₎, hidroxilo, halógeno, CN, mono a perfluoroalquilo de C₍₁₋₄₎, mono a perfluoroalcoxiarilo de C₍₁₋₄₎ y arilalquilo de C₍₁₋₄₎;

R² es hidrógeno, alquilo de C₍₁₋₈₎, el cual puede estar no sustituido o sustituido por 1, 2 ó 3 sustituyentes seleccionados de hidroxilo, halógeno, OR⁵, COR⁵, carboxi, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁸, mono o di(hidroxialquil de C₍₁₋₈₎)amino y N-hidroxialquil de C₍₁₋₈₎-N-alquil de C₍₁₋₈₎amino; o

R^2 es Het-alquilo de $C_{(0-4)}$, en el cual Het es un anillo heterocíclico de 5 a 7 miembros, que comprenden N y opcionalmente O o S, y en el cual N puede estar sustituido por COR^5 , $COOR^5$, $CONR^7R^8$, o alquilo de $C_{(1-6)}$ sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de hidroxí, halógeno, OR^5 , COR^5 , carboxi, $COOR^5$, $CONR^7R^8$ o NR^7R^8 , por ejemplo, piperidin-4-ilo, pirrolidin-3-ilo;

R^3 es un arilo o un anillo de heteroarilo sustituido opcionalmente por 1, 2, 3 ó 4 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de alquilo de $C_{(1-6)}$, alcoxi de $C_{(1-6)}$, alquiltio de $C_{(1-6)}$, arilalcoxi de $C_{(1-6)}$, hidroxí, halógeno, CN, COR^5 , carboxi, $COOR^5$, NR^5COR^6 , $CONR^7R^8$, $SO_2NR^7R^8$, $NR^5SO_2R^6$, NR^7R^8 , mono a perfluoroalquilo de $C_{(1-4)}$ y mono a perfluoroalcoxi de $C_{(1-4)}$;

R^4 es un arilo o anillo de heteroarilo, el cual puede adicionalmente estar sustituido opcionalmente por 1, 2, 3 ó 4 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de alquilo de $C_{(1-6)}$, alcoxi de $C_{(1-6)}$, alquiltio de $C_{(1-6)}$, alquilsulfonilo de $C_{(1-6)}$, arilalcoxi de $C_{(1-6)}$, hidroxí, halógeno, CN, COR^5 , carboxi, $COOR^5$, $CONR^7R^8$, NR^5COR^6 , $SO_2NR^7R^8$, $NR^5SO_2R^6$, NR^7R^8 , mono a perfluoroalquilo de $C_{(1-4)}$ y mono a perfluoroalcoxi de $C_{(1-4)}$, o alquilo de $C_{(5-10)}$;

W es un grupo alquileo de $C_{(2-4)}$, sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de metilo y etilo, $CH=CH$, $(CH_2)_nS$ o $(CH_2)_nO$, en donde n es 1, 2 ó 3;

X e Y son de manera independiente CH o N;

62

Z es NO₂, NR⁵R⁹, OR⁹, SR⁹, SOR⁹, SO₂R⁹ o R¹⁰;

R⁵ y R⁶ son de manera independiente hidrógeno o alquilo de C₍₁₋₁₂₎, por ejemplo alquilo de C₍₁₋₄₎ (por ejemplo metilo, etilo o t-butilo);

R⁷ y R⁸, los cuales pueden ser los mismos o diferentes, son cada uno seleccionados de hidrógeno o alquilo de C₍₁₋₁₂₎, o R⁷ y R⁸ junto con el nitrógeno al cual están unidos, forman un anillo de 5 a 7 miembros, que opcionalmente contiene uno o más heteroátomos adicionales seleccionados de oxígeno, nitrógeno y azufre, y sustituido opcionalmente por uno o dos sustituyentes seleccionados de hidroxí, oxo, alquilo de C₍₁₋₄₎, alquilcarboxi de C₍₁₋₄₎, anilo, por ejemplo, fenilo o aralquilo, por ejemplo, bencilo, por ejemplo morfolina o piperacina;

R⁹ es hidrógeno o alquilo de C₍₁₋₈₎ sustituido opcionalmente por 1, 2 ó 3 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de hidroxí, halógeno, OR⁵, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, anilo, heteroarilo y un anillo heterocíclico de 5 a 7 miembros, anilo o heteroarilo los cuales están sustituidos opcionalmente por 1, 2, 3 ó 4 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de alquilo de C₍₁₋₈₎, alcoxi de C₍₁₋₈₎, alquiltio de C₍₁₋₈₎, arilalcoxi de C₍₁₋₈₎, hidroxí, halógeno, CN, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, SO₂NR⁷R⁸, NR⁵SO₂R⁶, mono a perfluoroalquilo de C₍₁₋₄₎ y mono a perfluoroalcoxi de C₍₁₋₄₎, y anillo heterocíclico de 5 a 7 miembros el cual está sustituido opcionalmente por COR⁵, COOR⁵, CONR⁷R⁸, o alquilo de C₍₁₋₈₎ sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de hidroxí,

halógeno, OR^5 , COR^5 , carboxi, $COOR^5$, $CONR^7R^8$ o NR^7R^8 , por ejemplo, piperidin-4-ilo, pirrolidin-3-ilo; y

R^{10} es alquilo de $C_{(1-6)}$ sustituido opcionalmente por 1, 2 ó 3 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de hidroxí, halógeno, OR^5 , COR^5 , $COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , arilo, heteroarilo y un anillo heterocíclico de 5 a 7 miembros, arilo o heteroarilo los cuales están sustituidos opcionalmente por 1, 2, 3 ó 4 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de alquilo de $C_{(1-6)}$, alcoxi de $C_{(1-6)}$, alquiltio de $C_{(1-6)}$, arilalcoxi de $C_{(1-6)}$, hidroxí, halógeno, CN, COR^5 , $COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , $SO_2NR^7R^8$, $NR^6SO_2R^6$, mono a perfluoroalquilo de $C_{(1-4)}$ y mono a perfluoroalcoxi de $C_{(1-4)}$, y anillo heterocíclico de 5 a 7 miembros el cual está sustituido opcionalmente por COR^5 , $COOR^5$, $CONR^7R^8$ o alquilo de $C_{(1-6)}$ sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de hidroxí, halógeno, OR^5 , COR^5 , carboxi, $COOR^5$, $CONR^7R^8$ o NR^7R^8 , por ejemplo, piperidin-4-ilo, pirrolidin-3-ilo; o

R^{10} es un anillo heterocíclico de 5 a 7 miembros sustituido opcionalmente por COR^5 , $COOR^5$, $CONR^7R^8$ o alquilo de $C_{(1-6)}$ sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de hidroxí, halógeno, OR^5 , COR^5 , carboxi, $COOR^5$, $CONR^7R^8$ o NR^7R^8 , por ejemplo, piperidin-4-ilo, pirrolidin-3-ilo;

con la condición de que Z no es amino, y que el compuesto de fórmula (I) no es: *N*-(2-dietilaminoetil)-2-(2-(2-(2,3-difluorofenil)-etil)-7-

trifluorometil-4-oxo-4*H*-quinazolin-1-il)-*N*-(4'-trifluorometil-bifenil-4-ilmetil)-acetamida;

N-(2-dietilaminoetil)-2-[2-(2-(2,3-difluorofenil)etil)-7-metil-4-oxo-4*H*-quinazolin-1-il)-*N*-(4'-trifluorometil-bifenil-4-ilmetil)acetamida;

5 *N*-(1-etilpiperidin-4-il)-2-[2-(2-(2,3-difluorofenil)etil)-7-metil-4-oxo-4*H*-[1,8]naftiridin-1-il]-*N*-(4'-trifluorometilbifenil-4-ilmetil)acetamida;

N-(2-dietilaminoetil)-2-[2-(2-(2,3-difluorofenil)etil)-7-metil-4-oxo-4*H*-[1,8]naftiridin-1-il]-*N*-(4'-trifluorometilbifenil-4-ilmetil)acetamida;

10 *N*-(1-metilpiperidin-4-il)-2-[2-(2-(2,3-difluorofenil)etil)-7-metil-4-oxo-4*H*-[1,8]naftiridin-1-il]-*N*-(4'-trifluorometilbifenil-4-ilmetil)acetamida;

N-(1-isopropilpiperidin-4-il)-2-[2-(2-(2,3-difluorofenil)etil)-7-metil-4-oxo-4*H*-[1,8]naftiridin-1-il]-*N*-(4'-trifluorometilbifenil-4-ilmetil)acetamida; o

N-(1-(2-metoxietil)piperidin-4-il)-2-[2-(2-(2,3-difluorofenil)etil)-7-metil-4-oxo-4*H*-[1,8]naftiridin-1-il]-*N*-(4'-trifluorometilbifenil-4-ilmetil)acetamida.

15 En un aspecto, el grupo arilo de R¹ puede ser fenilo o naftilo. De manera preferida, R¹ es fenilo sustituido opcionalmente por halógeno, alquilo de C₍₁₋₆₎, trifluorometilo, alcoxi de C₍₁₋₆₎, de manera preferida, de 1 a 3 fluoro, de manera más preferida, 2,3-difluoro.

En otro aspecto, R² puede ser hidrógeno, metilo, etilo, isopropilo, 20 2-(dietilamino)etilo, 2-(piperidin-1-il)etilo, 2-(pirrolidin-1-il)etilo, 1-(2-metoxietil)piperidin-4-ilo, 1-metilpiperidin-4-ilo, 1-etil-piperidin-4-ilo o 1-etil-pirrolidin-2-ilmetilo. De manera preferida, R² es metilo, etilo, isopropilo o 1-etil-piperidin-4-ilo, especialmente metilo o etilo.



En otro aspecto, R^3 puede ser fenilo o piridilo. De manera preferida, R^3 es fenilo.

En otro aspecto, R^4 puede ser fenilo sustituido opcionalmente por halógeno o trifluorometilo, de manera preferida en la posición 4 o etilo. De manera preferida, R^4 es fenilo sustituido por trifluorometilo en la posición 4.

De manera preferida, R^3 y R^4 juntos, forman un sustituyente 4-(fenil)fenilo o un 2-(fenil)piridinilo, en el cual el anillo de fenilo remoto puede estar sustituido opcionalmente por halógeno o trifluorometilo, de manera preferida en la posición 4.

De manera preferida, W es $(CH_2)_n-S$ o CH alquileo de $(2-4)$, por ejemplo alquileo de $C(2-3)$, de manera más preferida, W es $(CH_2)_2$ o CH_2S .

En otro aspecto, X puede ser CH.

En otro aspecto, Y puede ser CH.

En otro aspecto, Z puede ser NO_2 , OR^9 o R^{10} .

En otro aspecto, Z puede ser:

NO_2 ;

NR^5R^9 , OR^9 , SR^9 , SOR^9 o SO_2R^9 , en donde R^9 es como se definió anteriormente; o R^{10} , en donde R^{10} es alquilo de $C(2-6)$, o alquilo de $C(1-6)$ sustituido por 1, 2 ó 3 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de hidroxilo, OR^5 , COR^5 , $COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , arilo, heteroarilo y un anillo heterocíclico de 5 a 7 miembros, arilo o heteroarilo el cual está sustituido opcionalmente por 1, 2, 3 ó 4 sustituyentes los cuales pueden ser los mismos o diferentes, seleccionados de alquilo de

C₍₁₋₆₎, alcoxi de C₍₁₋₆₎, alquiltio de C₍₁₋₆₎, arilalcoxi de C₍₁₋₆₎, hidroxí, halógeno, CN, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁸, SO₂NR⁷R⁸, NR⁵SO₂R⁸, mono a perfluoroalquilo de C₍₁₋₄₎ y mono a perfluoroalcoxi de C₍₁₋₄₎, y anillo heterocíclico de 5 a 7 miembros el cual está sustituido opcionalmente por

5 COR⁵, COOR⁵, CONR⁷R⁸ o alquilo de C₍₁₋₆₎ sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de hidroxí, halógeno, OR⁵, COR⁵, carboxi, COOR⁵, CONR⁷R⁸ o NR⁷R⁸, por ejemplo, piperidin-4-ilo, pirrolidin-3-ilo, o R¹⁰ es un anillo heterocíclico de 5 a 7 miembros sustituido opcionalmente por

10 COR⁵, COOR⁵, CONR⁷R⁸ o alquilo de C₍₁₋₆₎ sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de hidroxí, halógeno, OR⁵, COR⁵, carboxi, COOR⁵, CONR⁷R⁸ o NR⁷R⁸, por ejemplo, piperidin-4-ilo, pirrolidin-3-ilo.

En otro aspecto Z puede ser:

NO₂;

SOR⁹, SO₂R⁹ o NR⁵R⁹, en donde R⁹ es alquilo de C₍₁₋₆₎;

15 OR⁹, SR⁹, SOR⁹, SO₂R⁹ o NR⁵R⁹, en donde R⁹ es hidrógeno o mono a perfluoroalquilo de C₍₁₋₆₎;

OR⁹, SR⁹, SOR⁹, SO₂R⁹ o NR⁵R⁹, en donde R⁹ es alquilo de C₍₁₋₆₎ sustituido por 1, 2 ó 3 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de hidroxí, OR⁵, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁸, arilo, heteroarilo y un anillo heterocíclico de 5 a 7 miembros, arilo o

20 heteroarilo, el cual está sustituido opcionalmente por 1, 2, 3 ó 4 sustituyentes los cuales pueden ser los mismos o diferentes, seleccionados de alquilo de C₍₁₋₆₎, alcoxi de C₍₁₋₆₎, alquiltio de C₍₁₋₆₎, arilalcoxi de C₍₁₋₆₎, hidroxí, halógeno,

CN, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, SO₂NR⁷R⁸, NR⁵SO₂R⁶,
mono a perfluoroalquilo de C₍₁₋₄₎ y mono a perfluoroalcoxi de C₍₁₋₄₎, y anillo
heterocíclico de 5 a 7 miembros el cual está sustituido opcionalmente por
COR⁵, COOR⁵, CONR⁷R⁸ o alquilo de C₍₁₋₆₎ sustituido opcionalmente por 1, 2
5 ó 3 sustituyentes seleccionados de hidroxí, halógeno, OR⁵, COR⁵, carboxi,
COOR⁵, CONR⁷R⁸ o NR⁷R⁸, por ejemplo, piperidin-4-ilo, pirrolidin-3-ilo; o

R¹⁰, en donde R¹⁰ es alquilo de C₍₁₋₆₎ sustituido por 1, 2 ó 3
sustituyentes los cuales pueden ser los mismos o diferentes, seleccionados de
hidroxí, OR⁵, COR⁵, COOR⁵, CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, arilo, heteroarilo y
10 un anillo heterocíclico de 5 a 7 miembros, arilo o heteroarilo el cual está
sustituido opcionalmente por 1, 2, 3 ó 4 sustituyentes, los cuales pueden ser
los mismos o diferentes, seleccionados de alquilo de C₍₁₋₆₎, alcoxi de C₍₁₋₆₎,
alquiltio de C₍₁₋₆₎, arilalcoxi de C₍₁₋₆₎, hidroxí, halógeno, CN, COR⁵, COOR⁵,
CONR⁷R⁸, NR⁷R⁸, NR⁵COR⁶, SO₂NR⁷R⁸, NR⁵SO₂R⁶, mono a perfluoroalquilo
15 de C₍₁₋₄₎ y mono a perfluoroalcoxi de C₍₁₋₆₎, y anillo heterocíclico de 5 a 7
miembros el cual está sustituido opcionalmente por COR⁵, COOR⁵, CONR⁷R⁸,
o alquilo de C₍₁₋₆₎ sustituido opcionalmente por 1, 2 ó 3 sustituyentes
seleccionados de hidroxí, halógeno, OR⁵, COR⁵, carboxi, COOR⁵, CONR⁷R⁸ o
NR⁷R⁸, por ejemplo, piperidin-4-ilo, pirrolidin-3-ilo, o R¹⁰ es un anillo
20 heterocíclico de 5 a 7 miembros sustituido opcionalmente por COR⁵, COOR⁵,
CONR⁷R⁸ o alquilo de C₍₁₋₆₎ sustituido opcionalmente por 1, 2 ó 3
sustituyentes seleccionados de hidroxí, halógeno, OR⁵, COR⁵, carboxi,

COOR^5 , CONR^7R^8 o NR^7R^8 , por ejemplo, piperidin-4-ilo, pirrolidin-3-ilo; con la condición de que cuando X es CH, Z no es alcoxi de $\text{C}_{(1-3)}$ alquilo de $\text{C}_{(1-8)}$.

En otro aspecto, Z puede ser hidroxilo, nitro, mono o di-*N*-alquilamino de $\text{C}_{(1-8)}$ alquilo de $\text{C}_{(1-8)}$, mono o di-*N*-alquilamino de $\text{C}_{(1-8)}$ alcoxi de $\text{C}_{(1-8)}$, carboxialcoxi de $\text{C}_{(1-8)}$ o un éster del mismo, o arilalcoxi de $\text{C}_{(1-8)}$, arilalquilo de $\text{C}_{(1-8)}$, heteroarilalcoxi de $\text{C}_{(1-8)}$, heteroarilalquilo de $\text{C}_{(1-8)}$, heterociclilalcoxi de $\text{C}_{(1-8)}$ de 5 a 7 miembros sustituido opcionalmente por alquilo de $\text{C}_{(1-8)}$, o heterociclilalquilo de $\text{C}_{(1-8)}$ de 5 a 7 miembros sustituido opcionalmente por alquilo de $\text{C}_{(1-8)}$.

10 Cuando Z incluye un anillo de arilo, heteroarilo o heterocíclico, el anillo se selecciona de manera preferida de bencilo, piridinilo, isoxazolilo, piperidinilo, pirrolidinilo y morfolino, particularmente piperidinilo y morfolino.

En otro aspecto, Z puede ser 3-(dimetilamino)propilo, 3-(dimetilamino)propoxi, nitro, 2-(dimetilamino)etoxi, 2-(dietilamino)etoxi, 2-(piperidin-1-il)etoxi, 3-(piperidin-1-il)propoxi, $\text{OCH}_2\text{CO}_2\text{tBu}$, (piridin-2-il)metoxi, (5-metilisoxazol-3-il)metoxi, (1-metilpirrolidin-2-il)metoxi, benciloxi, hidroxilo, $\text{OCH}_2\text{CO}_2\text{H}$, dimetilaminometilo, dietilaminometilo, (pirrolidin-1-il)metilo, (piperidin-1-il)metilo, 2-dimetilaminoetilo, 2-dietilaminoetilo, 2-(pirrolidin-1-il)etilo, 3-dietilaminopropilo, 3-(pirrolidin-1-il)propilo, 3-(piperidin-1-il)propilo o
15
20 3-(4-morfolino)propilo, particularmente 3-(piperidin-1-il)propilo o 3-(4-morfolino)propilo.

Deberá apreciarse que los compuestos de la presente invención, pueden comprender uno o más centros quirales, tal que se pueden formar uno o más estereoisómeros.

La presente invención abarca todos los estereoisómeros de los compuestos de fórmula (I), incluyendo los isómeros geométricos e isómeros ópticos (por ejemplo, diastereoisómeros y enantiómeros), ya sea como estereoisómeros individuales aislados, para que estén sustancialmente libres de los otros estereoisómeros (es decir, puros) o como mezclas de los mismos que incluyen modificaciones racémicas. Un estereoisómero individual aislado para que esté sustancialmente libre de otro estereoisómero (es decir, puro), se aislará, de manera preferida, de manera que esté presente menos del 10%, de manera preferida menos del 1%, especialmente menos del 0.1% de los otros estereoisómeros.

Ciertos compuestos de fórmula (I) pueden existir en una de varias formas tautoméricas. Deberá entenderse que la presente invención abarca todos los tautómeros de los compuestos de fórmula (I), ya sea como tautómeros individuales o como mezclas de los mismos.

Deberá apreciarse que en algunos casos, los compuestos de la presente invención pueden incluir una función básica tal como un grupo amino como un sustituyente. Tales funciones básicas pueden ser utilizadas para formar sales de ácidos de adición, en particular, sales farmacéuticamente aceptables. Las sales farmacéuticamente aceptables incluyen aquellas descritas por Berge, Bighley, y Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19.

Tales sales pueden estar formadas de ácidos inorgánicos y orgánicos. Los ejemplos representativos de los mismas, incluyen a los ácidos maleico, fumárico, benzoico, ascórbico, pamoico, succínico, bismetilensalicílico, metansulfónico, etandisulfónico, acético, propiónico, tartárico, salicílico, cítrico, glucónico, aspártico, esteárico, palmítico, itacónico, glicólico, p-aminobenzoico, glutámico, taurocólico, ácido bencensulfónico, p-toluensulfónico, clorhídrico, bromhídrico, sulfúrico, ciclohexilsulfámico, fosfórico y nítrico.

Deberá apreciarse que en algunos casos, los compuestos de la presente invención pueden incluir un grupo carboxi como un sustituyente. Tales grupos carboxi pueden utilizarse para formar sales, en particular, sales farmacéuticamente aceptables. Las sales farmacéuticamente aceptables incluyen aquéllas descritas por Berge, Bighley, y Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Las sales preferidas incluyen las sales de metales alcalinos tales como las sales de sodio y potasio.

Cuando se utiliza aquí, el término "alquilo" y los términos similares tales como "alcoxi", incluyen todos los isómeros de cadena lineal y ramificada. Los ejemplos representativos de los mismos incluyen metilo, etilo, n-propilo, iso-propilo, n-butilo, sec-butilo, iso-butilo, t-butilo, n-pentilo y n-hexilo.

Cuando se utiliza aquí, el término "arilo" se refiere, a menos que se defina de otra manera, a un sistema anular mono o bicíclico que contiene hasta 10 átomos de carbono en el sistema anular, por ejemplo fenilo o naftilo.

7/8

Cuando se utiliza aquí, el término "heteroarilo" se refiere a un sistema anular heteroaromático mono o bicíclico que comprende hasta cuatro, de manera preferida 1 ó 2 heteroátomos, cada uno seleccionado de oxígeno, nitrógeno o azufre. Cada anillo puede tener de 4 a 7, de manera preferida de 5 ó 6 átomos en el anillo. Un sistema anular heteroaromático bicíclico puede incluir un anillo carbocíclico.

Cuando se utiliza aquí, el término "heterociclilo" se refiere, a menos que se defina de otra manera, a un anillo no aromático sencillo o fusionado que comprende hasta cuatro heteroátomos seleccionados de oxígeno, nitrógeno y azufre, y sustituido opcionalmente con hasta tres sustituyentes.

El anillo heterocíclico adecuado comprende 5 a 7, de manera preferida 5 ó 6 átomos en el anillo. Un sistema anular heterocíclico fusionado puede incluir anillos carbocíclicos y necesitan incluir únicamente un anillo heterocíclico.

Cuando se utilizan aquí, los términos "halógeno" y "halo", incluyen flúor, cloro, bromo y yodo y fluoro, cloro, bromo e yodo, respectivamente.

Deberá entenderse que la presente invención cubre todas las combinaciones de los grupos de sustituyentes referidos aquí anteriormente.

Los compuestos representativos de fórmula (I) son:

Bitartrato de la N-metil-2-(2-(2-(2,3-difluorofenil)etil)-7-(3-dimetilaminoprop-1-il)-4-oxo-4H-quinolin-1-il)-N-(4-(4-trifluorometilfenil)bencil)-acetamida;

5 Bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-4-oxo-7-(3-(dimetilamino)propoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

N-Metil-2-(2-(2-(2,3-difluorofenil)etil)-7-nitro-4-oxo-4H-quinolin-1-il)-N-(4-(4-trifluorometilfenil)bencil)acetamida;

10 Bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-7-(2-dimetilaminoetoxi)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

Bitartrato de la 2-(7-(2-dietilaminoetoxi)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

15 Bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-4-oxo-7-(2-(piperidin-1-il)etoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

Bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-4-oxo-7-(3-(piperidin-1-il)propoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)-acetamida;

20 Acetato de 2-(2-(2-(2,3-difluorofenil)etil))-1-(N-(4-(4-trifluorometilfenil)bencil)-N-metil-aminocarbonilmetil)-4-oxo-4H-quinolin-7-iloxi)ter-butilo;

Clorhidrato de la 2-(2-(2-(2,3-difluorofenil)etil)-4-oxo-7-(piridin-2-ilmetoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

2-(2-(2-(2,3-Difluorofenil)etil)-7-(5-metilisoxazol-3-ilmetoxi)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

- 5 Bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-7-(1-metilpimolidin-2-ilmetoxi)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)-acetamida;

2-(7-Benciloxi-2-(2-(2,3-difluorofenil)etil)-4-oxo-4-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

- 10 Bitartrato de la 2-(7-benciloxi-2-(2-(2,3-difluorofenil)etil)-4-oxo-4-quinolin-1-il)-N-(1-etil-piperidin-4-il)-N-(4-(4-trifluorometilfenil)bencil)acetamida;

2-(2-(2-(2,3-Difluorofenil)etil)-7-hidroxi-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

- 15 Bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-7-hidroxi-4-oxo-4H-quinolin-1-il)-N-(1-etil-piperidin-4-il)-N-(4-(4-trifluorometilfenil)bencil)acetamida;

Acido 2-(2-(2-(2,3-difluorofenil)etil))-1-(N-(4-(4-trifluorometilfenil)-bencil)-N-metil-aminocarbonilmetil)-4-oxo-4H-quinolin-7-iloxi)acético;

Bitartrato de la 2-(7-(dimetilaminometil)-2-(2-(2,3-difluorofenil)-etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

- 20 Bitartrato de la 2-(7-(dietilaminometil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

Bitartrato de la 2-(7-(dietilaminometil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

Bitartrato de la 2-(7-(dietilaminometil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-isopropil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

Bitartrato de la 2-(7-((pirrolidin-1-il)metil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometilfenil)bencil)-
5 acetamida;

Bitartrato de la 2-(7-((piperidin-1-il)metil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometilfenil)bencil)-
acetamida;

Bitartrato de la 2-(7-(2-dimetilaminoetil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-
10 bencil)acetamida;

Bitartrato de la 2-(7-(2-dietilaminoetil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida;

Bitartrato de la 2-(7-(2-(pirrolidin-1-il)etil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-
15 bencil)acetamida;

Bitartrato de la 2-(7-(3-dietilaminopropil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-
bencil)acetamida;

Bitartrato de la 2-(7-(3-(pirrolidin-1-il)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-
20 bencil)acetamida;

Bitartrato de la 2-(7-(3-(piperidin-1-il)propil)-2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometilfenil)-bencil)acetamida;

5 Bitartrato de la 2-(7-(3-(piperidin-1-il)propil)-2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-isopropil-N-(4-(4-trifluorometilfenil)-bencil)acetamida;

Bitartrato de la 2-(7-(dietilaminometil)-2-(2,3-difluorobenciltio)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida; y

10 Clorhidrato de la 2-(7-(3-(4-morfolino)propil)-2-(2,3-difluorobenciltio)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-bencil)acetamida.

Los compuestos preferidos son:

15 Bitartrato de la 2-(7-(3-(piperidin-1-il)propil)-2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometilfenil)bencil)-acetamida; y

Clorhidrato de la 2-(7-(3-(4-morfolino)propil)-2-(2,3-difluorobenciltio)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-bencil)acetamida.

Las sales preferidas son las sales de bitartrato y clorhidrato.

20 Puesto que los compuestos de la presente invención, en particular los compuestos de fórmula (I), se pretenden para el uso en composiciones farmacéuticas, se entenderá que cada uno se proporciona en forma sustancialmente pura, por ejemplo, al menos 50% puro, de manera más

adecuada, al menos 75% puro y de manera preferida al menos 95% puro (el % está en una base peso/peso). Las preparaciones impuras de los compuestos de fórmula (I) pueden utilizarse para preparar las formas más puras utilizadas en las composiciones farmacéuticas. Aunque la pureza de los compuestos intermediarios de la presente invención es menos crítica, se entenderá fácilmente que la forma sustancialmente pura se prefiere para los compuestos de fórmula (I). De manera preferida, 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 recrystalizan a partir de solventes orgánicos, el solvente de la cristalización puede estar presente en el producto cristalino. Esta invención incluye dentro de su alcance a tales solvatos. De manera similar, algunos de los compuestos de esta invención pueden ser cristalizados o recrystalizados a partir de solventes que contienen agua. En tales casos, puede formarse agua de la hidratación. Esta invención incluye dentro de su alcance, los hidratos estequiométricos, así como los compuestos que contienen cantidades variables de agua, que pueden ser producidos mediante procedimientos tales como la liofilización. Además, diferentes condiciones de cristalización pueden conducir a la formación de diferentes formas polimórficas de los productos cristalinos. Esta invención incluye dentro de su alcance, todas las formas polimórficas de los compuestos de fórmula (I).

Los compuestos de la presente invención son inhibidores de la fosfolipasa A2 asociada con la lipoproteína de la enzima (Lp-PLA₂) y como

tales, se espera que se utilicen en terapia, en particular en el tratamiento de la aterosclerosis. En un aspecto adicional de la misma, la presente invención proporciona un compuesto de fórmula (I) para utilizarse en terapia.

Los compuestos de fórmula (1) son inhibidores de la producción
5 de lisofosfatidilcolina por la Lp-PLA₂ y por lo tanto, pueden tener una aplicación general en cualquier trastorno que involucre la disfunción endotelial, por ejemplo, aterosclerosis, diabetes, hipertensión, angina pectoris y después de isquemia y reperfusión. Además, los compuestos de fórmula (1) pueden tener una aplicación general en cualquier trastorno que involucre la oxidación
10 lipídica, en conjunto con la actividad de la enzima, por ejemplo, además de condiciones tales como la aterosclerosis y la diabetes, otras condiciones tales como la artritis reumatoide, apoplejía, condiciones inflamatorias del cerebro tales como la Enfermedad de Alzheimer, infarto al miocardio, isquemia, lesión por reperfusión, sepsis e inflamación aguda y crónica.

15 Las aplicaciones adicionales incluyen cualquier trastorno que involucre los monocitos, macrófagos y linfocitos activados, puesto que todos estos tipos de células expresan la Lp-PLA₂. Los ejemplos de tales trastornos incluyen la psoriasis.

En consecuencia, en un aspecto adicional, la presente invención
20 proporciona un método para tratar un estado de enfermedad asociado con la actividad de la enzima Lp-PLA₂, método el cual involucra tratar a un paciente en necesidad del mismo, con una cantidad terapéuticamente efectiva de un inhibidor de la enzima. El estado de enfermedad puede estar asociado con la

implicación incrementada de los monocitos, macrófagos o linfocitos; con la formación de la lisofosfatidilcolina y los ácidos grasos libres oxidados; con la oxidación lipídica en conjunto con la actividad de la Lp-PLA₂ o con la disfunción endotelial.

5 Los compuestos de la presente invención también pueden ser útiles en el tratamiento de los estados de enfermedad mencionados anteriormente, en combinación con un agente antihiperlipidémico, antiaterosclerótico, antidiabético, antianginal, antiinflamatorio o antihipertensión o un agente para disminuir la Lp(a). Los ejemplos de lo
10 anterior incluyen los inhibidores de la síntesis del colesterol, tales como estatinas, antioxidantes tales como probucol, sensibilizadores de la insulina, antagonista del canal del calcio y fármacos antiinflamatorios, tales como NSAID. Los ejemplos de agentes para disminuir la Lp(a) incluyen los aminofosfonatos descritos en la WO 97/02037, WO 98/28310, WO 98/28311 y
15 WO 98/28312 (Symphar SA y SmithKline Beecham).

Una terapia de combinación preferida sería el uso de un compuesto de la presente invención y una estatina. Las estatinas son una clase bien conocida de agentes que disminuyen el colesterol e incluyen la atorvastatina, simvastatina, pravastatina, cerivastatina, fluvastatina,
20 lovastatina y ZD 4522 (también referido como S-4522, rosuvastatina, Astra Zeneca). Los dos agentes pueden administrarse sustancialmente al mismo tiempo o a diferentes tiempos, de acuerdo con la discreción del médico.

Una terapia de combinación preferida adicional, sería el uso de un compuesto de la presente invención y un agente antidiabético o un sensibilizador de la insulina, puesto que la enfermedad cardiaca coronaria es una causa principal de muerte para los diabéticos. Dentro de esta clase, los compuestos preferidos para utilizarse con un compuesto de la presente invención, incluyen los activadores PPARgamma, por ejemplo, GI262570 (GlaxoSmithKline) y la clase de compuestos de la glitazona, tales como la rosiglitazona (Avandia, GlaxoSmithKline), troglitazona y pioglitazona.

En uso terapéutico, los compuestos de la presente invención se administran usualmente en una composición farmacéutica estándar. La presente invención proporciona, por lo tanto, en un aspecto adicional, una composición farmacéutica que comprende un compuesto de fórmula (I) y un portador farmacéuticamente aceptable, opcionalmente con uno o más de otros compuestos terapéuticos, tales como una estatina o un antidiabético.

Las composiciones farmacéuticas adecuadas incluyen aquellas que están adaptadas para la administración oral o parenteral o como un supositorio, particularmente para la administración oral.

Los compuestos de fórmula (I), que son activos cuando se dan oralmente, pueden formularse como líquidos, por ejemplo jarabes, suspensiones o emulsiones, tabletas, cápsulas o pastillas. Una formulación líquida consistirá generalmente de una suspensión o solución del compuesto o la sal farmacéuticamente aceptable en un portador líquido adecuado, por ejemplo, etanol, glicerina, solvente no acuoso, por ejemplo polietilenglicol,

aceites o agua con un agente de suspensión, preservativo, saborizante o agente colorante. Una composición en la forma de una tableta puede prepararse utilizando cualquier portador farmacéutico adecuado, utilizado de manera rutinaria para preparar formulaciones sólidas. Los ejemplos de tales

5 portadores incluyen estearato de magnesio, almidón, lactosa, sucrosa y celulosa. Una composición en la forma de una cápsula puede prepararse utilizando procedimientos de encapsulación rutinarios. Por ejemplo, pueden prepararse gránulos que contengan el ingrediente activo utilizando portadores estándar, y a continuación llenarse en una cápsula de gelatina dura; de

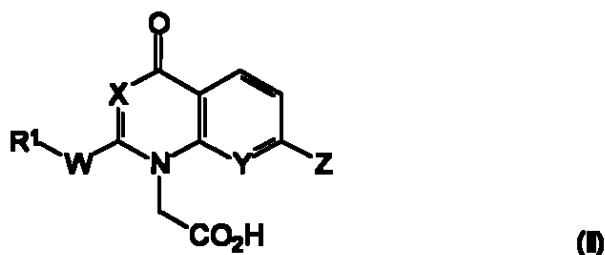
10 manera alterna, puede prepararse una dispersión o suspensión utilizando cualquier portador farmacéutico adecuado, por ejemplo, gomas acuosas, celulosas, silicatos o aceites y la dispersión o suspensión llenarse a continuación en una cápsula de gelatina blanda. Las composiciones parenterales típicas consisten de una solución o suspensión del compuesto de

15 fórmula (I) en un portador acuoso estéril o un aceite parenteralmente aceptable, por ejemplo, polietilenglicol, polivinil pirrolidona, lecitina, aceite de cacahuate o aceite de sésamo. De manera alterna, la solución puede liofilizarse y a continuación reconstituirse con un solvente adecuado justo antes de la administración. Una formulación de supositorio típica comprende

20 un compuesto de fórmula (I), el cual es activo cuando se administra de esta manera, con un agente aglutinante y/o lubricante, tal como glicoles poliméricos, gelatinas o manteca de cacao u otras ceras o grasas vegetales o sintéticas de baja fusión.

De manera preferida, la composición está en una forma de dosis unitaria tal como una tableta o cápsula. Cada dosis unitaria para la administración oral contiene, manera preferida de 1 a 500 mg (y para la administración parenteral contiene, de manera preferida, de 0.1 a 25 mg) de un compuesto de la fórmula (I). El régimen de dosificación diario para un paciente adulto puede ser, por ejemplo, una dosis oral de entre 1 mg y 1000 mg, de manera preferida entre 1 mg y 500 mg, o una dosis intravenosa, subcutánea o intramuscular de entre 0.1 mg y 100 mg, de manera preferida, de entre 0.1 mg y 25 mg, del compuesto de la fórmula (I), el compuesto se administra de 1 a 4 veces por día. De manera adecuada, los compuestos se administrarán durante un periodo de terapia continua, por ejemplo, durante una semana o más.

De acuerdo con un primer procedimiento A, un compuesto de fórmula (I) puede ser preparado haciendo reaccionar un compuesto ácido de fórmula (II):



20

en la cual W, X, Y, Z y R¹ son como se definieron anteriormente, con un compuesto de amina de fórmula (III):

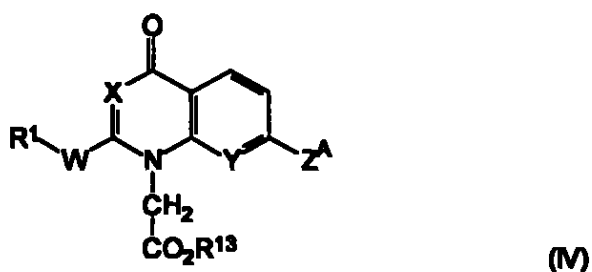


en la cual R^2 , R^3 y R^4 son como se definieron anteriormente; bajo condiciones de formación de amida.

5 Las condiciones de formación de amida adecuadas son bien conocidas en la técnica e incluyen el tratamiento del ácido de fórmula (II) con el compuesto de amina de fórmula (III), en la presencia de un agente de acoplamiento tal como la 1-(3-dimetil-aminopropil)-3-etilcarbodiimida (DEC) o hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio
10 (HATU) en un solvente aprótico tal como diclorometano o dimetilformamida (DMF).

Un compuesto de fórmula (II) puede ser preparado fácilmente a partir de un éster correspondiente de fórmula (IV):

15



en la cual W, X, Y y R^1 son como se definieron anteriormente, Z^A
20 es Z como se definió anteriormente o un grupo convertible a Z, y R^{13} es alquilo de $C_{(1-8)}$, por ejemplo etilo o t-butilo, tratando con un agente desesterificante, por ejemplo, para t-butilo, ácido trifluoroacético.

5

10

15



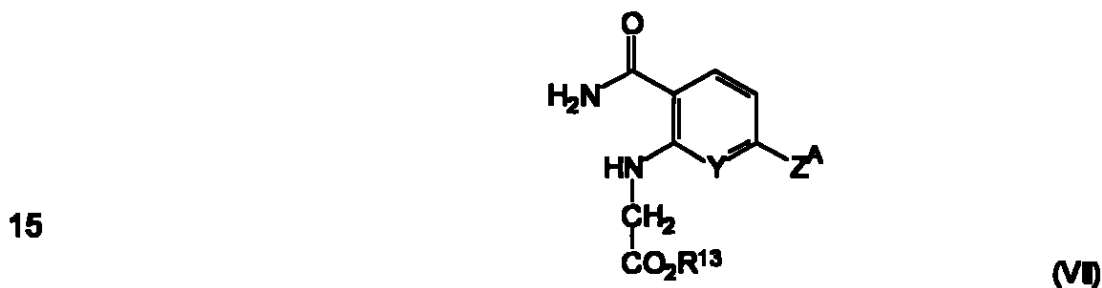
20



84

en la cual Z^A es Z como se definió anteriormente o un grupo convertible a Z, y R^{13} es como se definió anteriormente, por ejemplo etilo bajo condiciones estándar de formación del anillo de pirimidona, en la presencia de una base tal como piridina, para dar un éster intermediario (IV), el cual puede convertirse en un compuesto de fórmula (II), por ejemplo, mediante el tratamiento con hidróxido de sodio acuoso.

De manera alternativa, cuando X es N e Y es CH, el anillo de pirimidona puede ser formado reaccionando con un compuesto de fórmula (VII):



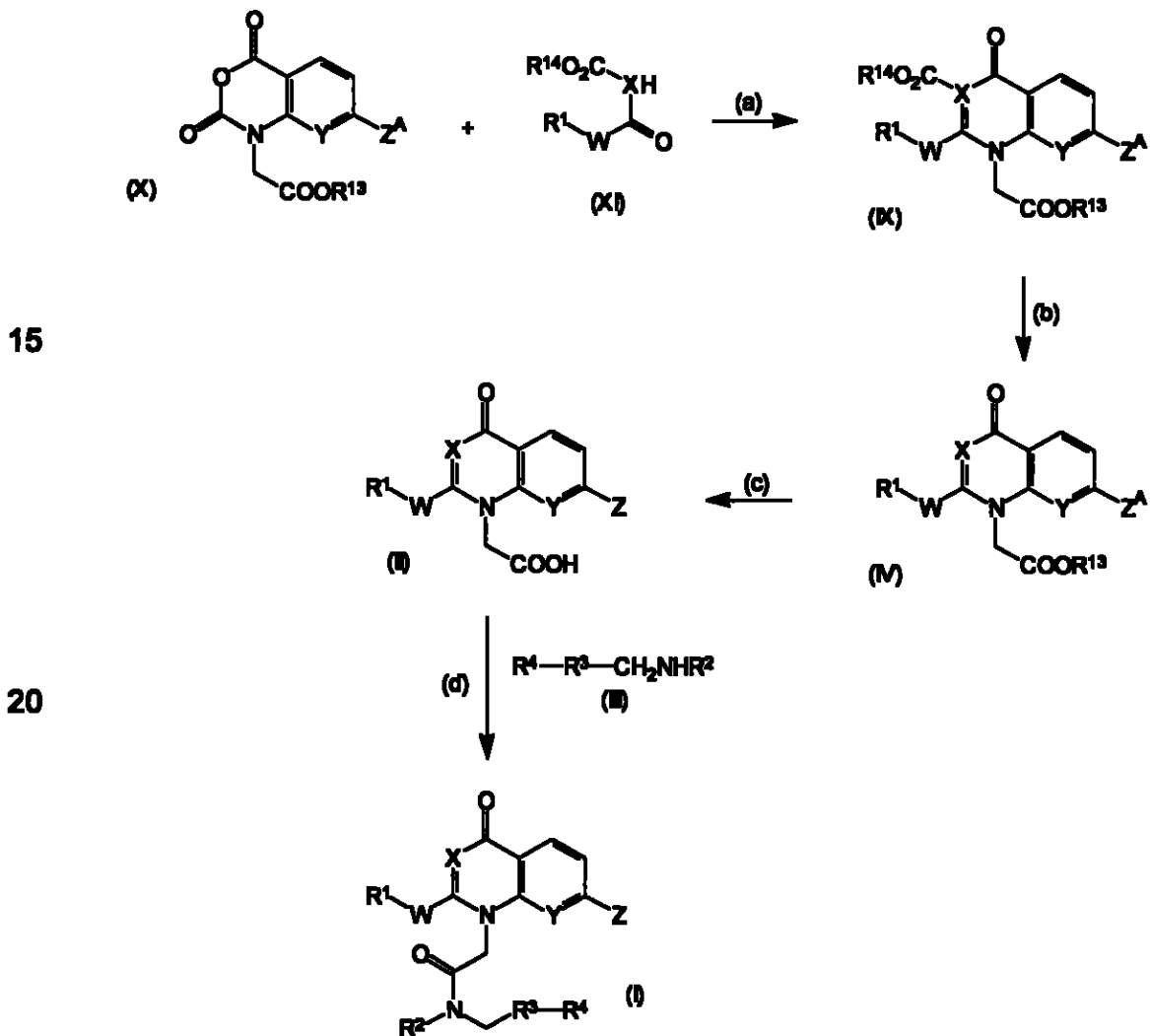
en la cual Z^A es Z como se definió anteriormente o un grupo convertible a Z, y R^{13} es como se definió anteriormente, por ejemplo etilo, con un compuesto de cloruro de acilo de la fórmula (VIII):



en la cual R^1 y W, son como se definieron anteriormente;

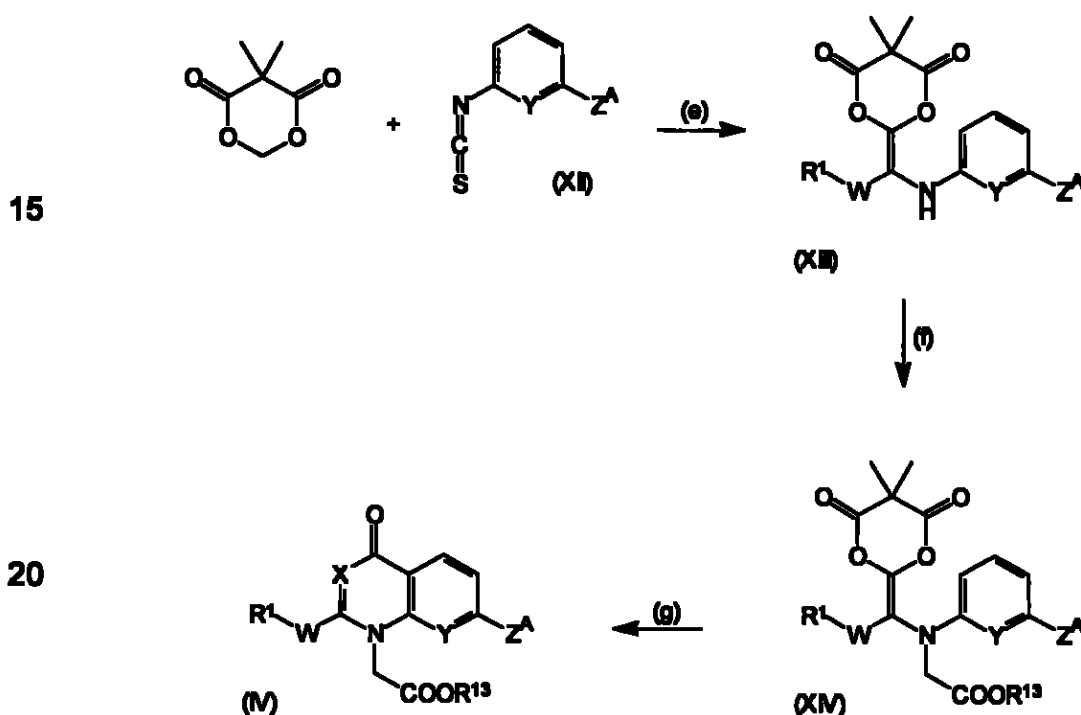
bajo las condiciones estándar de formación del anillo de pirimidona, en un solvente tal como benceno, o vía un procedimiento de dos pasos mediante el tratamiento con piridina, seguido por una base adecuada, por ejemplo, NaH en DMF, seguido por el tratamiento del intermediario así
5 formado con un ácido, por ejemplo ácido p-toluen sulfónico en tolueno a reflujo; para proporcionar un intermediario del éster (IV), el cual puede, a continuación, ser convertido en un compuesto de fórmula (II), por ejemplo, mediante el tratamiento con hidróxido de sodio acuoso.

Cuando X e Y son CH, la síntesis total de los compuestos de
10 fórmula (I), se ilustra en el siguiente esquema de reacción:



Refiriéndose al esquema de reacción, el intermediario clave (IV) puede ser sintetizado removiendo el grupo 3-éster del intermediario (IX), en donde R^{14} es alquilo de $C_{(1-6)}$, por ejemplo, calentando un éter de difenilo, en donde R^{14} es tBu (paso b). El intermediario (IX) se forma a partir de la 2,6-dioxo-1,3-oxacina (X) y el éster (XI) mediante el tratamiento con una base, por ejemplo 1,8-diazabicyclo[5.4.0]undec-7-eno en tetrahidrofurano o NaH en DMF.

De manera alterna, en donde W es S y X e Y son CH, la síntesis del intermediario (IV) se ilustra en el siguiente esquema de reacción:



Refiriéndose al esquema de reacción, el intermediario clave (IV) puede ser sintetizado mediante la ciclización catalizada ácida del intermedio (XIV), por ejemplo, calentando con ácido trifluorometansulfónico en diclorometano. El intermediario (XIV) se forma mediante la alquilación del

5 intermediario (XIII) con un compuesto de fórmula (XV):



en la cual L es un grupo saliente, por ejemplo cloro o bromo, en

10 la presencia de una base tal como *ter*-butoxido de potasio, en un solvente tal como N-metilpirrolidona. El intermediario (XIII) se forma mediante la reacción del ácido de Meldrum con un compuesto de fórmula (XII) en la presencia de una base tal como N,N-diisopropiletilamina en un solvente tal como N-metilpirrolidona, inmediatamente seguida por el tratamiento con un agente

15 alquilante para la fórmula (XVI):



por ejemplo bromuro de 2,3-difluorobencilo.

20 La conversión de Z^A a Z, de manera típica, surge si un grupo protector, o un grupo el cual toma parte en las reacciones posteriores tales como reacciones de acoplamiento, se necesita durante las reacciones anteriores o durante la preparación de los reactivos. La conversión de Z^A a Z

46

puede ser llevada a cabo en diferentes etapas en la síntesis de los compuestos de fórmula (I), dependiendo de la naturaleza de Z, incluyendo como un paso final.

5 Z^A puede ser, por ejemplo, un grupo hidroxil protegido. Los grupos protectores adecuados son aquellos bien conocidos en la técnica, que pueden removerse bajo condiciones convencionales y sin afectar el resto de la molécula. Una discusión más extensa de las maneras en las cuales los grupos pueden ser protegidos y los métodos para escindir los derivados protegidos resultantes se dan en por ejemplo, *Protective Groups in Organic*
10 *Chemistry*, T. W. Greene y P. G. M. Wuts, (Wiley-Interscience, New York, 2a edición, 1991). Los grupos protectores de hidroxil particularmente adecuados incluyen al bencilo.

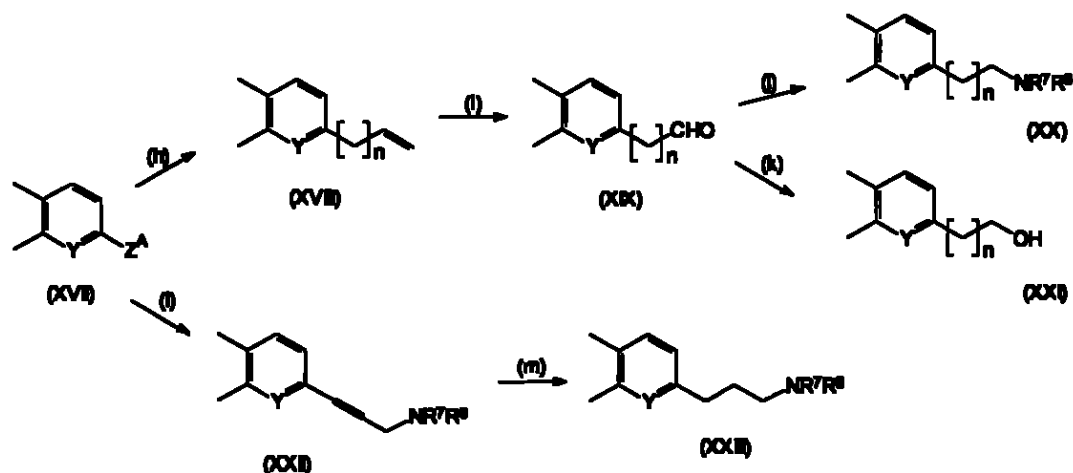
Así, de acuerdo con otro procedimiento C, un compuesto de fórmula (I) puede ser preparado sometiendo un derivado protegido de un
15 compuesto de fórmula (I) a la reacción, para remover el grupo o grupos protectores presentes, constituyendo un aspecto adicional de la presente invención.

Z^A también puede ser un grupo tal como halo, por ejemplo, cloro, bromo o yodo, el cual puede convertirse a Z en diferentes etapas en la
20 síntesis de los compuestos de fórmula (I), incluyendo como un paso final, el uso de uno de los métodos generales para la transformación del grupo funcional descrita en la literatura, con la condición de que el método elegido sea compatible con los otros grupos funcionales en la molécula. Las

transformaciones del grupo funcional son bien conocidas en la técnica y se describen en, por ejemplo, *Comprehensive Organic Functional Group Transformations*, eds. A. R. Katritzky, O. Meth-Cohn y C. W. Rees (Elsevier Science Ltd., Oxford, 1995), *Comprehensive Organic Chemistry*, eds. D. Barton y W. D. Ollis (Pergamon Press, Oxford, 1979) y *Comprehensive Organic Transformations*, R. C. Larock (VCH Publishers Inc., New York, 1989). Algunos ejemplos representativos de las transformaciones basadas en los intermediarios, en donde Z^A es halo, se muestran en el siguiente esquema de reacción (se muestran las estructuras parciales):

10

15



Así, un intermediario con una estructura parcial (XVI), en la cual Z^A es bromo o yodo, puede someterse a un acoplamiento catalizado con paladio con estannatos de vinilo para formar (XVIII), en donde $n=0$, o con estannatos de alilo para formar (XVIII), en donde $n=1$ (paso h). La escisión oxidativa del grupo alqueno terminal de (XVIII), por ejemplo, mediante oxidación con tetróxido de osmio, seguido por el tratamiento con peryodato

sódico (paso i), forma un aldehído de la estructura parcial (XIX). Para el caso en donde $n=2$, el acoplamiento de (XVII) con alcohol alílico da (X) directamente. Tales compuestos, en los cuales Z^A es $(CH_2)_nCHO$, a su vez, representan intermediarios versátiles. Por ejemplo, la aminación reductora con una amina de fórmula NHR^7R^8 y un agente reductor como triacetoxiborohidruro de sodio forma (XX), en el cual Z es $(CH_2)_{n+1}NR^7R^8$ o la reducción mediante medio estándar forma los alcoholes (XXI). En un ejemplo adicional, los sustituyentes de cadenas más largas pueden formarse de manera conveniente mediante el acoplamiento catalizado por paladio de los alquinos a (XVII), en el cual Z^A es bromo o yodo (paso 1) y la reducción posterior (paso m).

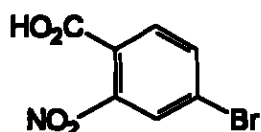
Así, de acuerdo con otro procedimiento D, un compuesto de fórmula (I) puede ser preparado a partir de un compuesto de fórmula (I), en la cual Z^A es un grupo convertible a Z, mediante una transformación del grupo funcional, constituyendo otro aspecto de la presente invención.

Se apreciará además, que los compuestos de fórmula (I) también pueden prepararse a partir de otros compuestos de fórmula (I), utilizando procedimientos de interconversión convencionales (procedimiento E), que constituyen aún otro aspecto de la presente invención.

Los siguientes Ejemplos ilustran la invención.

EJEMPLOS

La estructura y pureza de los intermediarios y ejemplos se confirmó mediante ^1H -RMN y (en casi todos los casos) espectroscopia de masas, incluso en donde no se indique de manera explícita a continuación.

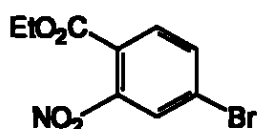
Intermediario A1 – Ácido 4-bromo-2-nitrobenzoico

10

Se agregó permanganato de potasio (29.6 g, 187 mmoles) en porciones durante 8 horas a una solución a reflujo de 4-bromo-2-nitrotolueno (10.1 g, 46.75 mmoles) en piridina (80 ml) y agua (70 ml). La suspensión se filtró mientras está todavía caliente y la solución amarilla resultante se evaporó a aproximadamente 1/4 del volumen. Se agregó hidróxido de sodio (2M, 20 ml), y la solución se extrajo con éter dietílico (para remover cualquier 4-bromo-2-nitrotolueno remanente). La solución se acidificó con ácido clorhídrico (concentrado), y el sólido resultante se recolectó y se secó bajo presión reducida para proporcionar el compuesto del título (5.72 g, 50%).

20

 ^1H RMN (d_6 -DMSO) δ 7.79 (1H, d), 7.98 (1H, dd), 8.23 (1H, d).

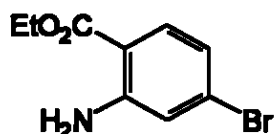
Intermediario A2 - 4-Bromo-2-nitrobenzoato de etilo

5 Una solución del intermediario A1 (8.9 g, 28.05 mmoles) y ácido
sulfúrico (concentrado, 10 ml) en etanol (80 ml), se calentó a reflujo durante
18 horas. Después de enfriar, el solvente se evaporó. El residuo se disolvió
en éter dietílico y se lavó con agua, bicarbonato de sodio saturado, se secó
(MgSO₄) y el solvente se evaporó para proporcionar el compuesto del título
10 (7.09 g, 92%).

¹H RMN (CDCl₃) δ 1.35 (3H, t), 4.39 (2H, c), 7.65 (1H, d), 7.78
(1H, dd), 8.00 (1H, d).

Intermediario A3 - 2-Amino-4-bromobenzoato de etilo

15

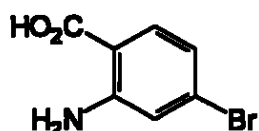


Una mezcla del intermediario A2 (7.09 g, 25.9 mmoles) y hierro
(14.5 g, 259 mmoles) en etanol acuoso al 10% (250 ml), se calentó a reflujo
20 durante 6 horas. La mezcla se filtró a través de celite y la solución resultante
se evaporó. La mezcla cruda se purificó mediante cromatografía (tapón de gel
de sílice) en diclorometano para proporcionar el compuesto del título (4.53 g,
72%).

^1H RMN (CDCl_3) δ 1.37 (3H, t), 4.32 (2H, c), 5.77 (2H, s amplio), 6.73 (1H, dd), 6.83 (1H, d), 7.71 (1H, d).

Intermediario A4 – Clorhidrato del ácido 2-amino-4-bromobenzoico

5

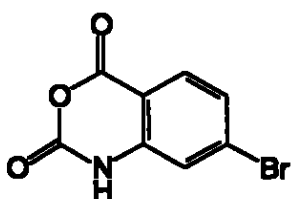


Se agregó hidróxido de sodio (2M, 28 ml) a una solución agitada del intermediario A3 (4.53g, 18.6 mmoles) en dioxano (150 ml) y agua (22 ml), y la solución resultante se calentó a 75°C durante 4 horas. Después de enfriar el solvente, se evaporó y el residuo se suspendió en agua. La mezcla se acidificó (HCl concentrado), y el sólido resultante se recolectó y se secó para proporcionar el compuesto del título (4.29 g, 89%).

^1H RMN (d_6 -DMSO) δ 6.64 (1H, dd), 6.97 (1H, d), 7.59 (1H, d).

15

Intermediario A5 - 7-Bromo-1H-benzof[d][1,3]oxacin-2,4-diona



20

Se agregó por goteo fosgeno (20% en tolueno, 12.9 ml) a una solución agitada del intermediario A4 (3.15 g, 12.5 mmoles) en dioxano (30

94

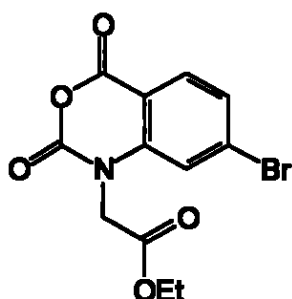
ml), la agitación se continuó durante 18 horas. El solvente se evaporó para proporcionar el compuesto del título (2.96 g, 98%).

^1H RMN (d_6 -DMSO) δ 7.33 (1H, d), 7.42 (1H, dd), 7.83 (1H, d), 11.87 (1H, s); ^{13}C RMN (d_6 -DMSO) 109.7, 117.6, 126.4, 130.1, 130.7, 142.4, 146.7 y 159.2.

Intermediario A6 – Acetato de (7-bromo-2,4-dioxo-4H-

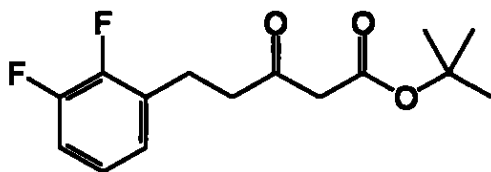
benzo[d][1,3]oxacina-1-Il)etilo

10



Se agregó por goteo bromoacetato de etilo (4 ml, 36.1 mmoles) a una solución agitada del intermediario A5 (8.74 g, 36.1 mmoles) y diisopropiletilamina (7.5 ml, 43.3 mmoles) en N metil-2-pirrolidinona (50 ml) a 0°C. La agitación se continuó a temperatura ambiente durante 18 horas. La solución se diluyó con agua (150 ml), y el sólido resultante se recolectó y secó (MgSO_4) para proporcionar el compuesto del título (10 g, 85%).

^1H RMN (d_6 -DMSO) δ 1.23 (3H, t), 4.20 (2H, c), 4.91 (2H, s), 7.41 (1H, dd), 7.81 (1H, d), 7.94 (1H, d).

Intermediario A7 - 5-(2,3-Difluorofenil)-3-oxopentanoato de ter-butilo

5

A una suspensión agitada enfriada con hielo de hidruro de sodio (1.96 g, 49.1 mmoles, dispersión en aceite al 60%) en tetrahidrofurano seco (100 ml), se agregó gota a gota bajo una atmósfera de argón, acetoacetato de ter-butilo (7.4 ml, 44.6 mmoles). Después de 15 minutos adicionales, se

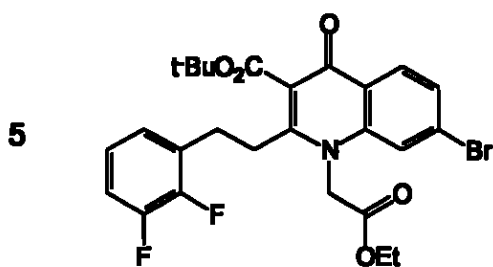
10 agregó gota a gota n-butilitio (18.7 ml, 48.8 mmoles, 2.5M en hexanos), manteniendo la temperatura de reacción por debajo de 10°C. Se agregó gota a gota bromuro de 2,3-difluorobencilo (11.08 g, 53.5 mmoles), 20 minutos más tarde, a continuación, la mezcla se dejó calentar a temperatura ambiente. Después de 15 minutos adicionales, la mezcla de reacción se vertió en una

15 mezcla de agua (150 ml) y ácido acético glacial (10 ml), se extrajo 3 veces con acetato de etilo y los extractos combinados se lavaron con carbonato ácido de sodio saturado, a continuación con salmuera, se secaron (MgSO₄) y se evaporaron hasta un aceite amarillo. La cromatografía (sílice fina, acetato de etilo-petróleo ligero) proporcionó el compuesto del título como un aceite

20 amarillo, rendimiento 9.05 g (71%).

¹H RMN (CDCl₃) δ 1.45 (9H, s), 2.84-2.91 (2H, m), 2.95-3.00 (2H, m), 3.35 (2H, s), 6.92-7.04 (3H, m).

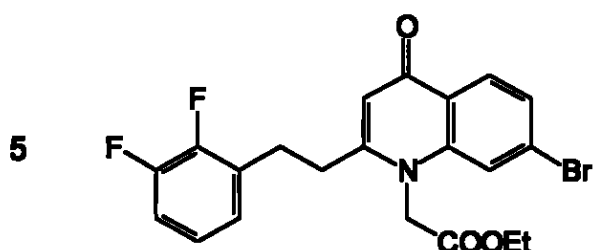
Intermediario A8 - (7-Bromo-2-(2-(2,3-difluorofenil)etil)-1-etoxycarbonil-4-oxo-4H-quinolin-1-il)-3-carboxilato de ter-butilo



Se agregó por goteo 1,8-diazabicyclo[5.4.0]undec-7-eno (9.1 ml, 61 mmoles) a una solución agitada del intermediario A6 (10 g, 30.5 mmoles) y el intermediario A7 (9.52 g, 33.5 mmoles) en tetrahidrofurano (100 ml) a 0°C. La agitación se continuó a temperatura ambiente durante 18 horas. La solución se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado, se secó (MgSO₄) y el solvente se evaporó. El residuo se purificó mediante cromatografía (petróleo/acetato de etilo), para proporcionar el compuesto del título (9.3 g, 55%).

¹H RMN (CDCl₃) δ 1.33 (3H, t), 1.62 (9H, s), 2.97 (2H, m), 3.07 (2H, m), 4.34 (2H, c), 4.94 (2H, s amplio), 7.00-7.12 (3H, m), 7.42 (1H, d), 7.49 (1H, dd), 8.29 (1H, d).

Intermediario A9 – Acetato de (7-bromo-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo

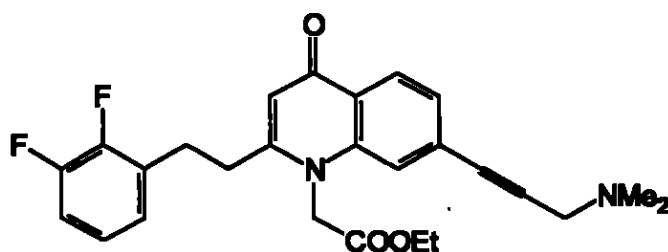


El intermediario A8 (9.3 g, 16.9 mmoles) en éter difenílico (30 ml) se calentó a reflujo durante 15 minutos. Después de enfriar se agregó
10 petróleo y el sólido resultante se recolectó mediante filtración. El producto crudo se purificó mediante cromatografía (gel de sílice, petróleo/acetato de etilo) para proporcionar el compuesto del título (2.8 g, 37%).

^1H RMN (CDCl_3) δ 1.31 (3H, t), 2.91 (2H, m), 3.05 (2H, m), 4.32 (2H, c), 4.86 (2H, s), 6.25 (1H, s), 6.93-7.14 (3H, m), 7.42 (1H, d), 7.49 (1H, dd), 8.29 (1H, d); MS (APCI+) encontrado ($M+1$) = 450, $\text{C}_{21}\text{H}_{18}^{79}\text{BrNO}_3$ requerido 449.
15

Intermediario A10 – Acetato de (2-(2-(2,3-difluorofenil)etil)-7-(3-dimetilaminoprop-1-ynil)-4-oxo-4H-quinolin-1-il)etilo

20



AB

Una mezcla del Intermediario A9 (0.43 g, 0.96 mmol), 3-dimetilaminopropino (0.41 ml, 3.8 mmol), cloruro de bis(trifenilfosfin)paladio (II) (0.07 g) y cobre (I) yodo (0.04 g) en 1,2-dimetoxietano (5 ml) y trietilamina (5 ml) se calentó a 75°C durante 2 horas. Después de enfriar, el solvente se evaporó y el residuo se suspendió en diclorometano y se lavó con bicarbonato de sodio saturado, se secó (MgSO₄) y el solvente se evaporó. El producto crudo se purificó mediante cromatografía (NH₃/MeOH/CH₂Cl₂) para proporcionar el compuesto del título (390 mg, 90%).

10 ¹H RMN (CDCl₃) δ 1.30 (3H, t), 2.39 (6H, s), 2.92 (2H, m), 3.05 (2H, m), 3.49 (2H, s), 4.30 (2H, c), 4.88 (1H, s), 6.25 (1H, s), 6.93-7.10 (3H, m), 7.32 (1H, d), 7.42 (1H, dd), 8.35 (1H, d); MS (APCI+) encontrado (M+1) = 453; C₂₈H₂₈F₂O₃N₂ requerido 452.

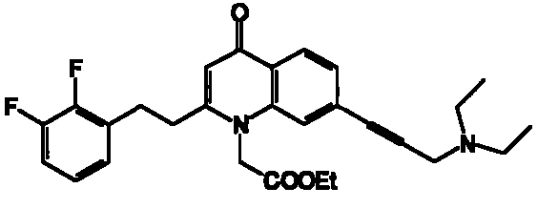
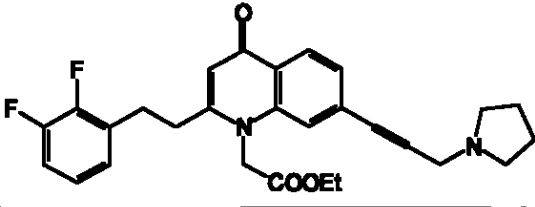
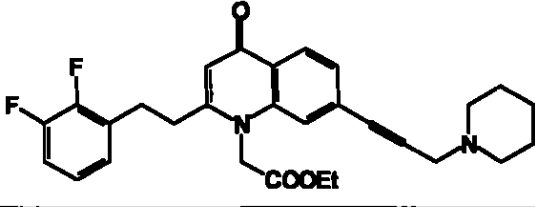
Los siguientes intermediarios se prepararon mediante el método del intermediario A10.

15

99

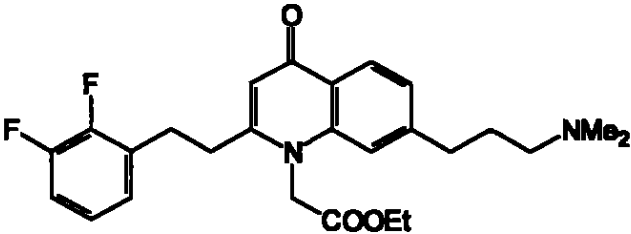
5

10

No.	Precursor	Estructura	Nombre
A90	A9		Acetato de (7-(3-dietilaminoprop-1-inil)-2-(2-(2,3-difluorofenil)-etil)-4-oxo-4 <i>H</i> -quinolin-1-il)etilo
A91	A9		Acetato de (7-(3-pirrolidin-1-il)prop-1-inil)-2-(2-(2,3-difluorofenil)-etil)-4-oxo-4 <i>H</i> -quinolin-1-il)etilo
A92	A9		Acetato de (7-(3-piperidin-1-il)prop-1-inil)-2-(2-(2,3-difluorofenil)-etil)-4-oxo-4 <i>H</i> -quinolin-1-il)etilo

Intermediario A11 – Acetato de (2-(2-(2,3-difluorofenil)etil)-7-(3-dimetilaminopropil)-4-oxo-4*H*-quinolin-1-il)etilo

15



20

Una mezcla del intermediario A10 (0.39 g, 0.86 mmoles) y Pd/C (40 mg) en etanol se hidrogenó a temperatura ambiente y presión hasta que la reacción está completa por HPLC. El catalizador se filtró y el solvente se evaporó para proporcionar el compuesto del título (0.29 g, 73%).

100

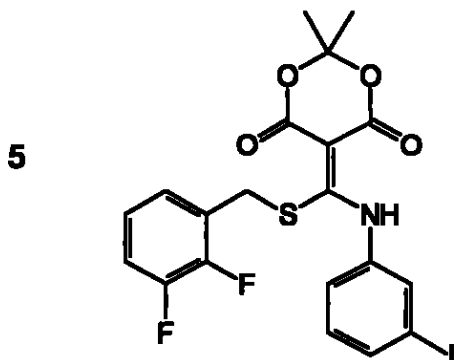
¹H RMN (CDCl₃) δ 1.28 (3H, t), 1.83 (2H, m), 2.24 (6H, s), 2.31 (2H, t), 2.78 (2H, t), 2.92 (2H, m), 3.05 (2H, m), 4.28 (2H, c), 4.90 (2H, s), 6.25 (1H, s), 6.96-7.11 (4H, m), 7.23 (1H, dd), 8.34 (1H, d); MS (APCI+) encontrado (M+1) = 457; C₂₈H₃₀F₂N₂O₃ requerido 456.

5 Los siguientes intermediarios se prepararon mediante el método del intermediario A11.

10

15

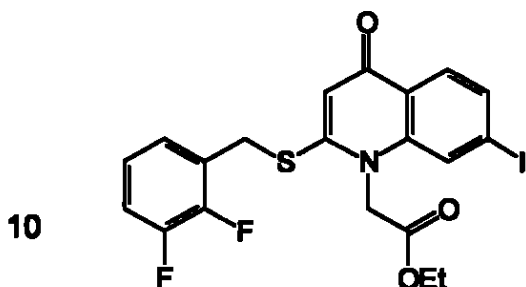
No.	Precursor	Estructura	Nombre
A100	A90		Acetato de (7-(3-diethylaminopropil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo
A101	A91		Acetato de (7-(3-pirrolidin-1-il)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo
A102	A92		Acetato de (7-(3-piperidin-1-il)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo

Intermediario A12 - 5-((2,3-difluorobencilidío)-(3-yodofenilamino)metilén)-**2,2-dimetil-1,3-dioxan-4,6-diona**

A una solución del ácido de Meldrum (13.4 g, 93 mmoles) en N-
 10 metilpirrolidinona (50 ml), enfriada a 15°C, se agregó *N,N*-diisopropiletilamina
 (15 ml, 86 mmoles). La mezcla se agitó a 15°C durante 1 hora, a continuación
 se agregó una solución de isotiocianato de 3-yodofenilo (20.9 g, 80 mmoles)
 en N-metilpirrolidinona (90 ml). La mezcla se agitó a temperatura ambiente
 durante 16 horas, a continuación se enfrió a 10°C. Se agregó bromuro de 2,3-
 15 difluorobencilo (16.5 g, 80 mmoles) durante 20 minutos. La mezcla de
 reacción se agitó a temperatura ambiente durante 3 horas, a continuación se
 vertió en una mezcla de EtOAc y agua. La fase acuosa se extrajo con EtOAc
 y las fases orgánicas combinadas se lavaron dos veces con agua, a
 continuación con salmuera, se secaron (Na₂SO₄) y se evaporaron. El aceite
 20 residual se agitó con Et₂O, el sólido resultante se recolectó mediante filtración
 para proporcionar el compuesto del título (36 g).

^1H RMN (CDCl_3) δ 1.77 (6H, s), 4.07 (2H, s), 6.9-7.2 (4H, m), 7.2-7.3 (1H, amplio), 7.6-7.75 (2H, amplio), 12.8 (1H, s); MS (APCI-) encontrado (M-1) = 530; $\text{C}_{20}\text{H}_{18}\text{F}_2\text{INO}_4\text{S}$ requerido 531.

5 **Intermediario A13 – Acetato de (7-yodo-2-(2,3-difluorobenciltio)-4-oxo-4H-quinolin-1-il)etilo**



A una solución del intermediario A12 (20 g, 38 mmoles) en NMP (50 ml) se agregó ter-butóxido de potasio (4.54 g, 40 mmoles). La mezcla se agitó a temperatura ambiente durante 1 hora, a continuación se agregó bromoacetato de etilo (4.6 ml, 40 mmoles). La mezcla se agitó a 70°C durante 8 horas. Se agregó EtOAc a la mezcla de reacción enfriada, la cual se lavó con agua, a continuación con salmuera, y se evaporó. El aceite residual se agitó con Et_2O , el sólido resultante se recolectó mediante filtración para proporcionar un sólido (13.6 g). A una solución de este sólido (9.6 g) en CH_2Cl_2 (80 ml) a reflujo, se agregó ácido trifluorometansulfónico (1.72 ml) en porciones durante 90 minutos. Después de 2 horas adicionales a reflujo, la mezcla de reacción se enfrió y se vertió en una mezcla de bicarbonato de sodio saturado y CH_2Cl_2 . La fase orgánica se lavó con agua, se secó

15

20

103

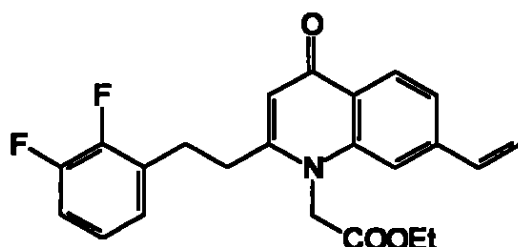
(Na₂SO₄) y se evaporó. La cromatografía (gel de sílice, MeOH/CH₂Cl₂) proporcionó el acetato de 2-(2-(2,3-difluorofenil)etil)-5-yodo-4-oxo-4*H*-quinolin-1-il)etilo (2.05 g) como el isómero que eluye antes, seguido por acetato de 2-(2,3-difluorobencilitio)-7-yodo-4-oxo-4*H*-quinolin-1-il)etilo (compuesto del título)

5 (1.1 g).

¹H RMN (CDCl₃) δ 1.31 (3H, t), 4.28 (2H, s), 4.30 (2H, c), 5.08 (2H, s amplio), 6.40 (1H, s), 7.02-7.19 (3H, m), 7.56 (1H, s), 7.69 (1H, d), 8.08 (1H, d); MS (APCI+) encontrado (M+1) = 516; C₂₀H₁₆F₂INO₃S requerido 515.

10 **Intermediario A110 – Acetato de (7-vinil-2-(2-(2,3-difluorofenil)etil)-4-oxo-4*H*-quinolin-1-il)etilo**

15



Una mezcla del intermediario A9 (0.6 g, 1.33 mmoles), tributil(vinil)estaño (1.0 ml, 3.42 mmoles) y cloruro de bis(trifenilfosfin)paladio (II) (0.1 g) en NMP (8 ml), se agitó a 100°C durante 1 hora. Después de enfriar la mezcla, se diluyó con acetato de etilo, se lavó con agua, a continuación con salmuera, se secó (MgSO₄) y se evaporó. La cromatografía (gel de sílice, MeOH/CH₂Cl₂), a continuación la cristalización (EtOAc) proporcionó el compuesto del título como un sólido gris claro (0.357 g, 67%).

20

80A

¹H RMN (CDCl₃) δ 1.29 (3H, t), 2.92-2.97 (2H, m), 3.03-3.09 (2H, m), 4.30 (2H, c), 4.91 (2H, s), 5.45 (1H, d), 5.90 (1H, d), 6.26 (1H, s), 6.80 (1H, dd), 6.96-7.11 (3H, m), 7.18 (1H, s), 7.50 (1H, d), 8.39 (1H, d); MS (APCI+) encontrado (M+1) = 398; C₂₃H₂₁F₂NO₃ requerido 397.

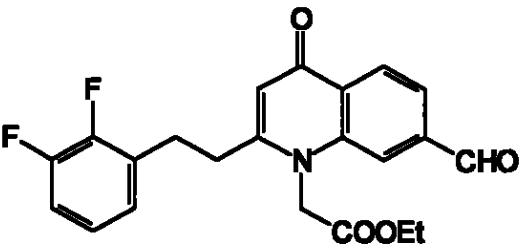
5 Los siguientes intermediarios se prepararon mediante el método del intermediario A110.

10

No.	Precursor	Estructura	Nombre
A111	A9		Acetato de (7-ali-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo
A112	A13		Acetato de (2-(2,3-difluorobencitio)-7-vinil-4-oxo-4H-quinolin-1-il)etilo

15 Intermediario A120 – Acetato de (7-formil-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo

20



A una solución del intermediario A110 (0.549 g, 1.38 mmoles) en una mezcla de acetona, agua y ter-butanol (30 ml, relación 4:2:1) se agregó

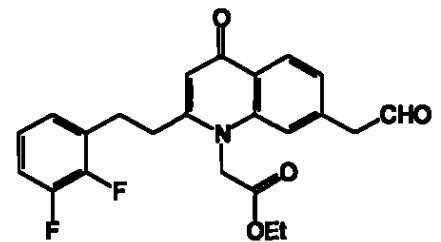
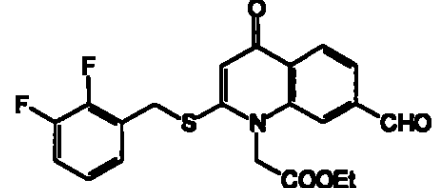
N-óxido de 4-metilmorfolina (0.336 g, 2.87 mmoles) y tetróxido de osmio (solución al 2.5% en peso en ter-butanol, 0.34 ml). La mezcla de reacción se agitó a temperatura ambiente durante 5 horas. Se agregó una solución de metabisulfito de sodio (10% en peso en agua, 17 ml), y la mezcla se agitó 5 durante 1 hora. Se agregaron agua (100 ml) y una mezcla de CH₂Cl₂ y MeOH (150 ml, 9:1). La capa acuosa se extrajo con tres porciones adicionales de CH₂Cl₂ y MeOH (9:1). Los extractos orgánicos se combinaron y evaporaron para proporcionar un producto, el cual se suspendió en THF (21 ml) y se agregó una solución de peryodato sódico (0.535 g, 2.5 mmoles) en agua (7 10 ml). La mezcla se agitó a temperatura ambiente durante 1 hora.. Se agregó agua y EtOAc, a continuación la fase orgánica se lavó con salmuera, se secó (Na₂SO₄) y se evaporó para proporcionar el compuesto del título (0.522 g, 95%).

¹H RMN (CDCl₃) δ 1.32 (3H, t), 2.95-2.99 (2H, m), 3.05-3.10 (2H, 15 m), 4.32 (2H, c), 5.00 (2H, s), 6.33 (1H, s), 6.96-7.13 (3H, m), 7.81 (1H, s), 7.86 (1H, d), 8.61 (1Hd, d), 10.15 (1H, s); MS (APCI+) encontrado (M+1) = 400; C₂₂H₁₉F₂NO₄ requerido 399.

Los siguientes intermediarios se prepararon mediante el método del intermediario A120.

106

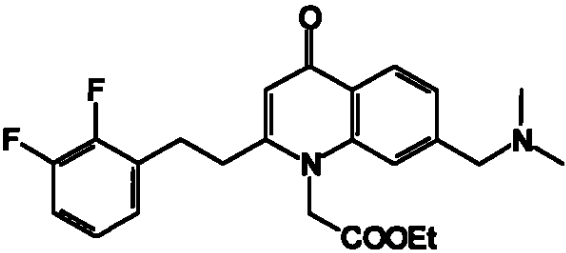
5

No.	Precursor	Estructura	Nombre
A121	A111		Acetato de (7-formilmetil-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo
A122	A112		Acetato de (2-(2,3-difluorobenciltio)-7-formil-4-oxo-4H-quinolin-1-il)etilo

10

Intermediario A130 – Acetato de (7-dimetilaminometil-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo

15



20

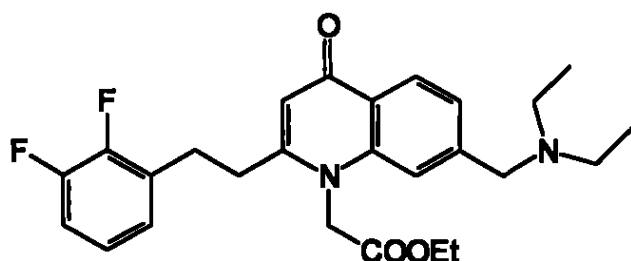
Una mezcla del intermediario A120 (0.07 g, 0.175 mmoles), clorhidrato de dimetilamina (0.041 g, 0.525 mmoles), triacetoxiborohidruro de sodio (0.074g, 0.35 mmoles) y ácido acético (0.01 ml) en DMF (1 ml) y THF (3 ml) se agitó a temperatura ambiente durante 16 horas, a continuación se evaporó bajo presión reducida. El residuo se agitó con EtOAc y carbonato de potasio acuoso. La fase orgánica se lavó con agua, a continuación con

salmuera, se secó (K_2CO_3) y se evaporó. La cromatografía (sílica, $CH_2Cl_2/MeOH/NH_3$) proporcionó el compuesto del título (0.0644 g, 86%).

^1H RMN ($CDCl_3$) δ 1.29 (3H, t), 2.25 (6H, s), 2.91-2.96 (2H, m), 3.01-3.07 (2H, m), 3.54 (2H, s), 4.28 (2H, c), 4.94 (2H, s), 6.25 (1H, s), 6.95-7.11 (3H, m), 7.28 (1H, s), 7.32 (1H, d), 8.38 (1H, d); MS (APCI+) encontrado (M+1) = 429; $C_{24}H_{28}F_2N_2O_3$ requerido 428.

Intermediario A131 – Acetato de (7-(dietilaminometil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etil

10



15

A una mezcla del intermediario A120 (0.2 g, 0.5 mmoles), ácido acético (0.03 ml) y dietilamina (0.155 ml, 1.5 mmoles) en CH_2Cl_2 (15 ml) se le agregó triacetoxiborohidruro de sodio (0.212 g, 1.0 mmoles) en porciones durante 10 minutos. Después de agitar a temperatura ambiente durante 16 horas, se agregó bicarbonato de sodio saturado. La fase orgánica se lavó con

20 agua, se secó (K_2CO_3) y se evaporó. La cromatografía (sílica, $CH_2Cl_2/MeOH/NH_3$) proporcionó el compuesto del título (0.2 g, 87%).

^1H RMN ($CDCl_3$) δ 1.04 (6H, t), 1.29 (3H, t), 2.53 (4H, c), 2.91-2.96 (2H, m), 3.03-3.08 (2H, m), 3.68 (2H, s), 4.28 (2H, c), 4.93 (2H, s), 6.25

108

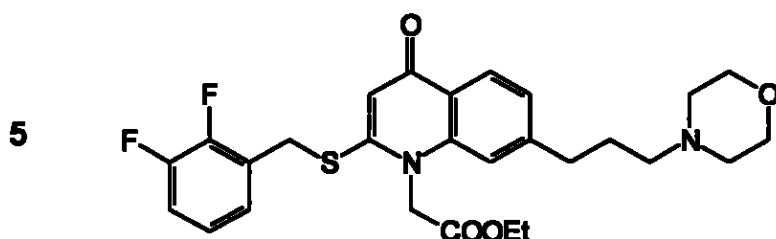
(1H, s), 6.96-7.11 (3H, m), 7.32 (1H, d), 7.37 (1H, s), 8.36 (1H, d); MS (APCI+) encontrado (M+1) = 457; C₂₈H₃₀F₂N₂O₃ requerido 456.

Los siguientes intermediarios se prepararon mediante el método del intermediario A131.

5				
	No.	Precursor	Estructura	Nombre
	A132	A120		Acetato de (7-(pirrolidin-1-ilmetil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo
10	A133	A120		Acetato de (7-(pirrolidin-1-ilmetil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo
	A134	A121		Acetato de (7-(2-dimetilaminoetil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo
15	A135	A121		Acetato de (7-(2-dietilaminoetil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo
	A138	A121		Acetato de (7-(2-pirrolidin-1-il)etil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo
20	A137	A122		Acetato de (2-(2,3-difluorobenciltio)-7-dimetilaminometil-4-oxo-4H-quinolin-1-il)etilo

109

Intermediario A140 – Acetato de (2-(2,3-difluorobencilitio)-7-(3-morfolinopropil)-4-oxo-4H-quinolin-1-il)etilo

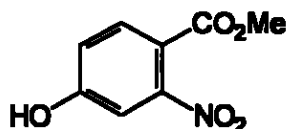


a) A una solución del intermediario A13 (0.4 g, 0.78 mmoles) en DMF (20 ml) se agregan bicarbonato de sodio (0.125 g, 1.5 mmoles),
10 cloruro de benciltriethylamonio (0.18 g, 0.79 mmoles), acetato de paladio (0.04 g, 0.15 mmoles) y alcohol alílico (0.1 ml, 1.5 mmoles). La mezcla se agitó a 50°C durante 2 horas. Se agregaron cantidades adicionales de alcohol alílico (0.1 ml) y acetato de paladio (0.04 g), y la mezcla se agitó durante 2 horas a 50°C, a continuación 16 horas a temperatura ambiente. Se agregó EtOAc, y
15 la mezcla se lavó con agua, a continuación con salmuera, se secó (Na₂SO₄) y se evaporó hasta un aceite (0.3 g). Este se disolvió en diclorometano (25 ml) y se agregó morfolina (0.2 ml, 2.3 mmoles) y ácido acético (0.03 ml). A esta solución se agregó triacetoxiborohidruro de sodio (0.2 g, 0.95 mmoles) en porciones durante 4 horas. Después de agitar a temperatura ambiente
20 durante 16 horas, la mezcla de reacción se lavó sucesivamente con bicarbonato de sodio saturado, agua, salmuera, a continuación se secó (K₂CO₃) y se evaporó. La cromatografía (sílice, EtOAc/MeOH/NH₃) proporcionó el compuesto del título (0.14 g, 40%).

^1H RMN (CDCl_3) δ 1.28 (3H, t), 1.85 (2H, quinteto), 2.35 (2H, t), 2.42 (4H, t amplio), 2.77 (2H, t), 3.72 (4H, t), 4.27 (2H, c), 4.28 (2H, s), 5.12 (2H, s amplio), 6.42 (1H, s), 6.98 (1H, s), 7.01-7.16 (3H, m), 7.23 (1H, d), 8.31 (1H, d); MS (APCI+) encontrado (M+1) = 517; $\text{C}_{27}\text{H}_{30}\text{F}_2\text{N}_2\text{O}_4\text{S}$ requerido 516.

5

Intermediario A15 - 4-Hidroxi-2-nitrobenzoato de metilo



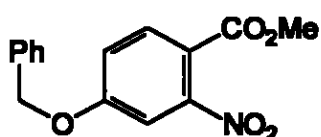
- 10 A una suspensión del ácido 4-amino-2-nitrobenzoico en ácido sulfúrico al 20% (200 ml) a 5-6°C en un baño de hielo, se agregó por goteo una solución de nitrito de sodio (0.5 g) en agua (1.5 ml), asegurándose que la temperatura permanece a $\leq 6^\circ\text{C}$. Tras completar la adición, se obtuvo una solución marrón homogénea, la cual se mantuvo a 5°C durante 20 minutos.
- 15 Esta solución se agregó por goteo a ácido sulfúrico al 40% a 130°C y se mantuvo a esta temperatura durante 30 minutos después de completar la adición. La solución roja se enfrió, se extrajo con acetato de etilo y las capas orgánicas combinadas se lavaron con agua y salmuera, y se secaron sobre MgSO_4 . El solvente se removió bajo presión reducida para proporcionar un
- 20 sólido marrón rojizo (0.58 g). Una porción de este sólido (0.10 g) se mezcló con metanol (5 ml) que contenía ácido sulfúrico concentrado (1 gota), y se calentó a reflujo durante 2 días. La solución se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se lavó con agua y salmuera

adicionales, y se secó sobre MgSO_4 . El solvente se removió bajo presión reducida y el residuo se sometió a cromatografía sobre gel de sílice, eluyendo con acetato de etilo. Esto proporcionó el compuesto del título como un sólido amarillo (0.063 g).

5 ^1H RMN (CDCl_3) δ 3.78 (3H, m), 7.11 (1H, dd), 7.24 (1H, d), 7.78 (1H, d), 11.2 (1H, s); MS (APCI-) encontrado (M-1) = 196; $\text{C}_8\text{H}_7\text{NO}_5$ requerido 197.

Intermediario A16 - 4-Benciloxi-2-nitrobenzoato de metilo

10



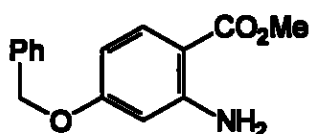
A una mezcla del intermediario A15 (7.0 g), trifenilfosfina (11.2 g) y alcohol bencílico (3.68 ml) en THF seco bajo argón en un baño de hielo, se le agregó azodicarboxilato de dietilo (7.42 g). La solución marrón rojiza oscura formada se agitó a temperatura ambiente durante la noche y el solvente se removió bajo presión reducida. El residuo se extrajo con acetato de etilo, se lavó con agua y salmuera, se secó sobre MgSO_4 , y carbón decolorante y se evaporó bajo presión reducida hasta un aceite marrón. Este material se sometió a cromatografía sobre gel de sílice para proporcionar el compuesto del título (6.17 g).

20 ^1H RMN (CDCl_3) δ 3.87 (3H, m), 5.15 (2H, s), 7.16 (1H, dd), 7.33 (1H, d), 7.3-7.5 (5H, m), 7.77 (1H, d).

132

Intermediario A17 - 2-Amino-4-benciloxibenzoato de metilo

5



A una mezcla del intermediario A16 (6.16 g) y polvo de hierro (17.96 g) en etanol acuoso al 10% (200 ml), se agregó ácido clorhídrico concentrado (1 ml), y la mezcla se sometió a reflujo durante 2 horas y se enfrió a temperatura ambiente. La mezcla se filtró a través de kieselguhr, y el

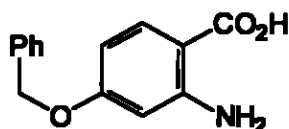
10 filtrado se evaporó bajo presión reducida hasta un sólido negro. Este material se sometió a cromatografía sobre sílice utilizando diclorometano como eluyente para proporcionar el compuesto del título como un sólido amarillo pálido (2.81 g).

^1H RMN (CDCl_3) δ 3.83 (3H, m), 5.05 (2H, s), 5.76 (2H, s amplio),

15 6.18 (1H, d), 6.31 (1H, dd), 7.25-7.5 (5H, m), 7.79 (1H, d).

Intermediario A18 - Acido 2-amino-4-benciloxibenzoico

20



A una solución del intermediario A17 (2.8 g) en metanol (30 ml), se agregó hidróxido de sodio (1.3 g) en agua (30 ml), y la mezcla se calentó a reflujo durante 5 horas. La mezcla se concentró y se diluyó con agua, a

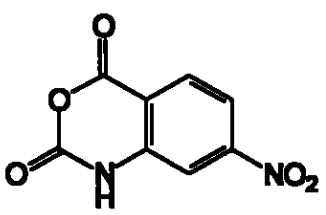
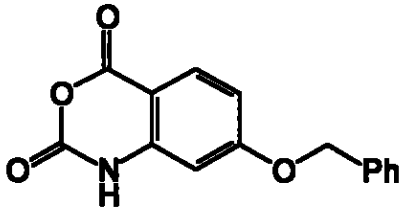
115

continuación se acidificó con ácido clorhídrico 5M. La mezcla se agitó durante 15 minutos, el sólido se filtró y se secó para proporcionar el compuesto del título (2.4 g).

^1H RMN (d_6 -DMSO) δ 5.06 (2H, s), 6.18 (1H, dd), 6.32 (1H, d), 7.2-7.5 (5H, m), 7.62 (1H, d).

Los siguientes intermediarios se prepararon mediante el método del intermediario A5.

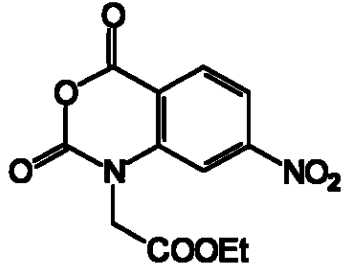
10

No.	Precursor	Estructura	Nombre
A21	Acido 4-nitroantranílico		7-Nitro-1H-benzo[d][1,3]oxazin-2,4-diona
A22	Int. 18		7-Benciloxi-1H-benzo[d][1,3]oxazin-2,4-diona

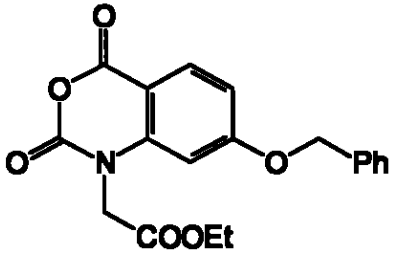
15

Los siguientes intermediarios se prepararon mediante el método del intermediario A6.

20

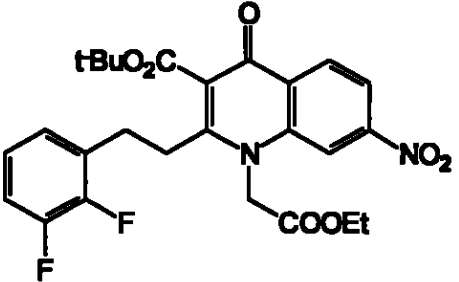
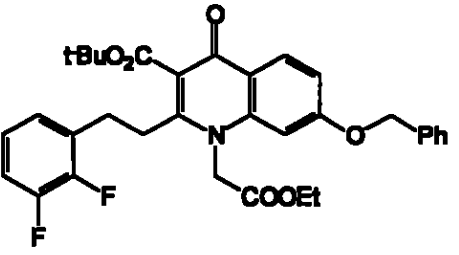
No.	Precursor	Estructura	Nombre
A31	Int. A21		Acetato de (7-nitro-2,4-dioxo-4H-benzo[d][1,3]oxazin-1-il)etilo

LA

A32	Int. A22		Acetato de (7-benciloxi-2,4-dioxo-4 <i>H</i> -benzo[d][1,3]-oxacin-1-il)etilo
-----	----------	---	---

5

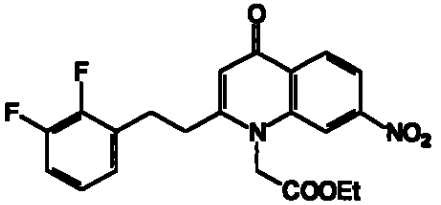
Los siguientes intermediarios se prepararon mediante el método del intermediario A8.

No.	Precursor	Estructura	Nombre
A41	Int. A31		(7-Nitro-2-(2-(2,3-difluorofenil)etil)-1-etoxi-carbonil-4-oxo-4 <i>H</i> -quinolin-1-il)-3-carboxilato de <i>ter</i> -butilo
A42	Int. A32		(7-Benciloxi-2-(2-(2,3-difluorofenil)etil)-1-etoxi-carbonil-4-oxo-4 <i>H</i> -quinolin-1-il)-3-carboxilato de <i>ter</i> -butilo

10

15

Los siguientes intermediarios se prepararon mediante el método del intermediario A9.

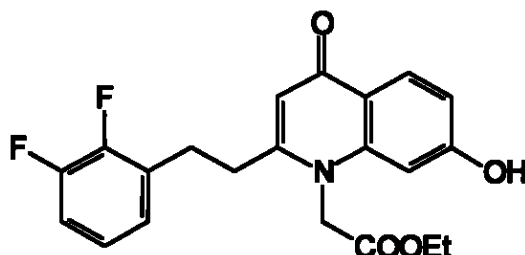
No.	Precursor	Estructura	Nombre
A51	Int. A41		Acetato de (7-nitro-2-(2-(2,3-difluorofenil)etil)-4-oxo-4 <i>H</i> -quinolin-1-il)etilo

20

A52	Int. A42		Acetato de (7-benciloxi-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)etilo
-----	----------	--	--

5 **Intermediario A61 – Acetato de (2-(2-(2,3-difluorofenil)etil)-7-hidroxi-4-oxo-4H-quinolin-1-il)etilo**

10



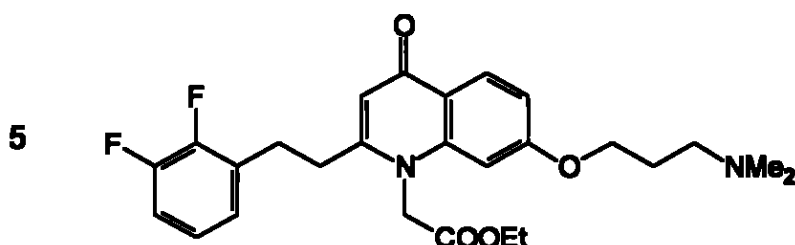
15

A una solución del intermediario A52 (0.235 g) en dimetilformamida (DMF) (5 ml), se agregó Pd/C al 10% que contiene 55% de agua (0.23 g), y la mezcla se hidrogenó a temperatura ambiente y presión durante 0.5 horas. La mezcla se filtró a través de kieselguhr, y el kieselguhr se lavó con DMF adicional. El filtrado se evaporó bajo presión reducida para proporcionar el compuesto del título un sólido amarillo pálido (0.192 g).

20

^1H RMN (d_6 -DMSO) δ 1.22 (3H, t), 2.98 (4H, s amplio), 4.21 (2H, c), 5.09 (2H, s amplio), 5.89 (1H, d), 6.70 (1H, d), 6.83 (1H, m), 7.05-7.4 (3H, m), 7.98 (1H, d), 10.35 (1H, s).

Intermediario A71 – Acetato de (2-(2-(2,3-difluorofenil)etil)-7-(3-(dimetilamino)propoxi)-4-oxo-4H-guinolin-1-il)etilo



A una solución del intermediario A61 (0.25 g) en dimetilformamida seca (4 ml) a temperatura ambiente bajo argón, se agregó

10 trifenilfosfina (0.508 g) y 3-dimetilaminopropan-1-ol (0.1 g) en DMF seco (2 ml). Se agregó azodicarboxilato de dietilo (0.337 g) en DMF seco (2 ml) durante 15 minutos. La mezcla anaranjada/roja oscura se mantuvo a temperatura ambiente durante 21 horas y se evaporó bajo presión reducida. El residuo se dividió entre diclorometano y agua. La capa acuosa se extrajo

15 con diclorometano adicional, y los extractos orgánicos combinados se lavaron con agua y salmuera, y se secaron sobre MgSO_4 . La evaporación bajo presión reducida y la cromatografía sobre gel de sílice utilizando diclorometano:metanol como eluyente proporcionaron una goma que se trituró con éter dietílico y hexano (1:1), para proporcionar el compuesto del título

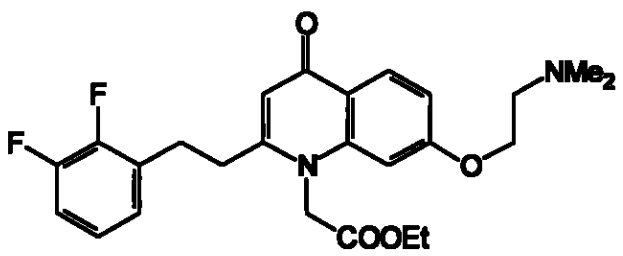
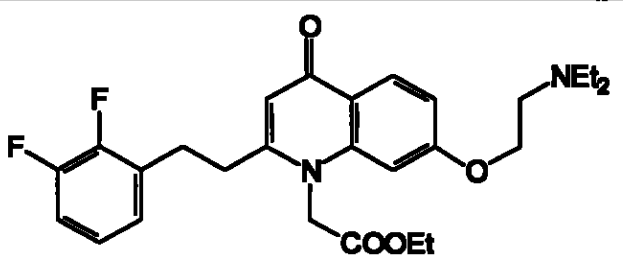
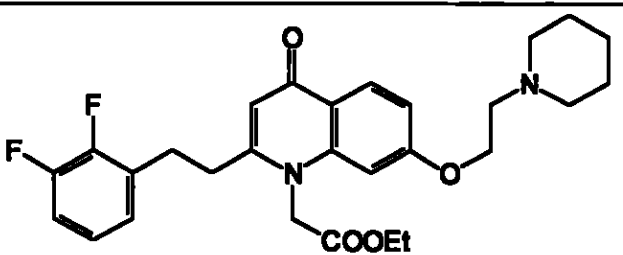
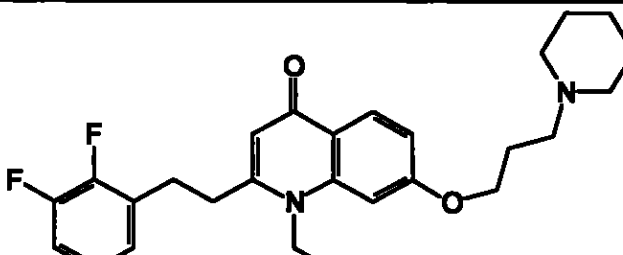
20 como un sólido anaranjado (0.179 g).

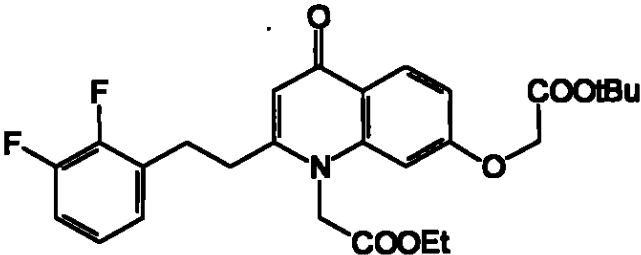
^1H RMN (CDCl_3) δ 1.29 (3H, t), 2.00 (2H, dt), 2.28 (6H, m), 2.48 (2H, t), 2.85-3.15 (4H, m), 4.11 (2H, t), 4.29 (2H, c), 4.85 (2H, s), 6.21 (1H, s),

117

6.64 (1H, d), 6.9-7.2 (4H, m), 8.35 (1H, d); MS (APCI+) encontrado (M+1) = 473; C₂₈H₃₀F₂N₂O₄ requerido 472.

Los siguientes intermediarios se prepararon mediante el método del intermediario A71 a partir del intermediario A61.

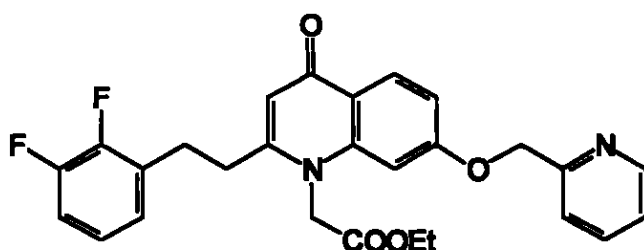
5	No.	Estructura	Nombre
	A72		Acetato de (2-(2-(2,3-difluorofenil)etil)-7-(2-dimetilaminoetoxi)-4-oxo-4 <i>H</i> -quinolin-1-il)etilo
10	A73		Acetato de (7-(2-dietilaminoetoxi)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4 <i>H</i> -quinolin-1-il)etilo
15	A74		Acetato de (2-(2-(2,3-difluorofenil)etil)-7-(2-(piperidin-1-il)etoxi)-4-oxo-4 <i>H</i> -quinolin-1-il)etilo
20	A75		Acetato de (2-(2-(2,3-difluorofenil)etil)-7-(3-(piperidin-1-il)propoxi)-4-oxo-4 <i>H</i> -quinolin-1-il)etilo

A76		Acetato de 2-(2-(2-(2,3-difluorofenil))-1-(etoxicarbonilmetil)-4-oxo-4H-quinolin-7-iloxy)ter-butilo
-----	--	---

5

Intermediario A85 – Acetato de (2-(2-(2,3-difluorofenil)etil)-7-(piridin-2-ilmetoxi)-4-oxo-4H-quinolin-1-il)etilo

10



A una suspensión del intermediario A61 (0.2 g) en DMF seca (4 ml) bajo argón, se agregó hidruro de sodio (0.025 g) a temperatura ambiente para formar una solución marrón. La mezcla se agitó a temperatura ambiente durante 15 minutos y se agregó bromhidrato de 2-(bromometil)piridina (0.157 g). Después de agitar a temperatura ambiente durante 1.5 horas, la mezcla se evaporó bajo presión reducida y se dividió entre diclorometano y salmuera diluida. La capa acuosa se extrajo con diclorometano adicional, y los extractos orgánicos combinados se lavaron con agua y salmuera y se secaron sobre MgSO₄. La evaporación bajo presión reducida, seguida por trituración (1:1 éter dietílico:hexano) del residuo formado, proporcionó el compuesto del título como un sólido amarillo (0.186 g).

8/19

¹H RMN (CDCl₃) δ 1.29 (3H, t), 2.8-3.0 (2H, m), 3.0-3.1 (2H, m), 4.26 (2H, c), 4.82 (2H, s amplio), 5.29 (2H, s), 6.21 (1H, s), 6.78 (1H, d), 6.9-7.15 (4H, m), 7.27 (1H, m), 7.51 (1H, d), 7.74 (1H, dt), 8.37 (1H, d), 8.63 (1H, m); MS (APCI+) encontrado (M+1) = 749; C₂₇H₂₄F₂N₂O₄ requerido 748.

5 Los siguientes intermediarios se prepararon mediante el método del intermediario A85.

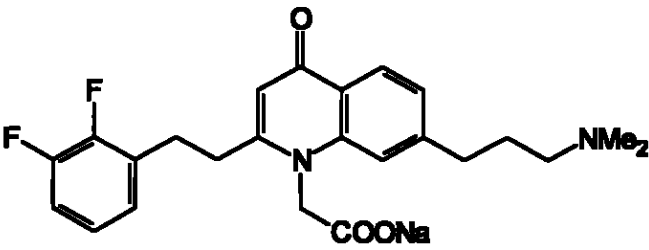
10

No.	Precursor	Estructura	Nombre
A86	Int. A61		Acetato de (2-(2-(2,3-difluorofenil)-etil)-7-(5-metil-isoxazol-3-il-metoxi)-4-oxo-4H-quinolin-1-il)etilo
A87	Int. A61 4-bromoetilo piperidina.HBr		Acetato de (2-(2-(2,3-difluorofenil)-etil)-7-(1-metil-pirrolidin-2-il-metoxi)-4-oxo-4H-quinolin-1-il)etilo

15

Intermediario B1 – Acetato de (2-(2-(2,3-difluorofenil)etil)-7-(3-dimetilamino-propil)-4-oxo-4H-quinolin-1-ilo) sódico.

20

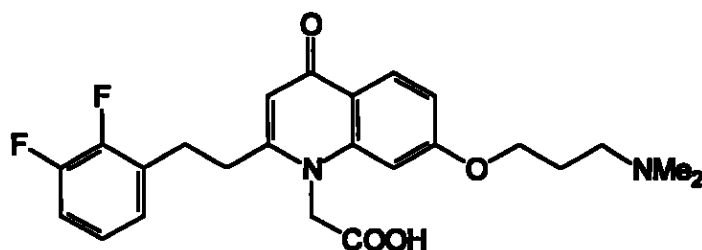


120

Una solución del intermediario A11 (0.29 g, 0.64 mmoles) e hidróxido de sodio (0.03 g, 0.7 mmoles) en dioxano (8 ml) y agua (3 ml), se agitó a temperatura ambiente durante 3 horas. El solvente se evaporó para proporcionar el compuesto del título (0.3 g, 100%).

¹H RMN (d₆-DMSO) δ 1.74 (2H, m), 2.13 (6H, s), 2.20 (2H, t), 2.69 (2H, t), 2.96 (2H, m), 3.05 (2H, m), 4.50 (2H, s), 5.87 (1H, s), 7.10-7.35 (5H, m), 8.03 (1H, d).

Intermediario B2 – Clorhidrato del ácido (2-(2-(2,3-difluorofenil)etil)-7-(3-(dimetilamino)propoxi)-4oxo-4H-quinolin-1-il)acético



A una solución agitada del intermediario A71 (0.161 g) en metanol (5 ml), se agregó hidróxido de sodio 0.5M (1.37 ml). Después de 3 horas, la mezcla se evaporó bajo presión reducida, se agregó agua y la solución se acidificó (ácido clorhídrico 2M) a pH 1, y el precipitado formado se centrífugo para proporcionar el compuesto del título (0.137 g).

¹H RMN (d₆-DMSO) δ 2.1-2.3 (2H, amplio), 2.79 (6H, s), 3.03 (4H, s amplio), 3.15-3.3 (2H, amplio), 4.1-4.3 (2H, amplio), 5.20 (2H, s amplio),

22

6.08 (1H, s amplio), 6.9-7.4 (5H, m), 8.11 (1H, d); MS (APCI-) encontrado (M-1) = 443; C₂₄H₂₆F₂N₂O₄ requerido 444.

El intermediario siguiente se preparó mediante el método del intermediario B1.

5

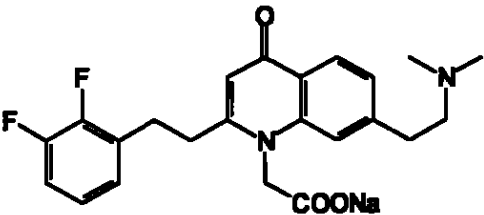
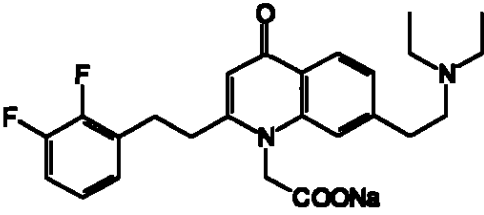
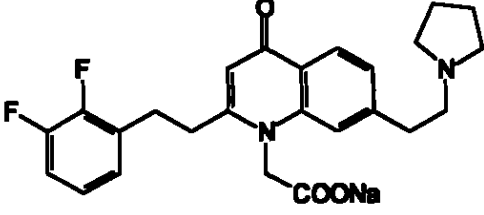
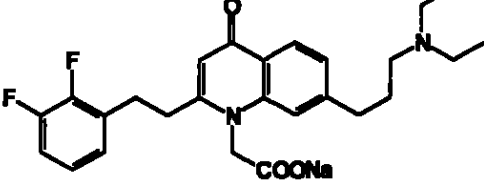
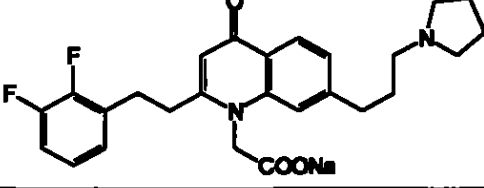
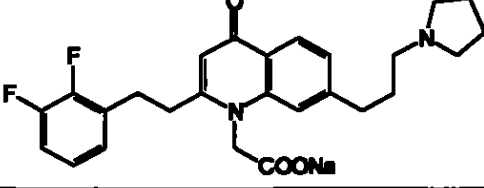
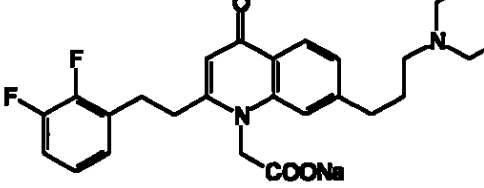
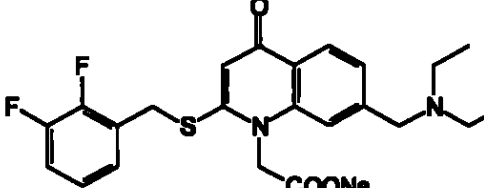
10

15

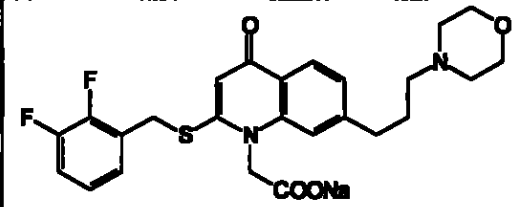
20

No.	Precursor	Estructura	Nombre
B3	Int. A51		Acetato de (7-nitro-2-(2-(2,3-difluorofenil)-etil)-4-oxo-4H-quinolin-1-ilo) sódico
B20	Int. A130		Acetato de (7-(dimetilaminometil)-2-(2-(2,3-difluorofenil)-etil)-4-oxo-4H-quinolin-1-ilo) sódico
B21	Int. A131		Acetato de (7-(dietilaminometil)-2-(2-(2,3-difluorofenil)-etil)-4-oxo-4H-quinolin-1-ilo) sódico
B22	Int. A132		Acetato de (7-((pirrolidin-1-il)metil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-ilo) sódico
B23	Int. A133		Acetato de (7-((piperidin-1-il)metil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-ilo) sódico

122

5	B24	Int. A134		Acetato de (7-(2-dimetilaminoetil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-ilo) sódico
	B25	Int. A135		Acetato de (7-(2-dietilaminoetil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-ilo) sódico
	B26	Int. A136		Acetato de (7-(2-(pirrolidin-1-il)etil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-ilo) sódico
10	B27	Int. A100		Acetato de (7-(3-dietilaminopropil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-ilo) sódico
	B28	Int. A101		Acetato de (7-(3-(pirrolidin-1-il)-propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-ilo) sódico
15	B28	Int. A101		Acetato de (7-(3-(pirrolidin-1-il)-propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-ilo) sódico
	B29	Int. A102		Acetato de (7-(3-(piperidin-1-il)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-ilo) sódico
20	B30	Int. A137		Acetato de (7-(dielaminometil)-2-(2,3-difluorobenciltio)-4-oxo-4H-quinolin-1-ilo) sódico

83

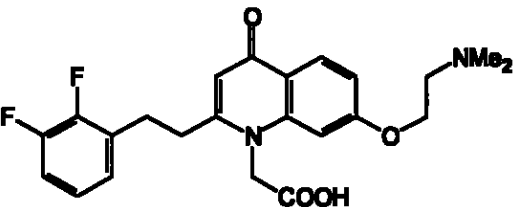
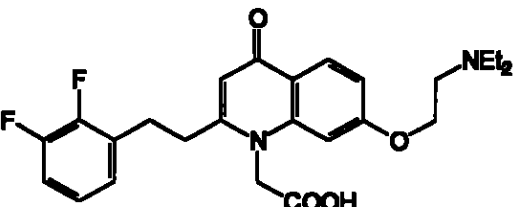
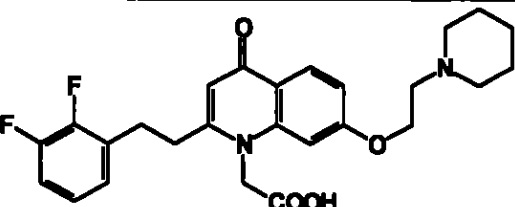
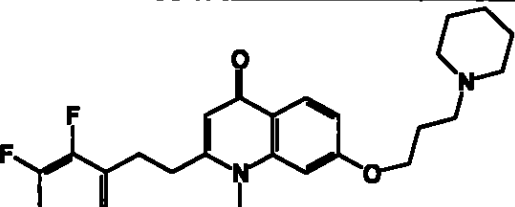
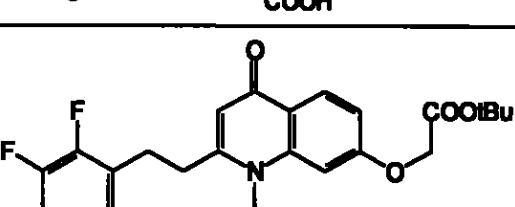
B31	Int. A140		Acetato de (7-(3-(4-morfolino)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-ilo) sódico
-----	-----------	--	---

5 Los siguientes intermediarios se prepararon mediante el método del intermediario B2.

10

15

20

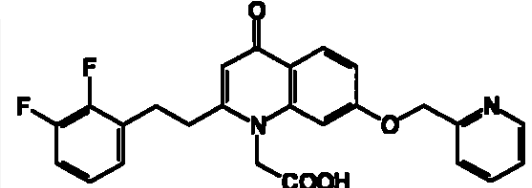
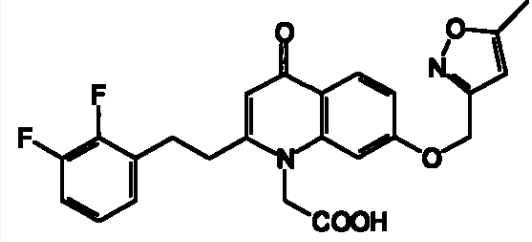
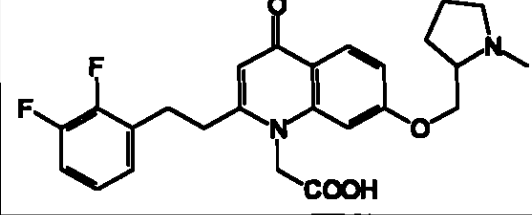
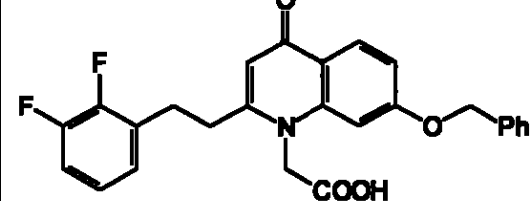
No.	Precursor	Estructura	Nombre
B10	Int. A72		Acido (2-(2-(2,3-difluorofenil)etil)-7-(2-dimetilaminoetoxi)-4-oxo-4H-quinolin-1-il)acético
B11	Int. A73		Acido (7-(2-dietilaminoetoxi)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)acético
B12	Int. A74		Acido (2-(2-(2,3-difluorofenil)etil)-7-(2-(piperidin-1-il)-etoxi)-4-oxo-4H-quinolin-1-il)acético
B13	Int. A75		Acido (2-(2-(2,3-difluorofenil)etil)-7-(3-(piperidin-1-il)-propoxi)-4-oxo-4H-quinolin-1-il)acético
B14	Int. A76		Acido (7-(ter-butoxicarbonilmetoxi)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)acético

1218

5

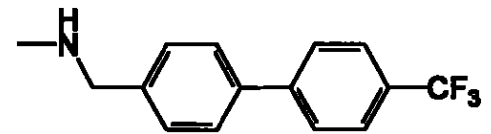
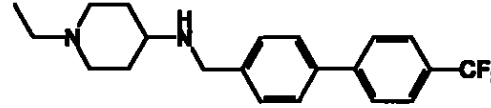
10

15

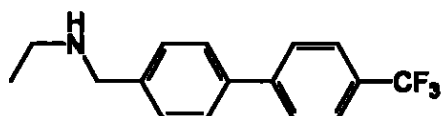
B15	Int. A85		Acido (2-(2-(2,3-difluorofenil)etil)-7-(piridin-2-ilmetoxi)-4-oxo-4H-quinolin-1-il)acético
B16	Int. A86		Acido (2-(2-(2,3-difluorofenil)etil)-7-(5-metilisoxazol-3-ilmetoxi)-4-oxo-4H-quinolin-1-il)acético
B17	Int. A87		Acido (2-(2-(2,3-difluorofenil)etil)-7-(1-metilpirrolidin-2-ilmetoxi)-4-oxo-4H-quinolin-1-il)acético
B18	Int. A52		Acido (7-benciloxi-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)acético

Las siguientes aminas se conocen en la literatura.

20

No.	Precursor	Estructura	Nombre
C1	WO00/68567		4-(4-Trifluorometil-fenil)-N-metilbencil-amina
C2	WO01/60805		N-(1-Etil-piperidin-4-il)-4-(4-trifluorometilfenil)bencil-amina

25

Intermediario C3 - 4-(4-Trifluorometilfenil)-N-etilbencilamina

5 A una solución de 4-(4-trifluorometilfenil)benzaldehído (5.0 g, 20 mmoles) en CH_2Cl_2 (100 ml), se agregó una solución de etilamina en THF (2M, 20 ml, 40 mmoles). Se agregan tamices moleculares de 4Å (15 g) y la mezcla se agitó suavemente durante 16 horas. La mezcla se filtró a través de celite, y el filtrado se evaporó. El residuo se disolvió en etanol (200 ml), y se

10 agregó borohidruro de sodio (1.3 g, 30 mmoles) en porciones durante 10 minutos. La mezcla se agitó a temperatura ambiente durante 1 hora, a continuación se concentró. Se agregaron CH_2Cl_2 y agua, la fase orgánica se lavó con agua, se secó (K_2CO_3) y se evaporó para proporcionar el compuesto del título como un sólido blanco. (4.9 g, 88%).

15 ^1H RMN (CDCl_3) δ 1.16 (3H, t), 2.72 (2H, c), 3.85 (2H, s), 7.43 (2H, d), 7.56 (2H, d), 7.68 (4H, s); MS (APCI+) encontrado ($\text{M}+1$) = 280; $\text{C}_{18}\text{H}_{18}\text{F}_3\text{N}$ requerido 279.

El siguiente intermediario se preparó mediante el método del intermediario C3.

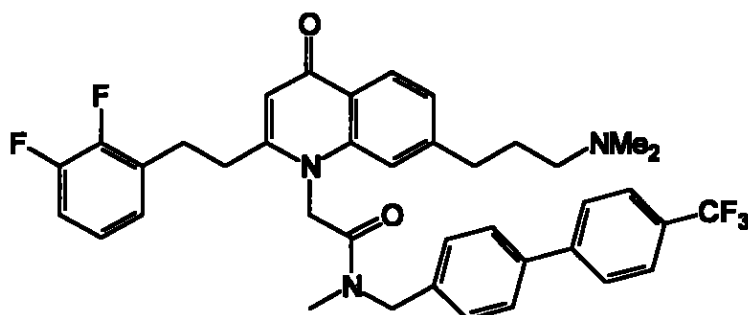
20

No.	Estructura	Nombre
C4		4-(4-Trifluorometilfenil)-N-isopropilbencilamina

EJEMPLO 1

Bitartrato de la N-metil-2-(2-(2-(2,3-difluorofenil)etil)-7-(3-dimetilaminoprop-1-il)-4-oxo-4H-guinolin-1-il)-N-(4-(4-trifluorometilfenil)bencil)acetamida

5



10

Se agrega hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU) (0.187 g, 0.6 mmoles) a una mezcla del intermediario B1 (0.195 g, 0.43 mmoles), amina C1 (0.115 g, 0.43 mmoles) y diisopropiletilamina (0.18 ml, 1.04 mmoles) en dimetilformamida (10 ml), y la

15 solución resultante se agitó durante 2 horas. El solvente se evaporó y el residuo se diluyó con diclorometano (30 ml) y se lavó sucesivamente con cloruro de amonio saturado y bicarbonato de sodio saturado. La capa orgánica se secó (K₂CO₃) y el solvente se evaporó. El residuo se purificó mediante cromatografía instantánea (NH₃/MeOH/CH₂Cl₂). La amina (0.18 g,

20 0.267 mmoles), se disolvió en metanol (10 ml) y se agregó ácido tartárico (0.04 g, 0.267 mmoles). Después de agitar durante 15 minutos, el solvente se evaporó y el residuo se trituró a partir de éter dietílico para proporcionar el compuesto del título (0.215 g).

827

¹H RMN (d₆-DMSO) δ 1.81 (2H, m), 2.19 (6H, 2x s), 2.27 (2H, m), 2.65 (6H, m), 3.2 (3H, 2x s), 4.12 (2H s), 4.63, 4.81 (2H, 2x s), 5.29, 5.39 (2H, 2x s amplio), 5.99 (1H, 2x s), 7.03-7.88 (13H, m), 8.07 (1H, 2x d); MS (APCI+) encontrado (M+1) = 676; C₃₉H₃₉F₅N₃O₂ requerido 675.

5 Los siguientes ejemplos se prepararon mediante el método del ejemplo 1, utilizando ya sea el ácido original o su sal sódica.

10

15

20

Ej.	Precursores	Estructura	Nombre
2	Int. B2 Amina C1		Bitartrato de la 2-(2-(2-(2,3-difluorofenil)-etil)-4-oxo-7-(3-(dimetilamino)propoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)-acetamida
3	Int. B3 Amina C1		N-Metil-2-(2-(2-(2,3-difluorofenil)etil)-7-nitro-4-oxo-4H-quinolin-1-il)-N-(4-(4-trifluorometilfenil)bencil)-acetamida
4	Int. B10 Amina C1		Bitartrato de la 2-(2-(2-(2,3-difluorofenil)-etil)-7-(2-dimetilaminoetoxi)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)-acetamida

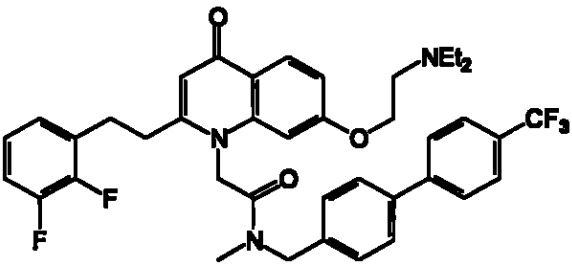
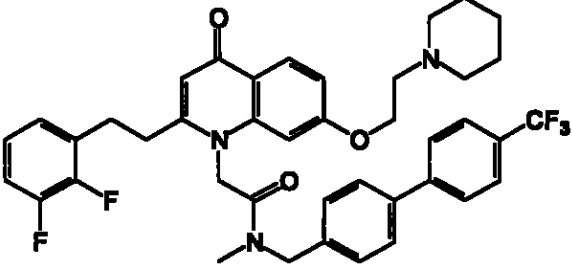
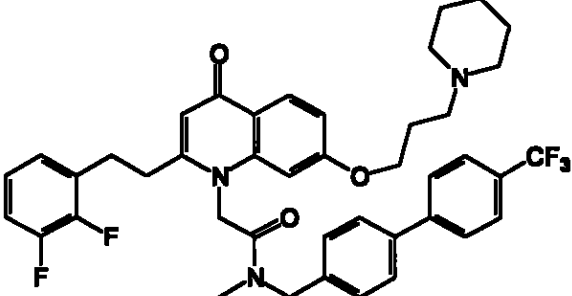
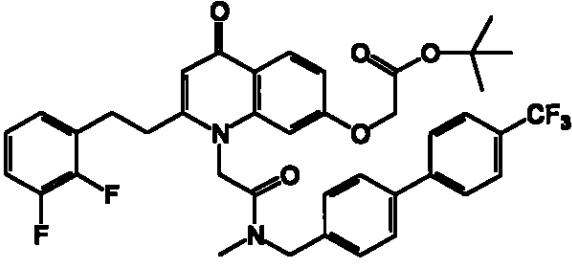
128

5

10

15

20

5	Int. B11 Amina C1		Bitartrato de la 2-(7-(2-dietilamino-etoxi)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
6	Int. B12 Amina C1		Bitartrato de la 2-(2-(2-(2,3-difluorofenil)-etil)-4-oxo-7-(2-(piperidin-1-il)etoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
7	Int. B13 Amina C1		Bitartrato de la 2-(2-(2-(2,3-difluorofenil)-etil)-4-oxo-7-(3-(piperidin-1-il)propoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
8	Int. B14 Amina C1		Acetato de 2-(2-(2-(2,3-difluorofenil)-etil))-1-(N-(4-(4-trifluorometilfenil)-bencil)-N-metil-aminocarbonil-metil)-4-oxo-4H-quinolin-7-iloxi ter-butilo

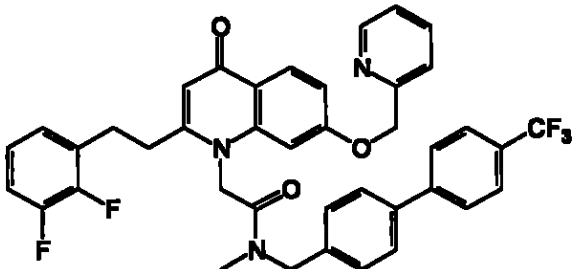
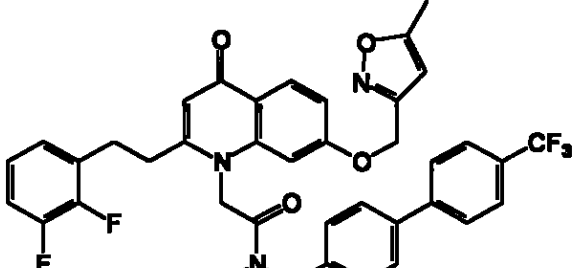
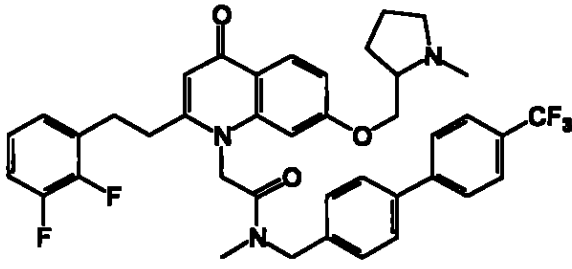
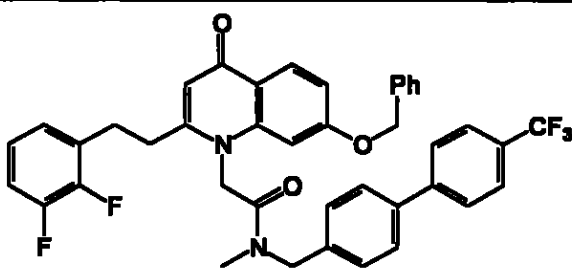
829

5

10

15

20

9	Int. B15 Amina C1		Clorhidrato de la 2-(2-(2-(2,3-difluorofenil)-etil)-4-oxo-7-(piridin-2-ilmetoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)encil)-acetamida
10	Int. B16 Amina C1		2-(2-(2-(2,3-Difluorofenil)-etil)-7-(5-metilisoxazol-3-ilmetoxi)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)encil)-acetamida
11	Int. B17 Amina C1		Bitartrato de la 2-(2-(2-(2,3-difluorofenil)-etil)-7-(1-metil-pirrolidin-2-ilmetoxi)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluoro-metilfenil)-encil)-acetamida
12	Int. B18 Amina C1		2-(7-Benciloxi-2-(2-(2,3-difluorofenil)etil)-4-oxo-4-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)encil)aceta mida

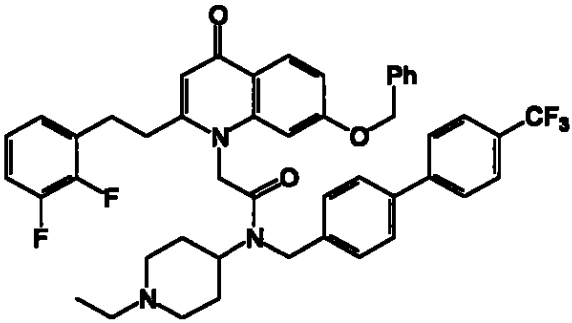
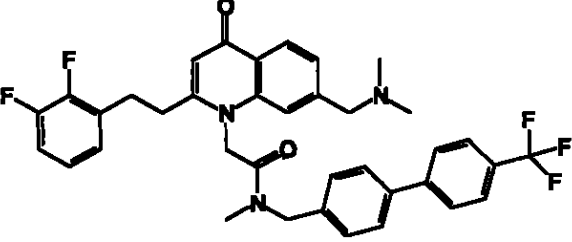
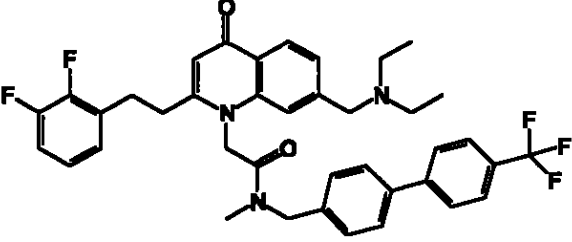
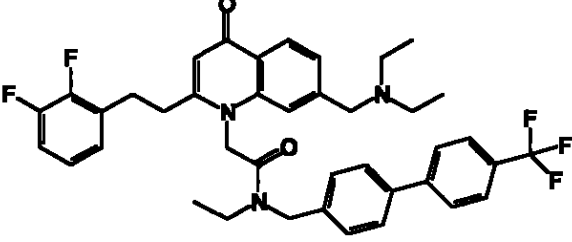
23

5

10

15

20

13	Int. B18 Amina C2		Bitartrato de la 2-(7-benciloxi-2-(2-(2,3-difluorofenil)-etil)-4-oxo-4-quinolin-1-il)-N-(1-etil-piperidin-4-il)-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
20	Int. B20 Amina C1		Bitartrato de la 2-(7-(dimetil-aminometil)-2-(2-(2,3-difluoro-fenil)-etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
21	Int. B21 Amina C1		Bitartrato de la 2-(7-(dietil-aminometil)-2-(2-(2,3-difluoro-fenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
22	Int. B21 Amina C3		Bitartrato de la 2-(7-(dietilamino-metil)-2-(2-(2,3-difluoro-fenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida

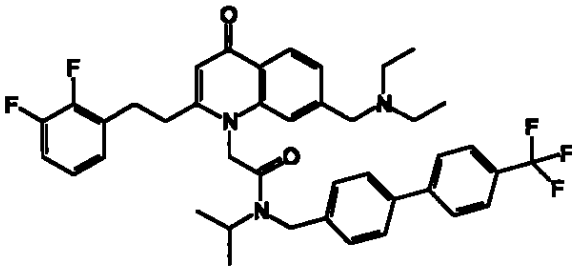
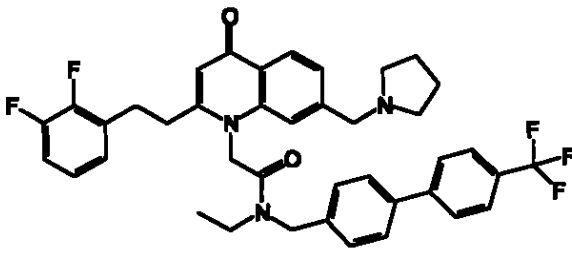
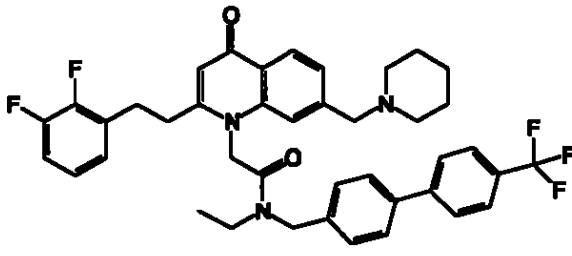
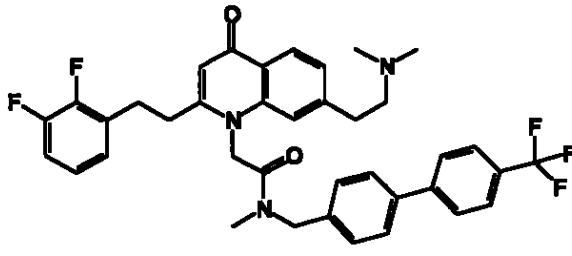
131

5

10

15

20

23	Int. B21 Amina C4		Bitartrato de la 2-(7-(dietilaminometil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-isopropil-N-(4-(4-trifluorometilfenil)-bencil)-acetamida
24	Int. B22 Amina C3		Bitartrato de la 2-(7-((pirrolidin-1-il)metil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometilfenil)-bencil)-acetamida
25	Int. B23 Amina C3		Bitartrato de la 2-(7-((piperidin-1-il)metil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometilfenil)-bencil)-acetamida
26	Int. B24 Amina C1		Bitartrato de la 2-(7-(2-dimetilaminoetil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-bencil)-acetamida

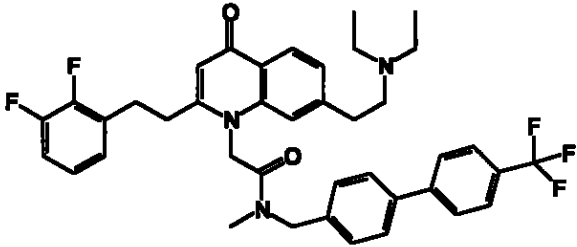
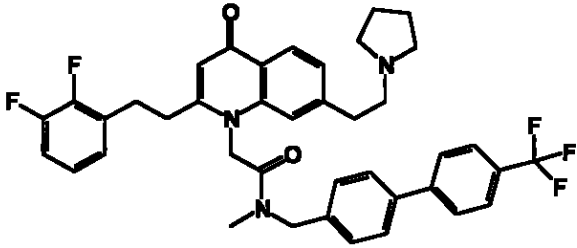
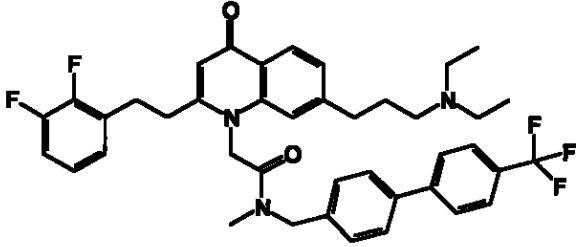
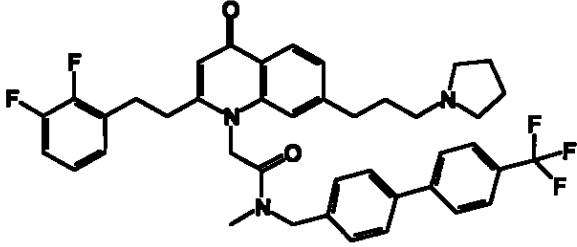
ASV

5

10

15

20

27	Int. B25 Amina C1		Bitartrato de la 2-(7-(2-dietil-aminoetil)-2-(2-(2,3-difluoro-fenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
28	Int. B26 Amina C1		Bitartrato de la 2-(7-(2-(pirrolidin-1-il)etil)-2-(2-(2,3-difluorofenil)-etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
29	Int. B27 Amina C1		Bitartrato de la 2-(7-(3-dietil-aminopropil)-2-(2-(2,3-difluoro-fenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
30	Int. B28 Amina C1		Bitartrato de la 2-(7-(3-(pirrolidin-1-il)propil)-2-(2-(2,3-difluoro-fenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida

5	31	Int. B29 Amina C3		Bitartrato de la 2-(7-(3-(piperidin-1-il)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometilfenil)bencil)-acetamida
10	32	Int. B29 Amina C4		Bitartrato de la 2-(7-(3-(piperidin-1-il)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-isopropil-N-(4-(4-trifluorometilfenil)bencil)-acetamida
15	33	Int. B30 Amina C1		Bitartrato de la 2-(7-(diethylaminometil)-2-(2-(2,3-difluorobenciltio)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)-acetamida
20	34	Int. B31 Amina C1		Clorhidrato de la 2-(7-(3-(4-morfolino)propil)-2-(2,3-difluorobenciltio)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)-acetamida

5

31	Int. B29 Amina C3		Bitartrato de la 2-(7-(3-(piperidin-1-il)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
----	----------------------	--	--

10

32	Int. B29 Amina C4		Bitartrato de la 2-(7-(3-(piperidin-1-il)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-isopropil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
----	----------------------	--	---

15

33	Int. B30 Amina C1		Bitartrato de la 2-(7-(dietil-aminometil)-2-(2,3-difluorobenciltio)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
----	----------------------	--	--

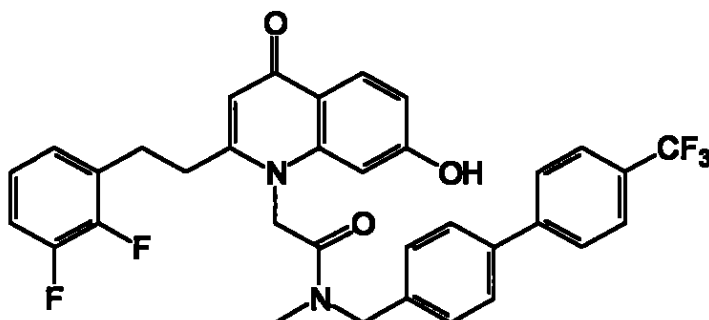
20

34	Int. B31 Amina C1		Clorhidrato de la 2-(7-(3-(4-morfolino)-propil)-2-(2,3-difluorobencil-tio)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-fenil)bencil)-acetamida
----	----------------------	--	---

EJEMPLO 15

2-(2-(2-(2,3-Difluorofenil)etil)-7-hidroxi-4-oxo-4H-guainolín-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida

5



10

A una solución del ejemplo 12 (0.382 g) en dimetilformamida (DMF) (30 ml) se agregó Pd/C al 10% (pasta que contiene 54% de agua), y la mezcla hidrogenada a temperatura ambiente durante 2.5 horas. La mezcla se diluyó con DMF adicional (70 ml), se calentó para disolver cualquier producto precipitado y se filtró a través de Celite y un pequeño tapón de gel de sílice fina. El solvente se removió bajo presión reducida y el residuo se trituró con

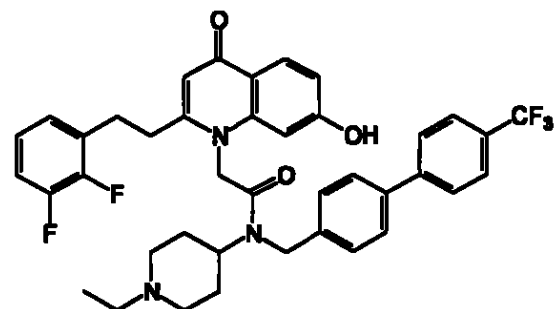
15

20

¹H RMN (d₆-DMSO) δ 2.75-3.1 (4H, m), 3.21 + 3.31 (3H, 2x s), 4.6 + 4.87 (2H, 2x s amplio), 5.18 + 5.26 (2H, 2x s amplio), 5.89 + 5.91 (1H, 2xs), 6.55-6.9 (2H, m), 7.05-7.5 (5H, m), 7.55-7.75 (2H, m), 7.75-7.90 (4H, m), 7.9-8.05 (1H, m), 10.23 + 10.28 (1H, 2xs).

El siguiente ejemplo se preparó a partir del método del Ejemplo 15, pero utilizando etanol como solvente.

JCS

Ej.	Precursor	Estructura	Nombre
16	Ej. 13		Bitartrato de la 2-(2-(2-(2,3-difluorofenil)-etil)-7-hidroxi-4-oxo-4H-quinolin-1-il)-N-(1-etil-piperidin-4-il)-N-(4-(4-trifluorometilfenil)bencil)-acetamida

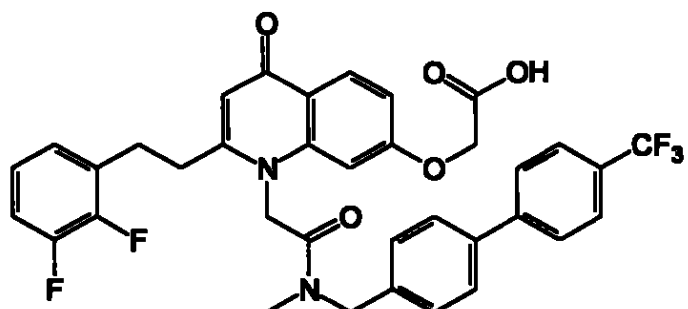
5

EJEMPLO 17

Acido 2-(2-(2-(2,3-difluorofenil)etil))-1-(N-(4-(4-trifluorometil-fenil)bencil)-N-metil-aminocarbonilmetil)-4-oxo-4H-quinolin-7-iloxi)acético

10

15



20

A una solución del ejemplo 8 (0.135 g) en diclorometano (3 ml) se agregó ácido trifluoroacético (0.5 ml), y la solución se agitó durante 66 horas a temperatura ambiente. El solvente se removió bajo presión reducida y el residuo se trituró con éter dietílico para proporcionar el compuesto del título (0.115 g).

^1H RMN (d_6 -DMSO) δ 2.8-3.1 + 3.22 (7H, m + s), 4.63 + 4.75-5.0 (4H, s amplio + m), 5.2-5.5 (2H, m), 6.01 + 6.04 (1H 2xs), 6.8-7.6 (7H, 2x s),

136

7.55-7.95 (6H, m), 8.05-8.2 (1H, m); MS (APCI-) encontrado (M-1) = 663 (weak); $C_{38}H_{28}F_5N_3O_5$ requerido 664.

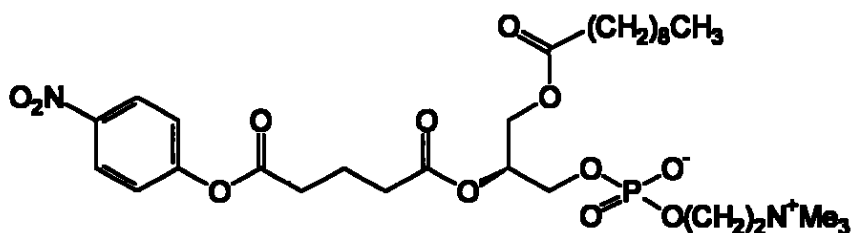
Datos Biológicos

5

1. Selección para la inhibición de la Lp-PLA₂.

La actividad enzimática se determinó midiendo la velocidad de transferencia del sustrato artificial (A) a 37°C en amortiguador HEPES 50 mM (ácido N-2-hidroxietilpiperacín-N'-2-etansulfónico) que contiene NaCl 150 mM, pH 7.4.

10



15

(A)

Los ensayos se realizaron en placas de titulación de 96 pozos.

La Lp-PLA₂ recombinante se purificó hasta homogeneidad a partir de células Sf9 infectadas con baculovirus, utilizando una columna quelante de zinc, cromatografía por afinidad con sefarosa azul y una columna de intercambio de aniones. Después de la purificación y la ultrafiltración, la enzima se almacenó a 6mg/ml a 4°C. Las placas de ensayo del compuesto o el vehículo más el amortiguador se ajustaron utilizando robóticos

20

231

automatizados hasta un volumen de 170 μ l. La reacción se inició mediante la adición de 20 μ l de 10x del sustrato (A) para proporcionar una concentración final del sustrato de 20 μ M y 10 μ l de enzima diluida a una Lp-PLA₂ aproximada final de 0.1 nM.

- 5 La reacción se siguió a 405 nm y 37°C durante 20 minutos, utilizando un lector de placas con mezclado automático. La velocidad de la reacción se midió como la velocidad del cambio de la absorbancia.

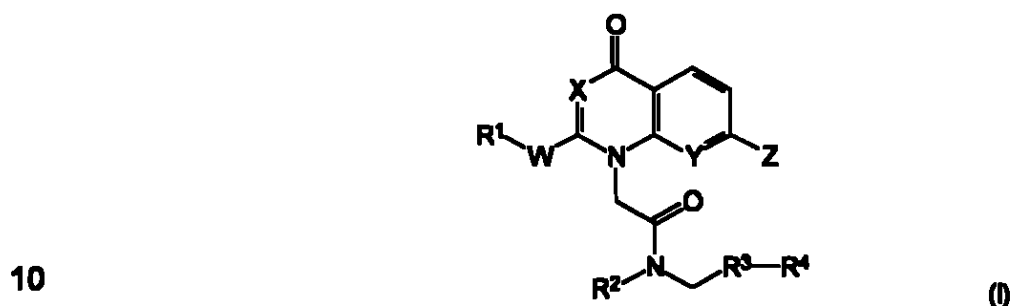
Resultados

- 10 Los compuestos descritos en los Ejemplos se probaron como se describió anteriormente y tienen valores de CI₅₀ en el intervalo < 0.1 a 100 nM.

NOVEDAD DE LA INVENCION

REIVINDICACIONES

5 1.- Un compuesto de fórmula (I):



en la cual: R^1 es un grupo arilo, sustituido opcionalmente por 1, 2, 3 ó 4 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de alquilo de $C_{(1-6)}$, alcoxi de $C_{(1-6)}$, alquiltio de $C_{(1-6)}$, hidroxilo, halógeno, CN, mono a perfluoroalquilo de $C_{(1-4)}$, mono a perfluoroalcoxiarilo de $C_{(1-4)}$ y arilalquilo de $C_{(1-4)}$; R^2 es hidrógeno, alquilo de $C_{(1-6)}$, el cual puede estar no sustituido o sustituido por 1, 2 ó 3 sustituyentes seleccionados de hidroxilo, halógeno, OR^5 , COR^5 , carboxi, $COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , mono o di(hidroxialquil de $C_{(1-6)}$)amino y N-hidroxialquil de $C_{(1-6)}$ -N-alquil de

15

20 $C_{(1-6)}$ amino; o R^2 es Het-alquilo de $C_{(0-4)}$, en el cual Het es un anillo heterocíclico de 5 a 7 miembros, que comprenden N y opcionalmente O o S, y en el cual N puede estar sustituido por COR^5 , $COOR^5$, $CONR^7R^8$, o alquilo de $C_{(1-6)}$ sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de

JBL

hidroxi, halógeno, OR^5 , COR^5 , carboxi, $COOR^5$, $CONR^7R^8$ o NR^7R^8 , por ejemplo, piperidin-4-ilo, pirrolidin-3-ilo; R^3 es un arilo o un anillo de heteroarilo sustituido opcionalmente por 1, 2, 3 ó 4 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de alquilo de $C(1-6)$, alcoxi de $C(1-6)$, alquiltio de $C(1-6)$, arilalcoxi de $C(1-6)$, hidroxi, halógeno, CN, COR^5 , carboxi, $COOR^5$, NR^5COR^8 , $CONR^7R^8$, $SO_2NR^7R^8$, $NR^5SO_2R^8$, NR^7R^8 , mono a perfluoroalquilo de $C(1-4)$ y mono a perfluoroalcoxi de $C(1-4)$; R^4 es un arilo o anillo de heteroarilo, el cual puede adicionalmente estar sustituido opcionalmente por 1, 2, 3 ó 4 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de alquilo de $C(1-6)$, alcoxi de $C(1-6)$, alquiltio de $C(1-6)$, alkilsulfonilo de $C(1-6)$, arilalcoxi de $C(1-6)$, hidroxi, halógeno, CN, COR^5 , carboxi, $COOR^5$, $CONR^7R^8$, NR^5COR^8 , $SO_2NR^7R^8$, $NR^5SO_2R^8$, NR^7R^8 , mono a perfluoroalquilo de $C(1-4)$ y mono a perfluoroalcoxi de $C(1-4)$, o alquilo de $C(5-10)$; W es un grupo alquilenos de $C(2-4)$, sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de metilo y etilo, $CH=CH$, $(CH_2)_nS$ o $(CH_2)_nO$, en donde n es 1, 2 ó 3; X e Y son de manera independiente CH o N; Z es NO_2 , NR^5R^8 , OR^8 , SR^8 , SOR^8 , SO_2R^8 o R^{10} ; R^5 y R^8 son de manera independiente hidrógeno o alquilo de $C(1-12)$, por ejemplo alquilo de $C(1-4)$ (por ejemplo metilo, etilo o t-butilo); R^7 y R^8 , los cuales pueden ser los mismos o diferentes, son cada uno seleccionados de hidrógeno o alquilo de $C(1-12)$, o R^7 y R^8 junto con el nitrógeno al cual están unidos, forman un anillo de 5 a 7 miembros, que opcionalmente contiene uno o más heteroátomos adicionales seleccionados de oxígeno, nitrógeno y azufre, y sustituido opcionalmente por

uno o dos sustituyentes seleccionados de hidroxilo, oxo, alquilo de $C_{(1-4)}$,
alquilcarboxi de $C_{(1-4)}$, arilo, por ejemplo, fenilo o aralquilo, por ejemplo,
bencilo, por ejemplo morfolina o piperacina; R^6 es hidrógeno o alquilo de $C_{(1-6)}$
sustituido opcionalmente por 1, 2 ó 3 sustituyentes, los cuales pueden ser los
5 mismos o diferentes, seleccionados de hidroxilo, halógeno, OR^5 , COR^5 , $COOR^5$,
 $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , arilo, heteroarilo y un anillo heterocíclico de 5 a
7 miembros, arilo o heteroarilo los cuales están sustituidos opcionalmente por
1, 2, 3 ó 4 sustituyentes, los cuales pueden ser los mismos o diferentes,
seleccionados de alquilo de $C_{(1-6)}$, alcoxi de $C_{(1-6)}$, alquiltio de $C_{(1-6)}$, arilalcoxi
10 de $C_{(1-6)}$, hidroxilo, halógeno, CN, COR^5 , $COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 ,
 $SO_2NR^7R^8$, $NR^5SO_2R^6$, mono a perfluoroalquilo de $C_{(1-4)}$ y mono a
perfluoroalcoxi de $C_{(1-4)}$, y anillo heterocíclico de 5 a 7 miembros el cual está
sustituido opcionalmente por COR^5 , $COOR^5$, $CONR^7R^8$, o alquilo de $C_{(1-6)}$
sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de hidroxilo,
15 halógeno, OR^5 , COR^5 , carboxi, $COOR^5$, $CONR^7R^8$ o NR^7R^8 , por ejemplo,
piperidin-4-ilo, pirrolidin-3-ilo; y R^{10} es alquilo de $C_{(1-6)}$ sustituido
opcionalmente por 1, 2 ó 3 sustituyentes, los cuales pueden ser los mismos o
diferentes, seleccionados de hidroxilo, halógeno, OR^5 , COR^5 , $COOR^5$,
 $CONR^7R^8$, NR^7R^8 , NR^5COR^6 , arilo, heteroarilo y un anillo heterocíclico de 5 a
20 7 miembros, arilo o heteroarilo los cuales están sustituidos opcionalmente por
1, 2, 3 ó 4 sustituyentes, los cuales pueden ser los mismos o diferentes,
seleccionados de alquilo de $C_{(1-6)}$, alcoxi de $C_{(1-6)}$, alquiltio de $C_{(1-6)}$, arilalcoxi
de $C_{(1-6)}$, hidroxilo, halógeno, CN, COR^5 , $COOR^5$, $CONR^7R^8$, NR^7R^8 , NR^5COR^6 ,

$\text{SO}_2\text{NR}^7\text{R}^8$, $\text{NR}^5\text{SO}_2\text{R}^6$, mono a perfluoroalquilo de $\text{C}_{(1-4)}$ y mono a perfluoroalcoxi de $\text{C}_{(1-4)}$, y anillo heterocíclico de 5 a 7 miembros el cual está sustituido opcionalmente por COR^5 , COOR^5 , CONR^7R^8 o alquilo de $\text{C}_{(1-6)}$ sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de hidroxí,

5 halógeno, OR^5 , COR^5 , carboxi, COOR^5 , CONR^7R^8 o NR^7R^8 , por ejemplo, piperidin-4-ilo, pirrolidin-3-ilo; o R^{10} es un anillo heterocíclico de 5 a 7 miembros sustituido opcionalmente por COR^5 , COOR^5 , CONR^7R^8 o alquilo de $\text{C}_{(1-6)}$ sustituido opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de hidroxí, halógeno, OR^5 , COR^5 , carboxi, COOR^5 , CONR^7R^8 o NR^7R^8 , por

10 ejemplo, piperidin-4-ilo, pirrolidin-3-ilo; y las sales farmacéuticamente aceptables de los mismos, con la condición de que Z no es amino, y que el compuesto de fórmula (I) no es: *N*-(2-dietilaminoetil)-2-(2-(2-(2,3-difluorofenil)-etil)-7-trifluorometil-4-oxo-4*H*-quinazolin-1-il)-*N*-(4'-trifluorometil-bifenil-4-ilmetil)-acetamida; *N*-(2-dietilaminoetil)-2-(2-(2-(2,3-difluorofenil)-etil)-7-metil-4-oxo-4*H*-quinazolin-1-il)-*N*-(4'-trifluorometil-bifenil-4-ilmetil)acetamida;

15 *N*-(1-etilpiperidin-4-il)-2-[2-(2-(2,3-difluorofenil)etil)-7-metil-4-oxo-4*H*]-[1,8]naftiridin-1-il]-*N*-(4'-trifluorometilbifenil-4-ilmetil)acetamida; *N*-(2-dietilaminoetil)-2-[2-(2-(2,3-difluorofenil)etil)-7-metil-4-oxo-4*H*]-[1,8]naftiridin-1-il]-*N*-(4'-trifluorometil-bifenil-4-ilmetil)acetamida;

20 *N*-(1-metilpiperidin-4-il)-2-[2-(2-(2,3-difluorofenil)etil)-7-metil-4-oxo-4*H*]-[1,8]naftiridin-1-il]-*N*-(4'-trifluorometilbifenil-4-ilmetil)-acetamida; *N*-(1-isopropilpiperidin-4-il)-2-[2-(2-(2,3-difluorofenil)etil)-7-metil-4-oxo-4*H*]-[1,8]naftiridin-1-il]-*N*-(4'-trifluorometilbifenil-4-ilmetil)acetamida; o *N*-(1-

(2-metoxietil)piperidin-4-il)-2-[2-(2-(2,3-difluorofenil)etil)-7-metil-4-oxo-4*H*-[1,8]-naftiridin-1-il]-*N*-(4'-trifluorometilbifenil-4-ilmetil)acetamida.

2.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque R^1 es fenilo sustituido opcionalmente por
5 halógeno, alquilo de $C_{(1-8)}$, trifluorometilo, alcoxi de $C_{(1-8)}$.

3.- El compuesto de conformidad con la reivindicación 1 o la reivindicación 2, caracterizado además porque R^2 es hidrógeno, metilo, etilo, isopropilo, 2-(dietilamino)etilo, 2-(piperidin-1-il)etilo, 2-(pirrolidin-1-il)etilo, 1-(2-metoxietil)piperidin-4-ilo, 1-metilpiperidin-4-ilo, 1-etil-piperidin-4-ilo o 1-etil-
10 pirrolidin-2-ilmetilo.

4.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque R^3 es fenilo.

5.- El compuesto de conformidad con cualquiera de las reivindicaciones 1, a 4, caracterizado además porque R^4 es fenilo sustituido
15 opcionalmente por halógeno, trifluorometilo o etilo.

6.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado además porque W es $(CH_2)_n-S$ o CH alquilenos de $(2-4)$.

7.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 6, caracterizado además porque Z es NO_2 , OR^9 o R^{10} .
20

8.- El compuesto de conformidad con la reivindicación 7, caracterizado además porque Z es hidroxilo, nitro, mono o di-*N*-alquilamino de $C_{(1-8)}$ alquilo de $C_{(1-8)}$, mono o di-*N*-alquilamino de $C_{(1-8)}$ alcoxi de $C_{(1-8)}$,

carboxialcoxi de C₍₁₋₈₎ o un éster del mismo, o arilalcoxi de C₍₁₋₈₎, arilalquilo de C₍₁₋₈₎, heteroarilalcoxi de C₍₁₋₈₎, heteroarilalquilo de C₍₁₋₈₎, heterociclilalcoxi de C₍₁₋₈₎ de 5 a 7 miembros sustituido opcionalmente por alquilo de C₍₁₋₈₎, o heterociclilalquilo de C₍₁₋₈₎ de 5 a 7 miembros sustituido opcionalmente por alquilo de C₍₁₋₈₎.

9.- El compuesto de conformidad con la reivindicación 7 o la reivindicación 8, caracterizado además porque Z incluye un anillo de arilo, heteroarilo o heterocíclico, el anillo se selecciona de bencilo, piridinilo, isoxazolilo, piperidinilo, pirrolidinilo y morfolino.

10. Bitartrato de la N-metil-2-(2-(2-(2,3-difluorofenil)etil)-7-(3-dimetilaminoprop-1-il)-4-oxo-4H-quinolin-1-il)-N-(4-(4-trifluorometilfenil)bencil)-acetamida; bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-4-oxo-7-(3-(dimetilamino)propoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-bencil)acetamida; N-Metil-2-(2-(2-(2,3-difluorofenil)etil)-7-nitro-4-oxo-4H-quinolin-1-il)-N-(4-(4-trifluorometilfenil)bencil)acetamida; bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-7-(2-dimetilaminoetoxi)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-bencil)acetamida; bitartrato de la 2-(7-(2-dietilaminoetoxi)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-bencil)acetamida; bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-4-oxo-7-(2-(piperidin-1-il)etoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida; bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-4-oxo-7-(3-(piperidin-1-il)propoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)-acetamida; acetato de 2-(2-(2-(2,3-

difluorofenil)etil))-1-(N-(4-(4-trifluorometilfenil)bencil)-N-metil-aminocarbonil-
 metil)-4-oxo-4H-quinolin-7-iloxi) ter-butilo; clorhidrato de la 2-(2-(2-(2,3-
 difluorofenil)etil)-4-oxo-7-(piridin-2-ilmetoxi)-4H-quinolin-1-il)-N-metil-N-(4-(4-
 trifluorometilfenil)bencil)acetamida; 2-(2-(2-(2,3-difluorofenil)etil)-7-(5-metil-
 5 isoxazol-3-ilmetoxi)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-
 fenil)bencil)acetamida; bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-7-(1-
 metilpirrolidin-2-ilmetoxi)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-
 fenil)bencil)-acetamida; 2-(7-benciloxi-2-(2-(2,3-difluorofenil)etil)-4-oxo-4-
 quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida; bitartrato de la
 10 2-(7-benciloxi-2-(2-(2,3-difluorofenil)etil)-4-oxo-4-quinolin-1-il)-N-(1-etil-
 piperidin-4-il)-N-(4-(4-trifluorometilfenil)bencil)acetamida; 2-(2-(2-(2,3-difluoro-
 fenil)etil)-7-hidroxi-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-
 fenil)bencil)acetamida; bitartrato de la 2-(2-(2-(2,3-difluorofenil)etil)-7-hidroxi-4-
 oxo-4H-quinolin-1-il)-N-(1-etil-piperidin-4-il)-N-(4-(4-trifluorometilfenil)-
 15 bencil)acetamida; acid 2-(2-(2-(2,3-difluorofenil)etil))-1-(N-(4-(4-trifluorometil-
 fenil)-bencil)-N-metil-aminocarbonilmetil)-4-oxo-4H-quinolin-7-iloxi)acético;
 bitartrato de la 2-(7-(dimetilaminometil)-2-(2-(2,3-difluorofenil)-etil)-4-oxo-4H-
 quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida; bitartrato de la
 2-(7-(dietilaminometil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-
 20 metil-N-(4-(4-trifluorometilfenil)bencil)acetamida; bitartrato de la 2-(7-
 (dietilaminometil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-
 (4-trifluorometilfenil)bencil)acetamida; bitartrato de la 2-(7-(dietilaminometil)-2-
 (2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-isopropil-N-(4-(4-trifluoro-

- metilfenil)bencil)acetamida; bitartrato de la 2-(7-((pirrolidin-1-il)metil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometilfenil)bencil)-acetamida; bitartrato de la 2-(7-((piperidin-1-il)metil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometilfenil)bencil)-acetamida;
- 5 bitartrato de la 2-(7-(2-dimetilaminoetil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-bencil)acetamida; bitartrato de la 2-(7-(2-dietilaminoetil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)bencil)acetamida; bitartrato de la 2-(7-(2-(pirrolidin-1-il)etil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-
- 10 (4-(4-trifluorometilfenil)-bencil)acetamida; bitartrato de la 2-(7-(3-dietilaminopropil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-bencil)acetamida; bitartrato de la 2-(7-(3-(pirrolidin-1-il)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-bencil)acetamida; bitartrato de la 2-(7-(3-(piperidin-1-
- 15 il)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-etil-N-(4-(4-trifluorometilfenil)-bencil)acetamida; bitartrato de la 2-(7-(3-(piperidin-1-il)propil)-2-(2-(2,3-difluorofenil)etil)-4-oxo-4H-quinolin-1-il)-N-isopropil-N-(4-(4-trifluorometilfenil)-bencil)acetamida; bitartrato de la 2-(7-(dietilaminometil)-2-(2,3-difluorobenciltio)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometil-
- 20 fenil)bencil)acetamida; y clorhidrato de la 2-(7-(3-(4-morfolino)propil)-2-(2,3-difluorobenciltio)-4-oxo-4H-quinolin-1-il)-N-metil-N-(4-(4-trifluorometilfenil)-bencil)acetamida.

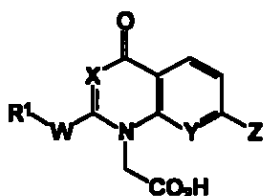
11.- Una composición farmacéutica que comprende un compuesto de fórmula (I), de conformidad con cualquiera de las reivindicaciones 1 a 10 y un portador farmacéuticamente aceptable.

12.- Un compuesto de fórmula (I) como se reclama en cualquiera de las reivindicaciones 1 a 10, para utilizarse en terapia.

13.- El uso de un compuesto de fórmula (I) como se reclama en cualquiera de las reivindicaciones 1 a 10, para la fabricación de un medicamento para tratarla aterosclerosis.

14.- Un método para tratar un estado de enfermedad asociado con la actividad de la enzima Lp-PLA₂, método el cual involucra tratar a un paciente en necesidad del mismo con una cantidad terapéuticamente efectiva de un compuesto de fórmula (I), de conformidad con cualquiera de las reivindicaciones 1 a 10.

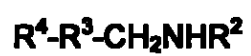
15.- Un procedimiento para preparar un compuesto de fórmula (I), de conformidad con la reivindicación 1, caracterizado además porque el procedimiento comprende hacer reaccionar un compuesto ácido de fórmula (II):



(II)

en la cual W, X, Y, Z y R¹ son como se definieron anteriormente, con un compuesto de amina de fórmula (III):

L.A.



(III)

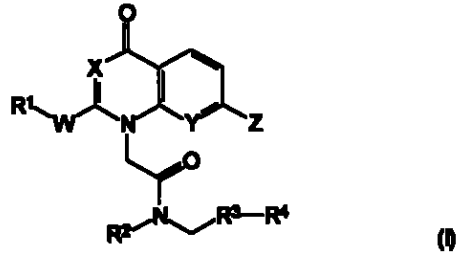
en la cual R^2 , R^3 y R^4 son como se definieron anteriormente; bajo condiciones de formación de amida.

VAB

RESUMEN DE LA INVENCION

Los compuestos de la fórmula (I)

5



son inhibidores de la enzima Lp-PLA₂ y son de uso en terapia, en particular
10 para el tratamiento de la aterosclerosis.

15

20

DH

P04/606F

PATENT CO PERATI N TREATY

289

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:	Received by: FORD
GIDDINGS, Peter John GLAXOSMITHKLINE Corporate Intellectual Property 980 Great West Road Brentford Middlesex TW8 9GS GRANDE BRETAGNE	27 FEB 2004 SAC/15K ATTY GEN.

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Applicant's or agent's file reference RHP32908/WO	Date of mailing (day/month/year) 25.02.2004 IMPORTANT NOTIFICATION
International application No. PCT/EP 02/12505	International filing date (day/month/year) 08.11.2002 Priority date (day/month/year) 10.11.2001
Applicant SMITHKLINE BEECHAM P.L.C.	

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:  European Patent Office - Gluckner Str. 109 D-10968 Berlin Tel. +49 30 25901-0 Fax +49 30 25901-840	Authorized Officer Geler, A Tel. +49 30 25901-708 
---	--

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RHP32908/WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA16)	
International application No. PCT/EP 02/12505	International filing date (day/month/year) 08.11.2002	Priority date (day/month/year) 10.11.2001	
International Patent Classification (IPC) or both national classification and IPC C07D215.08, C07D215.08			
Applicant SMITHKLINE BEECHAM P.L.C.			
1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 6 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets. 3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☒ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application			
Date of submission of the demand 30.05.2003		Date of completion of this report 25.02.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office - Glöckner Str. 103 D-10968 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840		Authorized Officer Hoepfner, W Telephone No. +49 30 25901-337 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 02/12505**

TSF

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-42 as originally filed

Claims, Numbers

1-15 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 02/12505**

852

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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

☐ the entire international application,

☒ claims Nos. 1-15

because:

☒ the said international application, or the said claims Nos. 1-15 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

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

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

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

33

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 02/12505**

- ☐ all parts.
- ☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-15
Inventive step (IS)	Yes: Claims	
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-13,15
	No: Claims	

2. Citations and explanations

see separate sheet

ISA

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Since it is at present not clear, on the basis of which subject-matter inventive step considerations could be carried out (see Re Item V below), no opinion will be formulated with respect to inventive step of the subject-matter of the present claims 1-15.

Claim 14 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, the International Examination Authority fully concurs with the objection put forward by the International Search Authority and no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

It appears that the present common feature of the compounds of formula (I) of the present claim 1 (i.e. the feature which renders claim 1 unitarian) is anticipated by D1, namely the bicyclic system with the acetic amide side chain (non-unity a posteriori).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Formal matters

On page 2, line 10, of the description it should possibly read "WO97/21675" and "WO97/21676".

Although in the present claims 1 and 8 the terms "aryl" and "heteroaryl" are clear as such, they introduce obscurity in that they unduly extend the scope of the claimed subject-matter. Consequently, they should be limited to the more concrete terms given in the description (see e.g. page 7).

It is to be noted that in the worked Examples preference is given to quinoline. Therefore, it would appear that the subject-matter of claim 1 is not supported over the whole scope.

In claim 15 in formula (II), it should presumably read "CO₂H".

155

Disclaimers

Disclaimers are only allowable in very rare exceptional cases, namely in order to avoid incidentally occurring novelty problems.

However, in the present claim 1 there are not less than 7 disclaimers. It is to be noted that, apart from the question, if such a big number can still be regarded as being reasonable, these disclaimers are only acceptable, if it could be convincingly shown that the disclaimed subject-matter cannot serve as solution to the problem underlying the present application.

Novelty

Reference is made to the following document:

D1: WO-A-0160805

The document D1 discloses LDL-PLA₂ inhibitors, methods for their preparation and their use in the treatment of atherosclerosis (see page 1, lines 4-6; page 2, formula (I); page 5, formula (IB); page 7, lines 21-24; page 9, lines 10-19; page 39, Table, Example No. 77).

The subject-matter of D1 overlaps with the subject-matter of the present independent claim 1 the overlapping portion being $Z=R^{10}=C_{(1-4)}$ alkyl.

In view of this prior art, at present novelty cannot be acknowledged for the subject-matter of the independent claims 1 and 10-15 and the dependent claims 2-9 now on file.

Industrial applicability

There is no doubt that the subject-matter of the present claims on file (except claim 14) is industrially applicable.

156

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 02/12505

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/06 A61K31/47 A61P9/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

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

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

CHEM ABS Data, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 60805 A (SMITH STEPHEN ALLAN ;IFE ROBERT JOHN (GB); PINTO IVAN LEO (GB); HI) 23 August 2001 (2001-08-23) page 1, line 4 - line 6 page 2, formula (I) page 5, formula (IB) page 7, line 21 - line 24 page 9, line 10 - line 19 page 39, Table, Example No. 77	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not mentioned to be of particular relevance
- *C* earlier document not published on or after the international filing date
- *L* document which may have double as priority claim(s) or which is cited to establish the publication date of another claim or other special reason (see specification)
- *O* document relating 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 underpin 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 considered with one or more other such documents, such combinations 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

17 February 2003

Date of mailing of the international search report

26/02/2003

Name and mailing address of the ISA
European Patent Office, P.O. Box 1 Patentamt 2
NL - 2000 HV The Hague
Tel. (+31-70) 240-2500, Tx. 21 651 650 01,
Fax. (+31-70) 240-2510

Authorized officer

Hoepfner, W

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/12505

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

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

- 1. ☒ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 14 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. ☐ Claim 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. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

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

Remark on Protest

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

157

158

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP 02/12505

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0160805	A	23-08-2001	AU 3546601 A	27-08-2001
			WO 0160805 A1	23-08-2001
			EP 1263740 A1	11-12-2002
			NO 20023828 A	30-09-2002
			US 2002103213 A1	01-08-2002

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	(✓)	()
Indicación de que se solicita la concesión de una patente	(✓)	()
Datos de identificación del solicitante o de la persona que se presenta la solicitud	(✓)	()
Descripción de la invención.	(✓)	()
Dibujos de ser estos pertinentes.	(✓)	()
Comprobante de Pago de las tasas establecidas.	(✓)	()
COMPLETA ()	INCOMPLETA ()	()

DISEÑO INDUSTRIAL ()

- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

ESQUEMA DE TRAZADO ()

- Indicación de que solicita el registro de un Esquema de trazado	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud	()	()
Representación gráfica del esquema de trazado	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable

Fecha

SUPERINDUSTRIA Y COMERCIO
Radicación : 04042942 00000000 Folios: 158
Fecha (RS) : 2004-05-07 17 11 13
Trámite : 011 PCT-PATENT 379 FASE 13021 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

2020
Bogotá D C

Doctor(a)
CARLOS R. OLARTE
Apoderado
SMITHKLINE BEECHAM P.L.C.

Oficio N° 05562

ASUNTO:

Radicación N°	04-042442
Solicitud internacional	PCT/EP02/12505
Fecha inicio fase nacional	10/06/2004
Trámite	011
Evento	379
Actuación	416
Folios	001

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:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha,
_____ 11/06/2004

202044

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Commutador: 3 820840 Fax: 3 505220
Sede CAN: Tr. 40A No. 38-50 3153263 al 69
Fax: 3 505220. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia