

PCT



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Organización y
Digitalización C.S.A. Ltda

Industria y Comercio
SUPERINTENDENCIA

09-107972

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIVISIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE
INVENCION

TITULO: DERIVADOS DE CARBOXAMIDA IMIDAZOLIDINA COMO
MODULADORES DE P2X7

SOLICITANTE: GLAXO GROUP LIMITED

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ Octubre 1 de 2009

P2009/000168

1001 03-11-2004

OLARTE RAISBECK

OLARTE RAISBECK MOURE & CASTRO LTDA.



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-107972- -00000-0000

Fecha: 2009-10-01 16:14:37 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 414

PETITORIO - FORMULARIO ÚNICO PATENTE PCT ENTRADA EN FASE NACIONAL

P2009/000168

SOLICITUD DE:



X

Patente de Invención.



Patente de Modelo de Utilidad.

X

Capítulo I.



Capítulo II.



**SOLICITANTE
(71)**

Nombre: GLAXO GROUP LIMITED

Dirección: Glaxo Wellcome House, Berkeley
Avenue, Greenford Middlesex UB6 0NN

Nacionalidad o Domicilio: Británica

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 79.782.747Bta
TP 74.295

**INVENTOR (ES)
(72)**

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

5

PCT (86)

Solicitud Internacional No. PCT/EP2008/053962 Fecha Abril 2, 2008

Publicación Internacional No. WO 2008/119825 Fecha Octubre 9, 2008



Título (54) DERIVADOS DE CARBOXAMIDA IMIDAZOLIDINA COMO MODULADORES DE P2X7

Clasificación Internacional (51) C07D 233/36, C07D 401/04, C07D 401/06,
C07D 403/04, A61K 31/4166, A61P 29/00

Prioridad

SI

X

NO



(33) País de Origen

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GB

GB

(32) Fecha

Abril 3, 2007

Octubre 22, 2007

Marzo 20, 2008

Marzo 26, 2008

(31) Número de Solicitud

0706501.4

0720653.5

0805272.2

0805504.8



Comprobante de pago No. 09

Fecha Octubre 1 de 2009

10

ANEXOS☒

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

☒

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

☒

Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 06- 018.321

☒Documento de cesión del inventor al solicitante o a su causante. *Declaración bajo la Regla 4.17 del PCT.*☐

Declaraciones.

☒

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

☒

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

☐

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

☐

Traducción del examen preliminar internacional efectuado por la IPEA.

☐

De ser el caso, copia del contrato de acceso.

☐

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

☐

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

☐

Arte final 12 x 12.

☐

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

☐

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

☒

Otros. Búsqueda Internacional.

11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTEFIRMA: C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/EP2008/053962

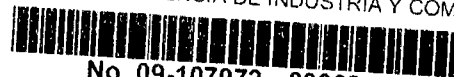
1. **Paul John BESWICK,**
New Frontiers Science
Park South, Third Avenue,
Harlow Essex CM19 5AW
Gran Bretaña
Nacionalidad: Britanica
2. **David Kenneth DEAN,**
New Frontiers Science
Park South, Third Avenue,
Harlow Essex CM19 5AW
Gran Bretaña
Nacionalidad: Britanica
3. **Robert James GLEAVE,**
New Frontiers Science
Park South, Third Avenue,
Harlow Essex CM19 5AW
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Nacionalidad: Britanica
4. **Andrew Peter MOSES,**
New Frontiers Science
Park South, Third Avenue,
Harlow Essex CM19 5AW
Gran Bretaña
Nacionalidad: Britanica
5. **Daryl Simon WALTER,**
New Frontiers Science
Park South, Third Avenue,
Harlow Essex CM19 5AW
Gran Bretaña
Nacionalidad: Británica

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 74,109
FECHA : OCTUBRE 1 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-107972- -00000-0000

Fecha: 2009-10-01 16:14:37 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 414

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGD	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105800063	30/09/2009	1,305,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL :	\$ 540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

APOSTILLA EN PODER DE REPRESENTACIÓN DE

GLAXO GROUP LIMITED

PODER DE REPRESENTACION

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

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

APOSTILLA

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

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

CERTIFICADO

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

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

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

Marlen Neira C


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

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

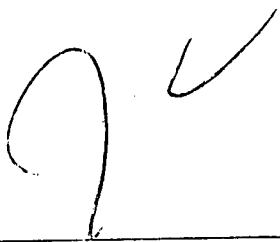
C E R T I F I C O:

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 "**GLAXO GROUP LIMITED**", Sociedad legalmente constituida y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **305979**, con domicilio social en Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra;

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

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

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



JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



X

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

Certified/Attesté
6. the/le **14 August 2003**

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

8. Number/sous No

G229474

9. Stamp:
timbre:

10. Signature: **J. Garbrah**

[Handwritten signature]



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

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

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, 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.

Poder

El suscrito,

Glaxo Group Limited

domiciliado en

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

Box No. VIII(ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII(I) to (v) (in general and the specific Notes to Box No. VIII(ii)). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to international application No. **PCT/EP2008/053962**

GLAXO GROUP LIMITED is entitled to apply for and be granted a patent by virtue of the following:

- (i) transfer of entitlement from inventors **Paul John BESWICK, David Kenneth DEAN, Robert James GLEAVE, Andrew Peter MOSES and Daryl Simon WALTER** to GlaxoSmithKline Services Unlimited by way of employment contract
- (ii) an assignment from GlaxoSmithKline Services Unlimited to Glaxo Group Limited effective 03-Apr-2007.

☒ This declaration is continued on the following sheet, "Continuation of Box No. VIII(ii)".

Form PCT/RO/101 (declaration sheet (ii)) (March 2001; reprint January 2003)
the request form

See Notes to

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
9 October 2008 (09.10.2008)

PCT

(10) International Publication Number
WO 2008/119825 A2

(51) International Patent Classification:

C07D 233/36 (2006.01) C07D 401/04 (2006.01)
C07D 401/06 (2006.01) A61K 31/4166 (2006.01)
C07D 403/04 (2006.01) A61P 29/00 (2006.01)

Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB).

(21) International Application Number:

PCT/EP2008/053962

(22) International Filing Date: 2 April 2008 (02.04.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0706501.4 3 April 2007 (03.04.2007) GB
0720653.5 22 October 2007 (22.10.2007) GB
0805272.2 20 March 2008 (20.03.2008) GB
0805504.8 26 March 2008 (26.03.2008) GB

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

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BESWICK, Paul, John** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **DEAN, David, Kenneth** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **GLEAVE, Robert, James** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **MOSES, Andrew, Peter** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **WALTER, Daryl, Simon** [GB/GB]; GlaxoSmithKline, New Frontiers

(74) Agents: **BREEN, Anthony, Paul et al.**; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

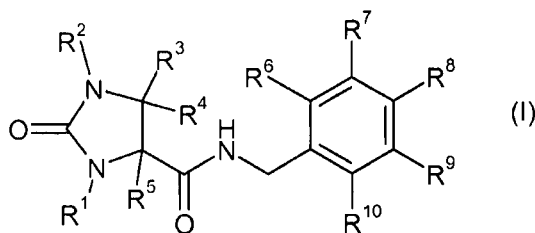
Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- without international search report and to be republished upon receipt of that report

(54) Title: IMIDAZOLIDINE CARBOXAMIDE DERIVATIVES AS P2X7 MODULATORS



(57) Abstract: The present invention relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The compounds or salts modulate P2X7 receptor function and are capable of antagonizing the effects of ATP at the P2X7 receptor (P2X7 receptor antagonists). The invention also provides the use of such compounds or salts, or pharmaceutical compositions thereof, in the treatment or prevention of disorders / diseases mediated by the P2X7 receptor, for example pain, inflammation or a neurodegenerative disease, in particular pain such as inflammatory pain, neuropathic pain or visceral pain.

Imidazolidine carboxamide derivatives as P2X7 modulators

The present invention relates to heterocyclic amide derivatives which modulate P2X7 receptor function and are capable of antagonizing the effects of ATP at the P2X7 receptor ("P2X7 receptor antagonists"); to processes for their preparation; to pharmaceutical compositions containing them; and to the use of such compounds in therapy.

The P2X7 receptor is a ligand-gated ion-channel which is expressed in cells of the hematopoietic lineage, e.g. macrophages, microglia, mast cells, and lymphocytes (T and B) (see, for example, Collo *et al.*, *Neuropharmacology*, Vol.36, pp.1277-1283 (1997)), and is activated by extracellular nucleotides, particularly adenosine triphosphate (ATP). Activation of P2X7 receptors has been implicated in giant cell formation, degranulation, cytolytic cell death, CD62L shedding, regulation of cell proliferation, and release of proinflammatory cytokines such as interleukin 1 (IL-1 β) and tumour necrosis factor (TNF α) (e.g. Hide *et al.*, *Journal of Neurochemistry*, Vol. 75., pp.965-972 (2000)). P2X7 receptors are also located on antigen presenting cells, keratinocytes, parotid cells, hepatocytes, erythrocytes, erythroleukaemic cells, monocytes, fibroblasts, bone marrow cells, neurones, and renal mesangial cells. Furthermore, the P2X7 receptor is expressed by presynaptic terminals in the central and peripheral nervous systems and has been shown to mediate glutamate release in glial cells (Anderson, C. *et al.*, *Drug. Dev. Res.*, Vol. 50, page 92 (2000)).

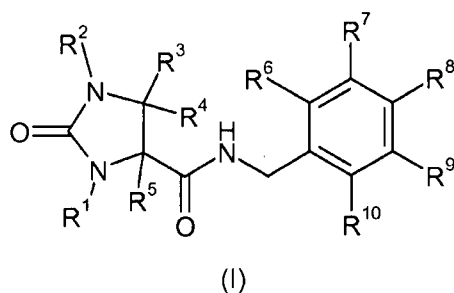
The localisation of the P2X7 receptor to key cells of the immune system, coupled with its ability to release important inflammatory mediators from these cells suggests a potential role of P2X7 receptor antagonists in the treatment of a wide range of diseases including pain and neurodegenerative disorders. Recent preclinical *in vivo* studies have directly implicated the P2X7 receptor in both inflammatory and neuropathic pain (Dell'Antonio *et al.*, *Neurosci. Lett.*, 327, pp.87-90, 2002; Chessell, I.P. *et al.*, *Pain*, 114, pp.386-396, 2005) while there is *in vitro* evidence that P2X7 receptors mediate microglial cell induced death of cortical neurons (Skaper, S.D. *et al.*, Program No. 937.7. 2005 *Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience, 2005. Online). In addition, up-regulation of the P2X7 receptor has been observed around β -amyloid plaques in a mouse model of Alzheimer's disease (Parvathenani, L. *et al.*, *J. Biol. Chem.*, Vol. 278(15), pp.13309-13317, 2003).

WO 01/10799 A1 (Aventis Pharmaceutical Products Inc.) discloses methods for preparing N-[(aliphatic or aromatic)carbonyl]-2-aminoacetamide compounds and for cyclising such compounds. JP 50-24287 (Sumitomo Chemical Co., Ltd.) discloses certain 5-substituted 2-oxo-4-imidazolidinecarboxamide compounds.

5

The present invention provides compounds which modulate P2X7 receptor function and are capable of antagonizing the effects of ATP at the P2X7 receptor ("P2X7 receptor antagonists").

- 10 A first aspect of the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



- 15 wherein:

R^1 represents hydrogen, C_{1-6} alkyl (e.g. methyl or ethyl), C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, pyridinylmethyl- or benzyl, and wherein any of said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, pyridinylmethyl- or benzyl is optionally substituted with 1, 2 or 3 (e.g. 1 or 2) halogen (e.g. fluorine or chlorine) atoms; or an unsubstituted phenyl;

20

R^2 represents hydrogen, C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl or i-propyl), C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, $-(CR^xR^y)_n-NR^{11}R^{12}$, C_{6-10} arylmethyl-, heterocyclyl- $(CR^xR^y)_n$ - or heteroaryl- $(CR^xR^y)_n$ -; and wherein any of said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, C_{6-10} arylmethyl-, heterocyclyl- $(CR^xR^y)_n$ - or heteroaryl- $(CR^xR^y)_n$ - is optionally substituted with 1, 2 or 3 (e.g. 1 or 2) halogen (e.g. fluorine or chlorine) atoms or C_{1-6} alkyl (e.g. methyl) groups, or the heteroaryl- $(CR^xR^y)_n$ - is optionally substituted on the heteroaryl ring with one C_{1-3} alkoxy (e.g. methoxy), cyano or trifluoromethyl group;

25

R^3 , R^4 and R^5 independently represent hydrogen, fluorine or methyl;

30

R^6 , R^7 , R^8 , R^9 and R^{10} independently represent hydrogen, halogen, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or phenyl, and wherein any of said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or phenyl is optionally substituted with 1, 2 or

B

3 halogen atoms; or R^9 and R^{10} together with the carbon atoms to which they are attached form a benzene ring which is optionally substituted with 1, 2 or 3 halogen atoms;

R^x and R^y independently represent hydrogen or C_{1-6} alkyl;

5 R^{11} and R^{12} independently represent hydrogen or C_{1-6} alkyl; and

n represents an integer from 0 to 4;

with the proviso that when R^6 and R^{10} independently represent hydrogen or fluorine, at least one of R^7 , R^8 and R^9 is a halogen atom, or only one of R^7 , R^8 and R^9 is a CF_3 group.

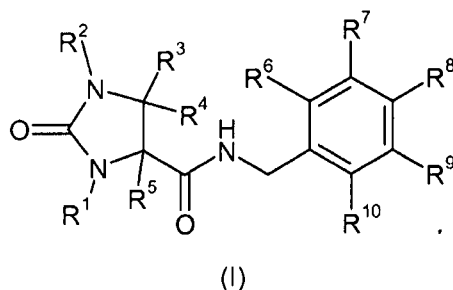
10

In a particular embodiment, R^2 represents hydrogen, C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl or i-propyl), C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, - $(CR^xR^y)_n$ -, $NR^{11}R^{12}$, C_{6-10} arylmethyl-, heterocyclyl- $(CR^xR^y)_n$ - or heteroaryl- $(CR^xR^y)_n$ -; and wherein any of said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, C_{6-10} arylmethyl-, heterocyclyl- $(CR^xR^y)_n$ - or heteroaryl- $(CR^xR^y)_n$ - is optionally substituted with 1, 2 or 3 (e.g. 1 or 2) halogen (e.g. fluorine or chlorine) atoms or C_{1-6} alkyl (e.g. methyl) groups.

15

In one embodiment, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof:

20



wherein:

25 R^1 represents C_{1-6} alkyl (e.g. methyl or ethyl), C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, pyridinylmethyl- or benzyl, any of which is optionally substituted with 1, 2 or 3 (e.g. 1 or 2) halogen (e.g. fluorine or chlorine) atoms; or an unsubstituted phenyl;

30 R^2 represents hydrogen, C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl or i-propyl), C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkylmethyl- or C_{6-10} arylmethyl-; and wherein any of said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkylmethyl- or C_{6-10} arylmethyl- is

optionally substituted with 1, 2 or 3 (e.g. 1 or 2) halogen (e.g. fluorine or chlorine) atoms;

R^3 , R^4 and R^5 independently represent hydrogen, fluorine or methyl; and

R^6 , R^7 , R^8 , R^9 and R^{10} independently represent hydrogen, halogen, cyano, C_{1-6} alkyl,

5 C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or phenyl, and wherein any of said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or phenyl is optionally substituted with 1, 2 or 3 halogen atoms; or R^9 and R^{10} together with the carbon atoms to which they are attached form a benzene ring which is optionally substituted with 1, 2 or 3 halogen atoms;

10 with the proviso that when R^6 and R^{10} independently represent hydrogen or fluorine, at least one of R^7 , R^8 and R^9 is a halogen atom, or only one of R^7 , R^8 and R^9 is a CF_3 group.

As used herein, the term "alkyl" (when used as a group or as part of a group) refers
15 to a straight or branched hydrocarbon chain containing the specified number of carbon atoms. For example, C_{1-6} alkyl means a straight or branched hydrocarbon chain containing at least 1 and at most 6 carbon atoms. Examples of alkyl include, but are not limited to; methyl (Me), ethyl (Et), n-propyl, i-propyl, t-butyl, n-hexyl and i-hexyl.

20 As used herein, the term "alkenyl" refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms wherein at least one carbon-carbon bond is a double bond. Examples of alkenyl include, but are not limited to ethenyl, propenyl, n-butenyl, i-butenyl, n-pentenyl and i-pentenyl.

25 As used herein, the term "alkynyl" refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms wherein at least one carbon-carbon bond is a triple bond. Examples of alkynyl include, but are not limited to ethynyl, propynyl, butynyl, i-pentynyl, n-pentynyl, i-hexynyl and n-hexynyl.

30 The term 'cycloalkyl' unless otherwise stated means a closed 3 to 6 membered non-aromatic ring, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term 'aryl' as used herein refers to a C_{6-10} monocyclic or bicyclic hydrocarbon
35 ring wherein at least one ring is aromatic. Examples of such groups include phenyl and naphthyl.

15

The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "heteroaryl" as used herein means a 5 to 6 membered monocyclic aromatic
5 or a fused 8 to 10 membered bicyclic aromatic ring system containing 1 to 3
heteroatoms selected from oxygen, nitrogen and sulfur. Suitable examples of such
monocyclic aromatic rings include thienyl, furanyl, pyrrolyl, triazolyl, imidazolyl,
oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl,
pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused bicyclic
10 aromatic ring systems include quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl,
cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl,
benzodioxinyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl,
benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.
Heteroaryl groups, as described above, may be linked to the remainder of the
15 molecule via a carbon atom or, when present, via a suitable nitrogen atom except
where otherwise indicated above.

The term 'heterocyclyl' refers to a 4-7 membered monocyclic ring or a fused 8-12
membered bicyclic ring which may be saturated or partially unsaturated containing 1
20 to 4 heteroatoms selected from oxygen, nitrogen or sulphur. Examples of such
monocyclic rings include pyrrolidinyl, azetidiny, pyrazolidinyl, oxazolidinyl, piperidinyl,
piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl,
oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl,
dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl,
25 tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl,
diazepanyl, azepanyl and the like. Examples of such bicyclic rings include indolinyl,
isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepine,
tetrahydroisoquinolinyl and the like.

30 It is to be understood that the present invention covers and discloses all possible
combinations of particular, preferred, suitable, or other embodiments of groups or
features (e.g. of R¹, R², R^x, R^y, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and/or n), e.g.
all possible combinations of embodiments of different groups or features, which
embodiments are described herein.

35 In certain particular embodiments of the invention, R¹ represents C₁₋₆ alkyl (e.g.
methyl or ethyl), C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkylmethyl-,

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pyridinylmethyl- or benzyl, any of which is optionally substituted with 1, 2 or 3 (e.g. 1 or 2) halogen (e.g. fluorine or chlorine) atoms; or an unsubstituted phenyl.

- In one embodiment of the invention, R¹ represents unsubstituted C₁₋₆ alkyl (e.g. methyl or ethyl) or C₃₋₆ cycloalkyl; or a benzyl optionally substituted with 1, 2 or 3 halogen (e.g. fluorine or chlorine) atoms. In a particular embodiment R¹ represents C₁₋₄ alkyl (e.g. methyl or ethyl). In a further embodiment, R¹ represents hydrogen or methyl.
- 10 In a particular embodiment of the invention, R¹ represents methyl, ethyl, or ethyl substituted with 1, 2 or 3 fluorine atoms (e.g. methyl, ethyl, -CH₂-CF₃, -CH₂-CHF₂ or -CH₂-CH₂F).
- In a preferred embodiment, R¹ represents methyl or ethyl, in particular methyl.
- 15 In certain particular embodiments of the invention, R² represents hydrogen, C₁₋₆ alkyl (e.g. methyl, ethyl, n-propyl or i-propyl), C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl (e.g. cyclopentyl), C₃₋₆ cycloalkylmethyl- (e.g. cyclopropylmethyl- or cyclobutylmethyl-), - (CR^xR^y)_n-NR¹¹R¹², C₆₋₁₀ arylmethyl-, heterocyclyl-(CR^xR^y)_n- or heteroaryl-(CR^xR^y)_n-; and wherein said C₁₋₆ alkyl is optionally substituted with 1, 2 or 3 (e.g. 1 or 2) halogen (e.g. fluorine) atoms, and wherein the heteroaryl-(CR^xR^y)_n- is optionally substituted (e.g. on the heteroaryl ring) with 1, 2 or 3 (e.g. 1 or 2, e.g. 1) halogen (e.g. fluorine or chlorine) atoms or C₁₋₆ alkyl (e.g. methyl, ethyl, n-propyl or i-propyl, e.g. methyl) groups, or the heteroaryl-
- 20 (CR^xR^y)_n- is optionally substituted on the heteroaryl ring with one C₁₋₃ alkoxy (e.g. methoxy), cyano or trifluoromethyl group.
- In certain particular embodiments of the invention, R² represents hydrogen, C₁₋₆ alkyl (e.g. methyl, ethyl, n-propyl or i-propyl), C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl (e.g. cyclopentyl), C₃₋₆ cycloalkylmethyl- (e.g. cyclopropylmethyl- or cyclobutylmethyl-), - (CR^xR^y)_n-NR¹¹R¹², C₆₋₁₀ arylmethyl-, heterocyclyl-(CR^xR^y)_n- or heteroaryl-(CR^xR^y)_n-; and wherein any of said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkylmethyl-, C₆₋₁₀ arylmethyl-, heterocyclyl-(CR^xR^y)_n- or heteroaryl-(CR^xR^y)_n- is optionally substituted with 1, 2 or 3 (e.g. 1 or 2) halogen (e.g. fluorine or chlorine) atoms or methyl groups, or the heteroaryl-(CR^xR^y)_n- is optionally substituted on the heteroaryl ring with one C₁₋₃ alkoxy (e.g. methoxy), cyano or trifluoromethyl group.
- 30
- 35

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In certain particular embodiments of the invention, R^2 represents hydrogen or unsubstituted C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl or i-propyl), benzyl or C_{3-6} cycloalkylmethyl- (e.g. cyclopropylmethyl- or cyclobutylmethyl-). In another embodiment R^2 represents hydrogen or C_{1-4} alkyl (e.g. methyl, ethyl, n-propyl or i-propyl).

In a more particular embodiment, R^2 represents hydrogen or methyl. In a preferred embodiment, R^2 represents methyl.

10 In a particular embodiment, R^2 represents hydrogen, C_{1-6} alkyl (e.g. methyl or ethyl), heterocyclyl- $(CR^xR^y)_n$ - or heteroaryl- $(CR^xR^y)_n$ -; and any of said C_{1-6} alkyl, heterocyclyl- $(CR^xR^y)_n$ - or heteroaryl- $(CR^xR^y)_n$ - is optionally substituted with 1, 2 or 3 halogen (e.g. fluorine or chlorine, in particular fluorine) atoms or C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl or i-propyl, in particular methyl) groups.

15 In a particular embodiment of the invention, R^2 represents hydrogen, methyl, ethyl, or ethyl substituted with 1, 2 or 3 fluorine atoms (e.g. hydrogen, methyl, ethyl, $-CH_2-CF_3$, $-CH_2-CHF_2$ or $-CH_2-CH_2F$).

20 In a particular embodiment, R^2 represents heteroaryl (e.g. pyridinyl, pyrimidinyl, imidazolyl or pyrazolyl) optionally substituted with 1, 2 or 3 C_{1-6} alkyl groups (e.g. methyl, ethyl, n-propyl or i-propyl, in particular methyl).

In a particular embodiment, R^2 represents pyridinyl, pyrimidinyl, imidazolyl or
25 pyrazolyl, wherein any of said groups are optionally substituted with 1 or 2 (e.g. one) fluorine or chlorine (e.g. fluorine) atoms, with 1 or 2 (e.g. one) methyl, ethyl, n-propyl or i-propyl (in particular methyl) groups, or with one C_{1-3} alkoxy (e.g. methoxy), cyano or trifluoromethyl group.

30 In a particular embodiment, R^2 represents heteroarylmethyl- (e.g. pyridinylmethyl or imidazolylmethyl) optionally substituted with 1, 2 or 3 C_{1-6} alkyl groups (e.g. methyl).

In a particular embodiment, R^2 represents heterocyclyl- $(CR^xR^y)_n$ - (e.g. piperidinyl, morpholinyl- $(CH_2)_2$ - or morpholinyl- $(CH_2)_3$ -). In one embodiment, n represents 2 or 3.

35 In a particular embodiment, R^x and R^y both represent hydrogen.

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In a particular embodiment, n represents 0 or 1, more particularly 0.

In a particular embodiment, R¹ and R² do not both represent hydrogen.

5 In a preferred embodiment of the invention, R¹ and R² both represent methyl.

In a particular embodiment of the invention, R¹ represents methyl and R² represents hydrogen.

10

In a particular embodiment of the invention, R³ and R⁴ both represent hydrogen. In a particular embodiment, R⁵ represents hydrogen. In a more particular embodiment, R³, R⁴ and R⁵ all represent hydrogen.

15

In a particular embodiment of the invention, R⁶, R⁷, R⁸, R⁹ and R¹⁰ independently represent hydrogen, halogen (e.g. chlorine or fluorine), cyano, trifluoromethyl or unsubstituted C₁₋₆ alkyl. In a more particular embodiment, R⁶, R⁷, R⁸, R⁹ and R¹⁰ independently represent hydrogen, halogen (e.g. chlorine or fluorine), cyano, methyl or trifluoromethyl. In a more particular embodiment, R⁶, R⁷, R⁸, R⁹ and R¹⁰ independently represent hydrogen, halogen (e.g. chlorine or fluorine), methyl or trifluoromethyl. In a still more particular embodiment, R⁶, R⁷, R⁸, R⁹ and R¹⁰ independently represent hydrogen, chlorine, fluorine, bromine, methyl or trifluoromethyl. In a yet more particular embodiment, R⁶, R⁷, R⁸, R⁹ and R¹⁰ independently represent hydrogen, chlorine, fluorine, methyl or trifluoromethyl.

20

In a particular embodiment, R⁶ represents hydrogen. In an alternative particular embodiment, R⁶ represents chlorine, fluorine or methyl; more particularly methyl.

30 Preferably, R⁷ represents hydrogen.

In a particular embodiment, R⁶ and R⁷ both represent hydrogen. In an alternative particular embodiment, R⁶ represents chlorine, fluorine or methyl (more particularly methyl), and R⁷ represents hydrogen.

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In a particular embodiment, R^8 represents hydrogen or halogen (e.g. chlorine or fluorine). In a more particular embodiment, R^8 represents hydrogen, chlorine or fluorine.

- 5 In a particular embodiment, R^9 represents hydrogen, halogen (e.g. chlorine or fluorine) or trifluoromethyl. In a more particular embodiment, R^9 represents hydrogen, chlorine, fluorine or trifluoromethyl.

- 10 In a particular embodiment, R^{10} represents halogen (e.g. chlorine or fluorine), C_{1-6} alkyl (e.g. methyl) or trifluoromethyl. In a more particular embodiment, R^{10} represents chlorine, fluorine, methyl or trifluoromethyl. In a still more particular embodiment, R^{10} represents chlorine, fluorine or methyl. Preferably, R^{10} represents chlorine or methyl.

- 15 In a more particular embodiment,
 R^6 and R^7 both represent hydrogen,
 R^8 represents hydrogen, chlorine or fluorine,
 R^9 represents hydrogen, chlorine, fluorine or trifluoromethyl, and
 R^{10} represents chlorine, fluorine, methyl or trifluoromethyl.

- 20 In a still more particular embodiment,
 R^6 and R^7 both represent hydrogen,
 R^8 represents hydrogen, chlorine or fluorine,
 R^9 represents hydrogen, chlorine, fluorine or trifluoromethyl, and
25 R^{10} represents chlorine, fluorine or methyl.

- Preferably,
 R^6 and R^7 both represent hydrogen,
 R^8 represents hydrogen, chlorine or fluorine,
30 R^9 represents hydrogen, chlorine, fluorine or trifluoromethyl, and
 R^{10} represents chlorine, fluorine or methyl (in particular, chlorine or methyl),
wherein one or both (e.g. one) of R^8 and R^9 is / are other than hydrogen.

- More preferably,
35 R^6 and R^7 both represent hydrogen,
 R^8 represents hydrogen or fluorine,
 R^9 represents trifluoromethyl, and

R¹⁰ represents chlorine or methyl.

Preferably,

R⁶ represents hydrogen, chlorine, fluorine or methyl,

5 R⁷ represents hydrogen,

R⁸ represents chlorine or fluorine,

R⁹ represents hydrogen, and

R¹⁰ represents chlorine or methyl.

10 More preferably,

R⁶ represents hydrogen, chlorine, fluorine or methyl,

R⁷ represents hydrogen,

R⁸ represents chlorine,

R⁹ represents hydrogen, and

15 R¹⁰ represents chlorine or methyl.

In a particularly preferred embodiment, R⁶, R⁷ and R⁸ each represent hydrogen, R⁹ represents trifluoromethyl, and R¹⁰ represents chlorine.

20

In a particularly preferred embodiment, R⁶, R⁷ and R⁹ each represent hydrogen and R⁸ and R¹⁰ both represent chlorine.

In a particularly preferred embodiment, R⁶ and R⁷ both represent hydrogen, R⁸ and R⁹ both represent fluorine, and R¹⁰ represents chlorine.

25

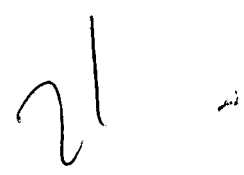
In a particularly preferred embodiment, R⁶, R⁷ and R⁸ each represent hydrogen, R⁹ represents trifluoromethyl, and R¹⁰ represents methyl.

30 In a particularly preferred embodiment, R⁶ and R⁷ both represent hydrogen, R⁸ represents fluorine, R⁹ represents trifluoromethyl, and R¹⁰ represents chlorine.

In a particularly preferred embodiment, R⁶ is methyl, R⁷ and R⁹ both represent hydrogen, and R⁸ and R¹⁰ both represent chlorine.

35

In a particularly preferred embodiment, R⁶, R⁸ and R¹⁰ each represent chlorine, and R⁷ and R⁹ both represent hydrogen.



In a preferred embodiment, R⁶, R⁷ and R⁸ each represent hydrogen, R⁹ represents trifluoromethyl, and R¹⁰ represents fluorine.

5

In a preferred embodiment, R⁶, R⁷ and R⁹ each represent hydrogen, R⁸ represents fluorine, and R¹⁰ represents chlorine.

10

In a preferred embodiment, R⁶, R⁷ and R⁹ each represent hydrogen, R⁸ represents chlorine, and R¹⁰ represents methyl.

In a preferred embodiment, R⁶, R⁷ and R⁸ each represent hydrogen, R⁹ represents chlorine, and R¹⁰ represents methyl.

15

In a preferred embodiment, R⁶ and R⁷ both represent hydrogen, R⁸ represents fluorine, and R⁹ and R¹⁰ both represent chlorine.

In a preferred embodiment, R⁶, R⁷ and R⁸ each represent hydrogen and R⁹ and R¹⁰ both represent chlorine.

20

In a preferred embodiment, R⁶ is fluorine, R⁷ and R⁹ both represent hydrogen, and R⁸ and R¹⁰ both represent chlorine.

25

In all embodiments of the invention herein described, when R⁶ and R¹⁰ independently represent hydrogen or fluorine, at least one of R⁷, R⁸ and R⁹ is a halogen atom, or only one of R⁷, R⁸ and R⁹ is a CF₃ group.

30

In a particular embodiment of the invention herein described, when R⁶ and R¹⁰ independently represent hydrogen or fluorine, at least one of R⁷, R⁸ and R⁹ is a halogen atom. In a more particular embodiment of the invention herein described, when R⁶ and R¹⁰ independently represent hydrogen or fluorine, at least one of R⁷, R⁸ and R⁹ is a halogen atom, and only one of R⁷, R⁸ and R⁹ is a CF₃ group.

35

In a particular embodiment of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein:

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R¹ represents unsubstituted C₁₋₆ alkyl, C₃₋₆ cycloalkyl; or a benzyl optionally substituted with 1, 2 or 3 halogen atoms;

R² represents hydrogen or methyl;

R³, R⁴ and R⁵ all represent hydrogen; and

- 5 R⁶, R⁷, R⁸, R⁹ and R¹⁰ independently represent hydrogen, chlorine, fluorine, bromine, methyl or trifluoromethyl;

with the proviso that when R⁶ and R¹⁰ independently represent hydrogen or fluorine, at least one of R⁷, R⁸ and R⁹ is a halogen atom, or only one of R⁷, R⁸ and R⁹ is a CF₃ group.

10

One particular aspect of the invention provides a compound or salt selected from a compound of examples E1 to E50, as shown and/or named below, or a pharmaceutically acceptable salt thereof.

15

One particular aspect of the invention provides a compound or salt selected from a compound of examples E51 to E127, as shown and/or named below, or a pharmaceutically acceptable salt thereof.

- 20 One preferred aspect of the invention provides a compound selected from Examples E1 to E5, E7, E8, E10 to E13, E15, E18, E19, E21, E23, E25 to E28, E30, E32 to E35, E39, E41, E42, E45, E51, E52, E54, E55, E57 to E61, E64 to E70, E72 to E79, E81, E82, E85, E86, E88, E89, E91 to E97, E99, E100, E102, E104 to E108, E110 to E113, E115 to E120, and E122 to E127, as a compound or a pharmaceutically acceptable salt thereof.

25

One preferred aspect of the invention provides a compound or a pharmaceutically acceptable salt thereof, which is:

- 30 *N*-{[2-chloro-3-(trifluoromethyl)phenyl]methyl}-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide (in particular, (4*S*)-*N*-{[2-chloro-3-(trifluoromethyl)phenyl]methyl}-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide),
N-{[(2,4-dichlorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
N-{[(2-chloro-3,4-difluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-
35 imidazolidinecarboxamide,
N-{[2-fluoro-3-(trifluoromethyl)phenyl]methyl}-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,

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- 1,3-dimethyl-2-oxo-*N*-[(2,3,4-trifluorophenyl)methyl]-4-imidazolidinecarboxamide,
N-[(2-chloro-4-fluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2-chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-2-oxo-4-
imidazolidinecarboxamide,
- 5 *N*-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-
imidazolidinecarboxamide,
N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-2-oxo-1-(4-piperidinyl)-4-
imidazolidinecarboxamide,
N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-2-oxo-1-(3-pyridinyl)-4-
- 10 imidazolidinecarboxamide,
N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(6-methyl-3-pyridinyl)-2-
oxo-4-imidazolidinecarboxamide,
N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(2-methyl-4-pyridinyl)-2-
oxo-4-imidazolidinecarboxamide,
- 15 *N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-
imidazolidinecarboxamide (in particular, (4*S*)-*N*-[(2,4-dichlorophenyl)methyl]-3-
methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide),
N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(2-methyl-4-pyridinyl)-2-
oxo-4-imidazolidinecarboxamide,
- 20 *N*-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-
imidazolidinecarboxamide,
N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-2-oxo-1-(2-pyridinyl)-4-
imidazolidinecarboxamide,
N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-
- 25 imidazolidinecarboxamide,
N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(3-methyl-2-pyridinyl)-2-
oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-
imidazolidinecarboxamide,
- 30 *N*-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-
imidazolidinecarboxamide,
N-[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-
- 35 imidazolidinecarboxamide,
N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-
imidazolidinecarboxamide,

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- N*-[(3-Chloro-2-methylphenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide,
N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxamide,
5 *N*-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(1-methyl-1H-pyrazol-5-yl)-2-oxo-4-imidazolidinecarboxamide,
N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxamide, or
N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-(5-pyrimidinyl)-4-
10 imidazolidinecarboxamide;

or a pharmaceutically acceptable salt thereof.

- One preferred aspect of the invention provides a compound or a pharmaceutically
15 acceptable salt thereof, which is:

- N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-
20 imidazolidinecarboxamide,
N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
25 *N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxamide,
N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(1-methyl-1H-imidazol-2-
30 yl)-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxamide,
N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxamide,
35 *N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-[6-(trifluoromethyl)-4-pyrimidinyl]-4-imidazolidinecarboxamide,

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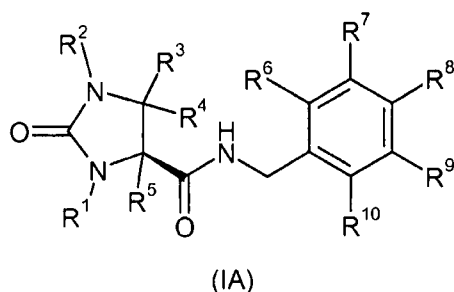
- N*-[(2,4-Dichlorophenyl)methyl]-1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-{[2-Chloro-3-(trifluoromethyl)phenyl]methyl}-1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- 5 *N*-[(2,4-Dichlorophenyl)methyl]-1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-{[2-Chloro-3-(trifluoromethyl)phenyl]methyl}-1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxamide,
- 10 *N*-{[2-chloro-3-(trifluoromethyl)phenyl]methyl}-3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichlorophenyl)methyl]-1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxamide,
- 15 *N*-[(2,4-Dichlorophenyl)methyl]-3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-{[2-Chloro-3-(trifluoromethyl)phenyl]methyl}-3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2-Chloro-4-fluorophenyl)methyl]-3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxamide,
- 20 *N*-{[2-Chloro-3-(trifluoromethyl)phenyl]methyl}-3-methyl-2-oxo-1-(2-pyrazinyl)-4-imidazolidinecarboxamide,
- 1-(2-Chloro-3-pyridinyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2-Chloro-3,4-difluorophenyl)methyl]-1-(2-chloro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- 25 1-(2-Chloro-3-pyridinyl)-*N*-{[2-chloro-3-(trifluoromethyl)phenyl]methyl}-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- 3-Methyl-*N*-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-2-oxo-4-imidazolidinecarboxamide,
- 30 *N*-[(2,3-Dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(3-Chloro-2-methylphenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichloro-6-methylphenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichlorophenyl)methyl]-1-(5-fluoro-2-pyrimidinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- 35 *N*-[(2,4-Dichlorophenyl)methyl]-3-ethyl-2-oxo-4-imidazolidinecarboxamide,
- N*-{[2-Chloro-3-(trifluoromethyl)phenyl]methyl}-3-ethyl-2-oxo-4-imidazolidinecarboxamide,

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- N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-[4-(methyloxy)-2-pyrimidinyl]-2-oxo-4-imidazolidinecarboxamide,
1-(5-Chloro-2-pyrimidinyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- 5 *N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-1-(2-fluoro-4-pyridinyl)-3-methyl-2-oxo-4-
- 10 imidazolidinecarboxamide,
N-[(2-Chloro-3,4-difluorophenyl)methyl]-1-(2-fluoro-4-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
N-[(3-Chloro-2-methylphenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
- 15 *N*-[(2,3-Dichlorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2,3-Dichloro-4-fluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2-Chloro-4-fluoro-3-(trifluoromethyl)phenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
- 20 *N*-[(2,4-Dichloro-6-methylphenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
1,3-Dimethyl-*N*-[(2-methyl-3-(trifluoromethyl)phenyl)methyl]-2-oxo-4-imidazolidinecarboxamide,
N-[(4-Chloro-2-methylphenyl)methyl]-1,3-dimethyl-2-oxo-4-
- 25 imidazolidinecarboxamide,
N-[(2-Chloro-4-cyanophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-(2,2-difluoroethyl)-1-methyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-1-(3-fluoro-2-pyridinyl)-3-methyl-2-oxo-4-
- 30 imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1*H*-pyrazol-5-yl)-2-oxo-4-imidazolidinecarboxamide,
1-(2-Cyano-3-pyridinyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- 35 *N*-[(2,4-Dichlorophenyl)methyl]-1-(2,2-difluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,

- N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-1-(2-fluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
 5 *N*-[(2,4-Dichlorophenyl)methyl]-1-ethyl-3-methyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichloro-6-fluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
 1,3-Dimethyl-2-oxo-*N*-[(2,4,6-trichlorophenyl)methyl]-4-imidazolidinecarboxamide,
N-[(2,4-Dichloro-6-fluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
 10 3-Methyl-2-oxo-*N*-[(2,4,6-trichlorophenyl)methyl]-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methylethyl)-2-oxo-4-imidazolidinecarboxamide,
 1-(Cyclopropylmethyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
 15 1-(Cyclobutylmethyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide, or
 1-Cyclopentyl-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide;
 20 or a pharmaceutically acceptable salt thereof.

A further particular aspect of the present invention provides a compound of formula (IA) or a pharmaceutically acceptable salt thereof:



wherein:

- R^1 represents C_{1-4} alkyl or C_{3-4} cycloalkyl, any of which is optionally substituted with 1, 2 or 3 halogen (e.g. fluorine) atoms,
 30 and R^2 , R^x , R^y , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and n are as defined herein for the compound of formula (I) or salt thereof,

and wherein more than 50% (e.g. more than 70%, in particular more than 90%, such as more than 95%) by molarity of the compound of formula (IA) or the pharmaceutically acceptable salt thereof has the indicated stereochemistry at the ring-carbon atom bonded to R⁵.

5

In a particular embodiment, the compound of formula (IA) or the pharmaceutically acceptable salt thereof has an enantiomeric excess of greater than 70% (e.g. more than 80%, in particular more than 90%) with respect to the indicated stereochemistry at the ring-carbon atom bonded to R⁵.

10

In a particular embodiment, in a compound of formula (IA) or a salt thereof, R¹ represents unsubstituted C₁₋₄ alkyl or C₃₋₄ cycloalkyl; more particularly methyl, ethyl, n-propyl, i-propyl, cyclopropyl, or cyclobutyl; still more particularly methyl, ethyl, n-propyl or i-propyl.

15

In a most particular embodiment, in a compound of formula (IA) or a salt thereof, R¹ represents methyl or ethyl.

20

In a particular embodiment, in a compound of formula (IA) or a salt thereof, R³, R⁴ and R⁵ all represent hydrogen.

25

All embodiments, e.g. particular or preferable features or aspects, of the invention (e.g. embodiments of the compound or salt of the invention and/or of pharmaceutical compositions and/or uses thereof) which are disclosed herein in relation to a compound of formula (I) or a salt thereof, are also hereby disclosed and contemplated in relation to a compound of formula (IA) or a salt thereof, to the extent appropriate or possible, with all necessary changes having been made to the wording.

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An alternative particular aspect of the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, as disclosed herein, wherein the compound or salt is substantially racemic (e.g. racemic) at the ring-carbon atom bonded to R⁵.

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Antagonists of P2X7 may be useful in preventing, treating, or ameliorating a variety of pain states (e.g. neuropathic pain, chronic inflammatory pain, and visceral pain),

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inflammation and neurodegeneration, in particular Alzheimer's disease. P2X7 antagonists may also constitute useful therapeutic agents in the management of rheumatoid arthritis and inflammatory bowel disease.

- 5 Compounds of the present invention which modulate P2X7 receptor function and are capable of antagonizing the effects of ATP at the P2X7 receptor ("P2X7 receptor antagonists") may be competitive antagonists, inverse agonists, or negative allosteric modulators of P2X7 receptor function.
- 10 Certain compounds of formula (I) may in some circumstances form acid addition salts thereof. It will be appreciated that for use in medicine compounds of formula (I) may be used as salts, in which case the salts should be pharmaceutically acceptable. Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, J. Pharm. Sci., 1977, 66, 1-19. When a compound of the present
- 15 invention is basic, in one embodiment a pharmaceutically acceptable salt is prepared from a pharmaceutically acceptable acid, such as an inorganic or organic acid, e.g. by admixture of the compound and the acid. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic,
- 20 methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. In a particular embodiment, the pharmaceutically acceptable acid is benzenesulfonic, camphorsulfonic, ethanesulfonic, hydrobromic, hydrochloric, methanesulfonic, nitric, phosphoric, sulfuric, or p-toluenesulfonic acid.
- 25 Examples of pharmaceutically acceptable salts include salts formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, hydrochloric, sulfuric, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic,
- 30 benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

- The compounds of formula (I) or salts thereof may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, e.g. as the hydrate. This invention includes within its scope solvates (e.g. hydrates), such as
- 35 stoichiometric solvates (e.g. hydrates), of the compounds or salts thereof, as well as compounds or salts thereof containing variable amounts of solvent (e.g. water).

30

Compounds of formula (I) or salts thereof are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. In examples where the stereochemical composition of the final product has been determined by chiral HPLC (more specifically by methods (A), (B), (C) or (D) as set out in the Examples), the corresponding stereospecific name and structure have generally been assigned to the final product where the enantiomeric excess (e.e.) of said product is greater than 70%. Assignment of absolute stereochemistry is based on the known chirality of the starting material. In examples where the composition of the final product has not been characterised by chiral HPLC, the stereochemistry of the final product has not been indicated. However, the chirality of the main component of the product mixture of the compound or salt will generally be expected to reflect that of the starting material; and/or the enantiomeric excess will generally depend on the synthetic method used and is likely to be similar to that measured for an analogous example (where such an example exists). Thus compounds or salts shown in one chiral form are expected to be able to be prepared in the alternative chiral form using the appropriate starting material. Alternatively, if racemic starting materials are used, it would be expected that a racemic product would be produced and the single enantiomers could be separated by the usual methods. The invention also extends to any tautomeric forms and mixtures thereof.

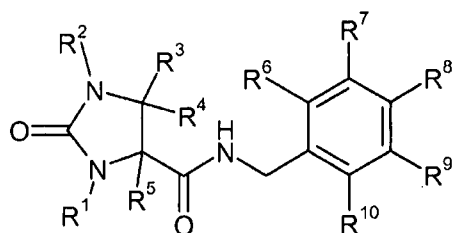
The subject invention also includes isotopically-labeled compounds, which are identical to those recited in formula (I), or salts thereof, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds or salts of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^3H , ^{11}C , ^{14}C , ^{18}F , ^{123}I and ^{125}I .

Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds or salts of the present invention, for example those into which radioactive isotopes such as ^3H , ^{14}C are incorporated, are potentially useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are for

example optionally chosen for their ease of preparation and detectability. ^{11}C and ^8F isotopes are generally useful in PET (positron emission tomography), and ^{125}I isotopes are generally useful in SPECT (single photon emission computerized tomography). PET and SPECT are useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can sometimes afford certain effects resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be chosen in some circumstances. Isotopically labeled compounds of formula (I) or salts thereof of this invention are in one embodiment and in some cases prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

A further particular aspect of the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof which is not a radioactive isotopically labeled compound or salt. In a particular embodiment, the compound or salt is not an isotopically labeled compound or salt.

Preparation of compounds



(I)

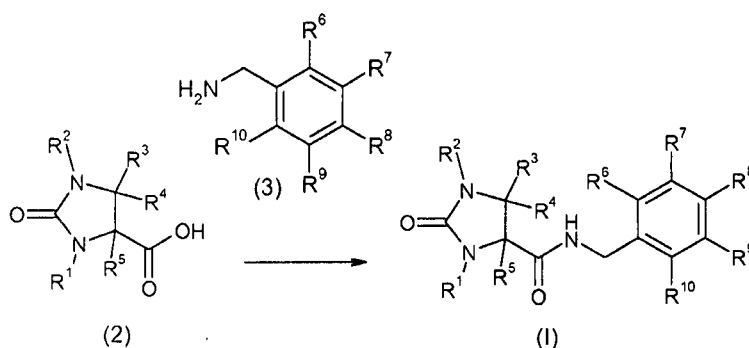
Compounds of formula (I), wherein the variables are as defined above, and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof which comprises:

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- (a) Coupling of a carboxylic acid of formula (2) (or an activated derivative thereof) with an amine of formula (3) (see Scheme 1), wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} are as defined above. Compounds (2) and (3) are optionally protected.
- 5 (b) Deprotecting a compound of formula (I) which is protected. Examples of protecting groups and the means for their removal can be found in T.W. Greene and P.G.M. Wuts 'Protective Groups in Organic Synthesis' (J.Wiley and Sons, 3rd Ed. 1999).
- 10 (c) Interconversion of compounds of formula (I) to other compounds of formula (I). Examples of conventional interconversion procedures include epimerisation, oxidation, reduction, alkylation, aromatic substitution, nucleophilic substitution, amide coupling and ester hydrolysis. One example of interconversion is interconversion of a compound of formula (I) wherein R^2 represents hydrogen to a compound of formula
- 15 (I) wherein R^2 represents a group other than hydrogen as defined herein.

Scheme 1.



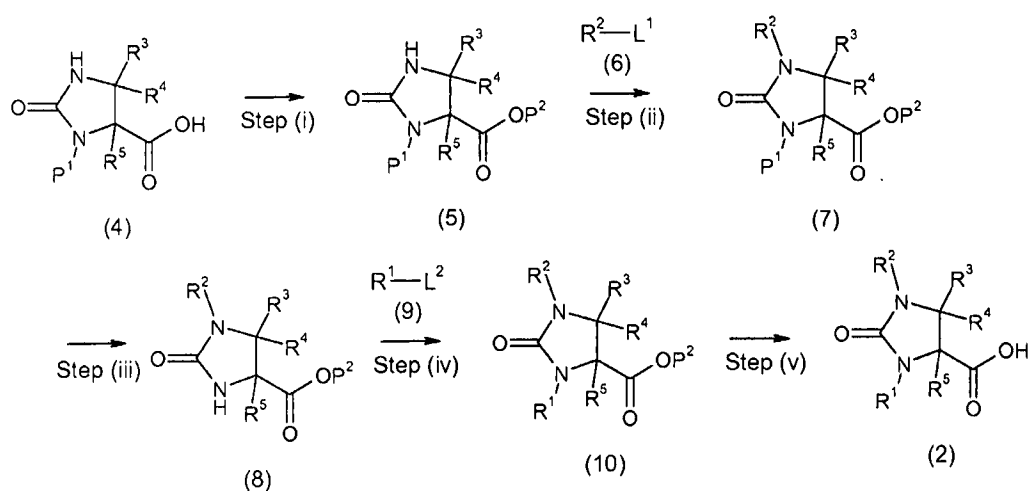
- 20 The coupling of an acid of formula (2) and an amine of formula (3) typically comprises the use of activating agents, such as N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride or polymer-supported carbodiimide, 1-hydroxybenzotriazole (HOBt) or 1-Hydroxy-7-azabenzotriazole (HOAt), and optionally a suitable base such as a tertiary alkylamine (e.g. diisopropylethylamine,
- 25 N-ethyl morpholine, triethylamine) or pyridine, in a suitable solvent such as DMF and/or dichloromethane and at a suitable temperature e.g. between 0°C and room temperature. Alternatively the coupling of (2) and (3) may be accomplished by treatment with O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and a suitable tertiary alkylamine such as
- 30 diisopropylethylamine in a suitable solvent such as dimethylformamide at a suitable

temperature such as room temperature. Alternatively, the compound of formula (2) may be employed as an activated derivative (e.g. acid chloride, mixed anhydride, active ester (e.g. O-acyl-isourea)), and under such circumstances process (a) typically comprises treatment of said activated derivative with an amine (Ogliaruso,

- 5 M.A.; Wolfe, J.F. in *The Chemistry of Functional Groups* (Ed. Patai, S.) *Suppl.B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp442-8; Beckwith, A.L.J. in *The Chemistry of Functional Groups* (Ed. Patai, S.) *Suppl.B: The Chemistry of Amides* (Ed. Zabricky, J.) (John Wiley and Sons, 1970), pp 73 ff).

- 10 Representative methods for the preparation of compounds of formula (2) are shown in Schemes 2 and 3 below:

Scheme 2



Wherein R¹, R², R³, R⁴ and R⁵ are as defined above. P¹ represents a suitable amino protecting group such as benzyloxy carbonyl and P² represents a suitable carboxylate protecting group such as C₁₋₆ alkyl, e.g. t-butyl or methyl. L¹ and L² represent suitable leaving groups such as halogen (e.g. bromine, iodine).

Step (i) typically comprises standard protection of the carboxylic acid (4) as the corresponding carboxylic ester for example by treatment with thionyl chloride in a suitable solvent such as methanol at a suitable temperature such as between 0°C and room temperature.

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Step (ii) typically comprises treatment of compound (5) with a suitable base such as potassium carbonate and an alkylating agent (6) such as an alkyl halide (e.g. methyl iodide) at a suitable temperature, such as between room temperature and 80°C, in a suitable solvent, such as dimethoxyethane, to afford compound (7).

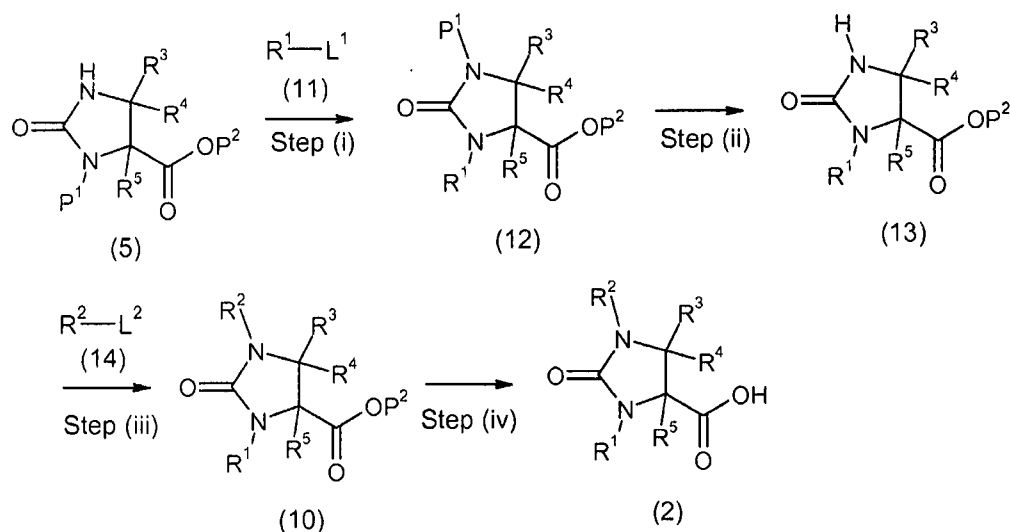
5

Step (iii) comprises deprotection of (7) using standard procedures such as treatment with hydrogen and 5-10% palladium on charcoal in a suitable solvent such as ethyl acetate and at a suitable temperature such as room temperature.

10 Step (iv) typically comprises treatment of compound (8) with a suitable base such as sodium hydride and an alkylating agent (9) such as an alkyl halide (e.g. methyl iodide) at a suitable temperature, such as between -10°C and room temperature, in a suitable solvent, such as dimethylformamide or tetrahydrofuran.

15 Deprotection step (v) typically comprises a standard procedure for conversion of a carboxylic ester (10) to an acid (2), such as use of an appropriate hydroxide salt (e.g. lithium hydroxide) in an appropriate solvent such as a mixture of tetrahydrofuran and water at a suitable temperature such as between 0°C and room temperature.

20 **Scheme 3**



Wherein R^1 , R^2 , R^3 , R^4 and R^5 are as defined above. P^1 represents a suitable amino protecting group such as benzyloxy carbonyl and P^2 represents a suitable carboxylate protecting group such as C_{1-6} alkyl, e.g. t-butyl or methyl. L^1 and L^2 represent suitable leaving groups such as halogen (e.g. bromine, iodine or chlorine).

25

Analogous methods to those described in Scheme 3 and below have been reported previously in S. Saijo et al., *Chem. Pharm. Bull.*, 1980, 28(5), 1459-1467 (e.g. see pp.1459-60 and 1463-1464, incorporated herein by reference), for preparation of certain examples of compounds (12), (13) and (10) from Scheme 3 herein, wherein R^1 and R^2 represent methyl, P^1 represents benzyloxycarbonyl and P^2 represents methyl.

Step (i) typically comprises treatment of (5) with a suitable base such as sodium hydride and a suitable alkylating agent (11) such as methyl iodide in a suitable solvent such as dimethylformamide and at a suitable temperature such as between 0°C and room temperature.

Step (ii) typically comprises deprotection of (12) using standard procedures such as treatment with hydrogen and 10% palladium on charcoal (in the case where P^1 = benzyloxy carbonyl) in a suitable solvent such as methanol and at a suitable temperature such as room temperature.

When the leaving group L^2 is attached to an sp^3 hybridised carbon, for example, R^2-L^2 is an alkyl halide, step (iii) typically comprises treatment of (13) with a suitable base such as sodium hydride and a suitable alkylating agent (14) such as methyl iodide in a suitable solvent such as dimethylformamide and at a suitable temperature such as between 0°C and room temperature. Alternatively, where $R^2 = H$ step (iii) can be omitted.

When the leaving group L^2 is attached to an sp^2 hybridised carbon, for example, R^2-L^2 is an aryl or heteroaryl halide, step (iii) typically comprises the use of a palladium (0) complex such as tris(dibenzylideneacetone)dipalladium(0) in the presence of a base such as cesium carbonate, a ligand such as XantphosTM, in an appropriate solvent such as 1,4-dioxane, at an appropriate temperature such as reflux. Alternatively, step (iii) typically comprises the use of a copper (I) salt, such as copper (I) iodide, in the presence of a base such as potassium phosphate, a ligand such as trans-N,N-dimethylcyclohexane-1,2-diamine, in an appropriate solvent such as 1,4-dioxane, at an appropriate temperature such as reflux.

When the leaving group L^2 is attached to an activated sp^2 hybridised carbon, for example, R^2-L^2 is a 2-bromopyrimidine, step (iii) typically comprises the use of a

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suitable base, such as lithium hexamethyldisilazide, in an appropriate solvent such as tetrahydrofuran, at an appropriate temperature.

5 Deprotection step (iv) typically comprises a standard procedure for conversion of a carboxylic ester (10) to an acid (2), such as use of an appropriate hydroxide salt (e.g. lithium hydroxide) in an appropriate solvent such as a mixture of tetrahydrofuran and water at a suitable temperature such as between 0°C and room temperature.

10 When P² is a tertiary butyl group, deprotection step (iv) typically comprises reaction of a compound of formula (10) with an acid, for example trifluoroacetic acid in a appropriate solvent such as dichloromethane at an appropriate temperature such as room temperature.

15 Compounds of the general formulae (3), (4), (6), (9), (11) and (14) are typically either available from commercial sources or can be prepared by a person skilled in the art using methods described in the chemical literature (or using analogous methods).

20 Where relevant, pharmaceutically acceptable salts may for example be prepared conventionally by reaction with the appropriate acid or acid derivative.

Clinical Indications

25 It is believed that, as compounds or pharmaceutically acceptable salts of the present invention modulate P2X7 receptor function and are capable of antagonizing the effects of ATP at the P2X7 receptor (P2X7 receptor antagonists), they may be useful in the treatment of pain, including acute pain, chronic pain, chronic articular pain, musculoskeletal pain, neuropathic pain, inflammatory pain, visceral pain, pain associated with cancer, pain associated with migraine, tension headache and cluster headaches, pain associated with functional bowel disorders, lower back and neck

30 pain, pain associated with sprains and strains, sympathetically maintained pain; myositis, pain associated with influenza or other viral infections such as the common cold, pain associated with rheumatic fever, pain associated with myocardial ischemia, post operative pain, cancer chemotherapy, headache, toothache and dysmenorrhea.

35 Chronic articular pain conditions include rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis.

Pain associated with functional bowel disorders includes non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome.

Neuropathic pain syndromes include: diabetic neuropathy, sciatica, non-specific
5 lower back pain, trigeminal neuralgia, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, post-herpetic neuralgia, trigeminal neuralgia, and pain resulting from physical trauma, amputation, phantom limb syndrome, spinal surgery, cancer, toxins or chronic inflammatory conditions. In addition, neuropathic pain conditions include pain associated with normally non-painful sensations such as "pins and
10 needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static, thermal or cold allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

15 Other conditions which could potentially be treated by compounds or pharmaceutically acceptable salts of the present invention include fever, inflammation, immunological diseases, abnormal platelet function diseases (e.g. occlusive vascular diseases), impotence or erectile dysfunction; bone disease
20 characterised by abnormal bone metabolism or resorption; hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors, cardiovascular diseases; neurodegenerative diseases and/or neurodegeneration, neurodegeneration following trauma, tinnitus, dependence on a dependence-inducing agent such as opioids (e.g. morphine), CNS depressants (e.g.
25 ethanol), psychostimulants (e.g. cocaine) and nicotine; complications of Type I diabetes, kidney dysfunction, liver dysfunction (e.g. hepatitis, cirrhosis), gastrointestinal dysfunction (e.g. diarrhoea), colon cancer, overactive bladder and urge incontinence. Depression and alcoholism could potentially also be treated by compounds or pharmaceutically acceptable salts of the present invention.

30 Inflammatory conditions include skin conditions (e.g. sunburn, burns, eczema, dermatitis, allergic dermatitis, psoriasis), meningitis, ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis), inflammatory lung disorders (e.g. asthma, bronchitis, emphysema,
35 allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease (COPD), airways hyperresponsiveness); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis,

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- gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation and other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia,
- 5 Hodgkin's disease, sclerodoma, myaesthesia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Bechet's syndrome, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.
- 10 Immunological diseases include autoimmune diseases, immunological deficiency diseases or organ transplantation.
- Bone diseases characterised by abnormal bone metabolism or resorption include osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia,
- 15 hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculosis, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendinitis and bursitis.
- 20 Cardiovascular diseases include hypertension or myocardial ischemia; atherosclerosis; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).
- 25 Neurodegenerative diseases include dementia, particularly degenerative dementia (including senile dementia, dementia with Lewy bodies, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, Amyotrophic Lateral Sclerosis (ALS) and motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial
- 30 space occupying lesions; trauma; infections and related conditions (including HIV infection, meningitis and shingles); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.
- 35 The compounds of formula (I) or pharmaceutically acceptable salts may also be useful for neuroprotection and in the treatment of neurodegeneration following

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trauma such as stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

5 The compounds or pharmaceutically acceptable salts of the present invention may also be useful in the treatment of malignant cell growth and/or metastasis, and myoblastic leukaemia.

10 Complications of Type 1 diabetes include diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy, macular degeneration, glaucoma, nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

Kidney dysfunction includes nephritis, glomerulonephritis, particularly mesangial proliferative glomerulonephritis and nephritic syndrome.

15 It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

20 According to a further aspect of the invention, we therefore provide a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in therapy and/or for use in human or veterinary medicine.

25 According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment or prevention (e.g. treatment) of a condition which is mediated by P2X7 receptors, for example a condition or disease disclosed herein (in particular pain, inflammation or a neurodegenerative disease, more particularly pain such as inflammatory pain, neuropathic pain or visceral pain), e.g. in a mammal such as a human or rodent e.g. human or rat e.g. human.

30 According to a further aspect of the invention, we provide a method of treating a human or animal (e.g. rodent e.g. rat) subject, for example a human subject, suffering from a condition which is mediated by P2X7 receptors, for example a condition or disease disclosed herein (in particular pain, inflammation or a neurodegenerative disease, more particularly pain such as inflammatory pain, neuropathic pain or visceral pain), which comprises administering to said subject an
35 effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

40

According to a further aspect of the invention we provide a method of treating a human or animal (e.g. rodent e.g. rat) subject, for example a human subject, suffering from pain, inflammation, an immunological disease, a bone disease or a neurodegenerative disease (in particular pain, inflammation or a neurodegenerative disease, more particularly pain such as inflammatory pain, neuropathic pain or visceral pain), which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

10 According to a yet further aspect of the invention we provide a method of treating a human or animal (e.g. rodent e.g. rat) subject, for example a human subject, suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

15 According to a further aspect of the invention we provide a method of treating a subject, for example a human subject, suffering from Alzheimer's disease which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

20 According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention (e.g. treatment) of a condition which is mediated by the action of P2X7 receptors, for example a condition or disease disclosed herein (in particular pain, inflammation or a neurodegenerative disease, more particularly pain such as inflammatory pain, neuropathic pain or visceral pain), e.g. in a mammal such as a human or rodent e.g. human or rat e.g. human.

30 According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention (e.g. treatment) of pain, inflammation, an immunological disease, a bone disease or a neurodegenerative disease (in particular pain, inflammation or a neurodegenerative disease, more particularly pain such as inflammatory pain, neuropathic pain or visceral pain), e.g. in a mammal such as a human or rodent e.g. human or rat e.g. human.



According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention (e.g. treatment) of inflammatory pain, neuropathic pain or visceral pain, e.g. in a mammal such as a human or rodent e.g. human or rat e.g. human.

In one aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention (e.g. treatment) of Alzheimer's disease, e.g. in a mammal such as a human or rodent e.g. human or rat e.g. human.

In order to use a compound of formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, adapted for use in human or veterinary medicine.

In order to use a compound of formula (I) a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable carrier or excipient.

The pharmaceutical composition may be for use in a method of treatment or in a use or in a treatment or prevention, as described herein.

A pharmaceutical composition of the invention, which may be prepared by admixture, for example at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration. As such, the pharmaceutical composition may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain excipients, such as binding agents, fillers, tableting lubricants, disintegrants and/or acceptable wetting agents. The tablets may be coated, e.g. according to methods known in normal pharmaceutical practice.

5

- Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

10

For parenteral administration, fluid unit dosage forms are for example prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. In one particular embodiment, the compound or salt, depending on the vehicle and concentration used, is either suspended or dissolved in the vehicle. In preparing solutions, the compound or salt can e.g. be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. In one embodiment, adjuvant(s) such as a local anaesthetic, a preservative and/or a buffering agent are dissolved in the vehicle. To enhance the stability, the composition can for example be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are typically prepared in substantially the same manner, except that the compound or salt is typically suspended in the vehicle instead of being dissolved, and sterilization is not usually readily accomplished by filtration. The compound or salt can be sterilised e.g. by exposure to ethylene oxide before suspension in a sterile vehicle. In a particular embodiment, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound or salt of the invention.

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In one embodiment, the composition contains from 0.1% to 99% by weight, in particular from 10 to 60% by weight, of the active material (the compound or pharmaceutically acceptable salt of the invention), e.g. depending on the method of administration.

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The dose of the compound or pharmaceutically acceptable salt thereof used in the treatment or prevention (e.g. treatment) of the aforementioned disorders / diseases / conditions may vary in the usual way with the seriousness of the disorders, the

weight of the sufferer, and/or other similar factors. However, as a general guide, in one embodiment a suitable unit dose of 0.05 to 1000 mg, for example 0.05 to 200 mg, such as 20 to 40 mg, of the compound or pharmaceutically acceptable salt of the invention (measured as the compound), may be used. In one embodiment, such a unit dose is for administration once a day e.g. to a mammal such as a human; alternatively such a unit dose may be for administration more than once (e.g. twice) a day e.g. to a mammal such as a human. Such therapy may extend for a number of weeks or months.

10 Combinations

Compounds of formula (I) or salts thereof may be used in combination with other therapeutic agents, for example medicaments claimed to be useful in the treatment of the above mentioned disorders.

15

Suitable examples of other such therapeutic agents may include a β 2-agonist (also known as β 2 adrenoceptor agonists; e.g. formoterol) and/or a corticosteroid (e.g. budesonide, fluticasone (e.g. as propionate or furoate esters), mometasone (e.g. as furoate), beclomethasone (e.g. as 17-propionate or 17,21-dipropionate esters), ciclesonide, triamcinolone (e.g. as acetate), flunisolide, rofleponide and butixocort (e.g. as propionate ester), for the treatment of respiratory disorders (such as asthma and chronic obstructive pulmonary disease (COPD)) as described in WO 2007/008155 and WO 2007/008157.

25

A further therapeutic agent may include a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor (e.g. atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) for the treatment of cardiovascular disorders (such as atherosclerosis) as described in WO 2006/083214.

30

A further therapeutic agent may include a non-steroid anti-inflammatory drug (NSAID; e.g. ibuprofen, naproxen, aspirin; celecoxib, diclofenac, etodolac, fenoprofen, indomethacin, ketoprofen, ketoralac, oxaprozin, nabumetone, sulindac, tolmetin, rofecoxib, valdecoxib, lumiracoxib, meloxicam, etoricoxib and parecoxib) for the treatment of an inflammatory disease or disorder (such as rheumatoid arthritis or osteoarthritis) as described in WO 2005/025571.

35

A further therapeutic agent may include a tumour necrosis factor α (TNF α) inhibitor (e.g. Etanercept or an anti- TNF α antibody such as Infliximab and Adalimumab) for the treatment of an inflammatory disease or disorder (such as rheumatoid arthritis or osteoarthritis) as described in WO 2004/105798.

5

A further therapeutic agent may include 2-hydroxy-5- [[4- [(2- pyridinylamino) sulfonyl] phenyl] azo] benzoic acid (sulfasalazine) for the treatment of an inflammatory disease or disorder (such as rheumatoid arthritis) as described in WO 2004/105797.

10

A further therapeutic agent may include N-[4-[[(2, 4-diamino-6-pteridiny) methyl] methylamino] benzoyl]- L-glutamic acid (methotrexate) for the treatment of an inflammatory disease or disorder (such as rheumatoid arthritis) as described in WO 2004/105796.

15

A further therapeutic agent may include an inhibitor of pro TNF α convertase enzyme (TACE) for the treatment of an inflammatory disease or disorder (such as rheumatoid arthritis) as described in WO 2004/073704.

20

A further therapeutic agent may include:

a) sulfasalazine;

b) a statin, such as atorvastatin, lovastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, crilvastatin, dalvastatin, rosuvastatin, tenivastatin, fluindostatin, velostatin, dalvastatin, nisvastatin, bervastatin, pitavastatin, rivastatin, glenvastatin, eptastatin, tenivastatin, flurastatin, rosuvastatin or itavastatin;

25

c) a glucocorticoid agent, such as dexamethasone, methylprednisolone, prednisolone, prednisone and hydrocortisone;

d) an inhibitor of p38 kinase;

e) an anti-IL-6-receptor antibody;

30

f) anakinra;

g) an anti-IL-1 monoclonal antibody;

h) an inhibitor of JAK3 protein tyrosine kinase;

i) an anti-macrophage colony stimulation factor (M-CSF) monoclonal antibody; or

j) an anti-CD20 monoclonal antibody, such as rituximab, PRO70769, HuMax-CD20

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(Genmab AJS), AME-133 (Applied Molecular Evolution), or hA20 (Immunomedics, Inc.)

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for the treatment of an IL-1 mediated disease (such as rheumatoid arthritis) as described in WO 2006/003517.

5 When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

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

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

20 When a compound of formula (I) or a pharmaceutically acceptable salt thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone.

25 The following Descriptions and Examples illustrate the preparation of compounds or salts of the invention but are not intended to be limiting.

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Examples:

The general methods (a)-(c), along with the synthetic methods outlined in Schemes 1, 2 and 3 above, for the preparation of compounds or salts of the present invention are further illustrated by the following examples.

Some abbreviations used herein:

DCM - dichloromethane

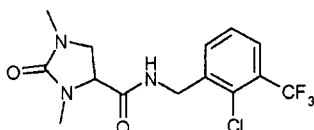
DMF – N,N-dimethylformamide

TFA - trifluoroacetic acid

XantphosTM refers to 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, which is commercially available e.g. from Aldrich; CAS no. 161265-03-8.

(4S)-2-Oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid, which is used herein as the original starting material in many of the examples e.g. Examples 1 and 13, is commercially available, e.g. from Sigma-Aldrich, UK or US (catalogue no. 392308); and has CAS number 59760-01-9. This compound and its preparation is also described in M. P. Doyle and J. T. Colyer, *Tetrahedron: Asymmetry*, 2003, 14(22), 3601-3604 (see e.g. Experimental 4.2, and Results and discussion section first paragraph and Equation (1)), incorporated herein by reference.

Example 1 N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide (**E1**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



Crude 1,3-Dimethyl-2-oxo-4-imidazolidinecarboxylic acid (0.098 g, ~0.619 mmol, prepared as described below) was dissolved in dimethylformamide (5 ml) and treated with 1-hydroxybenzotriazole (0.092 g, 0.681 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.131 g, 0.681 mmol), [(2-chloro-3-trifluoromethylphenyl)methyl]amine (0.156 g, 0.743 mmol) and N-ethylmorpholine (0.166 ml, 1.30 mmol). The mixture was stirred at room temperature (22°C) for 18

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- hours then reduced *in vacuo* to give a residue which was purified by mass-directed automated HPLC to give a colourless gum. Trituration of the gum with diethyl ether (1 ml) and drying gave a pale yellow gum which was further purified by flash silica-gel column chromatography (eluting with a gradient of 0-100% ethyl acetate in dichloromethane (in 10% steps)) to give partially pure (~80%) product as a white solid (0.042 g). A final purification step, again using mass-directed automated HPLC, gave *N*-{[2-chloro-3-(trifluoromethyl)phenyl]methyl}-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide as a white solid (0.031 g). LC/MS $[M+H]^+ = 350$, retention time = 2.29 minutes.
- Enantiomeric excess = 99.1%, as determined by chiral chromatography Method (C), indicative of (4*S*)-*N*-{[2-chloro-3-(trifluoromethyl)phenyl]methyl}-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide, retention time = 8.30 minutes

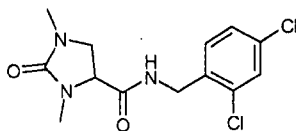
- The 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:
- (i) (4*S*)-2-Oxo-3-[(phenylmethyl)oxy]carbonyl-4-imidazolidinecarboxylic acid (10.25 g, 38.8 mmol) was dissolved in anhydrous methanol (100 ml) and cooled to 0°C under argon. Thionyl chloride (4.25 ml, 58.2 mmol) was then added dropwise to the mixture and then the mixture was allowed to warm to room temperature and stirred overnight. The mixture was reduced *in vacuo* and the residue was partitioned between dichloromethane (300 ml) and saturated aqueous sodium hydrogen carbonate (100 ml). The aqueous layer was separated and extracted with dichloromethane (300 ml). The organic layers were then combined, passed through a hydrophobic frit and reduced *in vacuo* to give 5-methyl 1-(phenylmethyl) 2-oxo-1,5-imidazolidinedicarboxylate (10.67 g) as a white solid.
- (ii) 5-Methyl 1-(phenylmethyl) 2-oxo-1,5-imidazolidinedicarboxylate (10.67 g, 38 mmol) and potassium carbonate (10.6 g, 76 mmol) were suspended in dimethoxyethane (150 ml) and treated with methyl iodide (9.46 ml, 152 mmol). The reaction mixture was heated to reflux and stirred under argon for 18 hrs. The mixture was then cooled and evaporated *in vacuo* and the resulting residue was partitioned between ethyl acetate (750 ml) and brine (200 ml). The organic layer was separated, passed through a hydrophobic frit and reduced *in vacuo*. The resulting residue was purified by automated flash silica gel column chromatography (Biotage SP4), eluting with a 20-60% gradient of ethyl acetate in hexane, to give 5-methyl 1-(phenylmethyl) 3-methyl-2-oxo-1,5-imidazolidinedicarboxylate (5.77 g) as an orange oil.
- (iii) A suspension of 5-Methyl 1-(phenylmethyl) 3-methyl-2-oxo-1,5-imidazolidinedicarboxylate (5.77 g) and 5% palladium on carbon (5 g) in ethyl acetate

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(300 ml) was placed under a hydrogen atmosphere and stirred for 24 hrs. The mixture was then filtered and reduced *in vacuo* to yield methyl 1-methyl-2-oxo-4-imidazolidinecarboxylate (2.76 g) as a white solid which was used without further purification.

- 5 (iv) A solution of methyl 1-methyl-2-oxo-4-imidazolidinecarboxylate (1.76 g, 11.1 mmol) in anhydrous dimethylformamide (20 ml) was cooled to -10°C under argon and treated with methyl iodide (2.76 ml, 44.4 mmol). Sodium hydride (60% in oil, 0.422 g, 10.5 mmol) was then added in portions over a period of 20 minutes. The mixture was allowed to warm to room temperature (in the cooling bath) and stirred for 18 hrs.
- 10 The reaction mixture was then reduced *in vacuo* and the residue partitioned between ethyl acetate (150 ml) and brine (50 ml). The aqueous layer (containing a fine suspension) was separated and extracted with more ethyl acetate (100 ml). The organic extracts were then combined, passed through a hydrophobic frit, and reduced *in vacuo* to give an orange oil. This material was purified by flash silica gel
- 15 column chromatography, eluting with 50% ethyl acetate in hexane and then with a gradient of 50-100% in hexane, to give methyl 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylate (1.123 g) as a colourless oil which was used without further purification.
- (v) Methyl 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylate (1.12 g) was dissolved in
- 20 10 ml of a 3:2 mixture of tetrahydrofuran and water respectively, then cooled to 0°C and treated with lithium hydroxide (0.156 g). The reaction was stirred between 0-5°C for 4 hrs, then acidified with 2N aqueous hydrogen chloride (4 ml) and reduced *in vacuo*. The residue was dissolved in methanol and loaded onto 2 x 10g NH₂ solid-phase extraction (SPE) cartridges and eluted with methanol (2 column volumes) and
- 25 then with a 10% mixture of 2N aqueous hydrogen chloride in methanol (2 column volumes). The latter fractions were combined and evaporated to give crude 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylic acid (0.098 g) as a colourless gum which was used without any additional purification.

- 30 **Example 2** *N*-[(2,4-dichlorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide (**E2**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[{(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



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N-[(2,4-dichlorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide (**E2**) was prepared in an analogous manner to that described above for the synthesis of *N*-{[2-chloro-3-(trifluoromethyl)phenyl]methyl}-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide (**E1**) but using [(2,4-dichlorophenyl)methyl]amine in the place of [(2-chloro-3-trifluoromethylphenyl)methyl]amine. LC/MS [M+H]⁺ = 316, retention time = 2.19 minutes.

Furthermore the methyl 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylate used in the above procedure (see description of method used to prepare 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylic acid) was prepared in a slightly different manner and is described below:

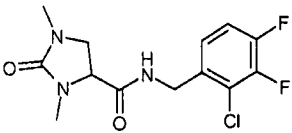
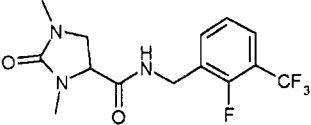
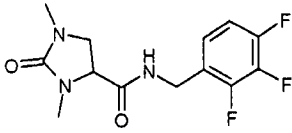
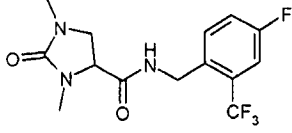
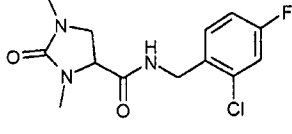
Methyl 1-methyl-2-oxo-4-imidazolidinecarboxylate (1g, 6.32 mmol) (prepared as described in step (iii) of Example 1, starting from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) was dissolved in anhydrous tetrahydrofuran (10 ml), cooled to -10°C under argon, and treated with methyl iodide (1.57 ml, 25.3 mmol). Sodium hydride (60% in oil, 0.24 g, 6.0 mmol) was then added in portions over a period of 15 minutes and the mixture was allowed to warm to room temperature and stirred for 18 hrs. The reaction mixture was then reduced *in vacuo* and the residue partitioned between ethyl acetate (40 ml) and brine (20 ml). The organic layer was separated, passed through a hydrophobic frit, and reduced *in vacuo* to give a yellow oil. This material was purified by automated flash silica gel column chromatography (Biotage SP4), eluting with 50% ethyl acetate in hexane (5 column volumes) and then with a gradient of 50-80% in hexane (15 column volumes), to give methyl 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylate (0.479 g) as a yellow oil which was used without further purification.

Examples 3-7 (in forms obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

In a manner analogous to that described for Example 2 above the compounds tabulated below (Table 1) were prepared by substituting the appropriate amine (or salt thereof) for the [(2,4-dichlorophenyl)methyl]amine used in the above procedure. All of the amines used to make the amines shown in Table 1 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

Table 1

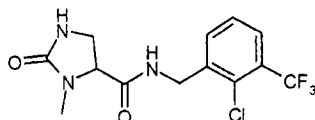
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Exempl e no.	Chemical name	[M+H] ⁺	Retentio n time (mins)
E3	 N-[(2-chloro-3,4- difluorophenyl)methyl]-1,3- dimethyl-2-oxo-4- imidazolidinecarboxamide	318	2.06
E4	 N-{[2-fluoro-3- (trifluoromethyl)phenyl]met hyl}-1,3-dimethyl-2-oxo-4- imidazolidinecarboxamide	334	2.18
E5	 1,3-dimethyl-2-oxo-N- [(2,3,4- trifluorophenyl)methyl]-4- imidazolidinecarboxamide	302	1.93
E6	 N-{[4-fluoro-2- (trifluoromethyl)phenyl]met hyl}-1,3-dimethyl-2-oxo-4- imidazolidinecarboxamide	334	2.16
E7	 N-[(2-chloro-4-fluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide	300	1.97

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Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
	N-[(2-chloro-4-fluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide		

Example 8 N-[(2-chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E8**) (e.g. in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



Crude 3-methyl-2-oxo-4-imidazolidinecarboxylic acid (~0.63 mmol, prepared as described below) was dissolved in dimethylformamide (3 ml) and treated with 1-hydroxybenzotriazole (0.094 g, 0.69 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.132 g, 0.69 mmol), [(2-chloro-3-trifluoromethylphenyl)methyl]amine (0.145 g, 0.69 mmol) and N-ethylmorpholine (0.169 ml, 1.32 mmol). The mixture was stirred at 22°C for 20 hours then reduced *in vacuo* to give a residue which was purified by mass-directed automated HPLC to give N-[(2-chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide as a white solid (0.105 g). LC/MS [M+H]⁺ = 336, retention time = 2.18 minutes.

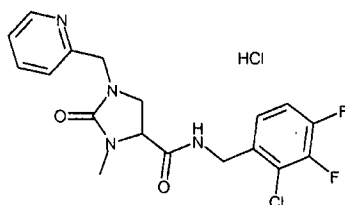
The 3-methyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

(i) A solution of 5-methyl 1-(phenylmethyl) 2-oxo-1,5-imidazolidinedicarboxylate (5 g, 18 mmol) (prepared as described in step (i) of Example 1, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) in dimethylformamide (27 ml) was added dropwise to a suspension of sodium hydride (60% in oil, 0.72 g, 18 mmol) in dimethylformamide (45 ml) at 0°C under an argon atmosphere. The cooling bath was removed and the mixture stirred under argon for 1 hr then treated with methyl iodide (5.6 ml). The mixture was stirred at 22°C for a further 18 hrs and

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- then reduced *in vacuo* to give a residue which was partitioned between ethyl acetate (250 ml) and brine (75 ml). The organic layer was separated, using a hydrophobic frit, and then reduced *in vacuo* to give an orange oil. The oil was purified flash-silica gel column chromatography, eluting with 30% ethyl acetate in hexanes (3 column volumes) and then with a 30-70% gradient of ethyl acetate in hexanes (10 column volumes), to give 4-methyl 1-(phenylmethyl) 3-methyl-2-oxo-1,4-imidazolidinedicarboxylate (3.65 g) as a colourless oil.
- (ii) 4-Methyl 1-(phenylmethyl) 3-methyl-2-oxo-1,4-imidazolidinedicarboxylate (3.65 g, 12.5 mmol) was dissolved in methanol (300 ml) and hydrogenated in the presence of 10% palladium on carbon (0.5 g). The mixture was stirred for 18 hrs at 22°C, then filtered and reduced *in vacuo* to give methyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (1.90 g) as a white solid which was used in the next step without further purification.
- (iii) Methyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (0.150 g, 0.948 mmol) was dissolved in a 3:2 mixture of tetrahydrofuran and water respectively (2.5 ml) and cooled to 0°C. The mixture was then treated with lithium hydroxide (0.068 g, 2.84 mmol) and stirred with ice/water cooling for a further 5 hrs. The mixture was acidified to pH1 by addition of 2N hydrochloric acid (3 ml) and the resulting mixture was then reduced *in vacuo* to give 3-methyl-2-oxo-4-imidazolidinecarboxylic acid as a white solid (0.260 g) which was used without any further purification.

Example 9 N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyridinylmethyl)-4-imidazolidinecarboxamide hydrochloride (**E9**)



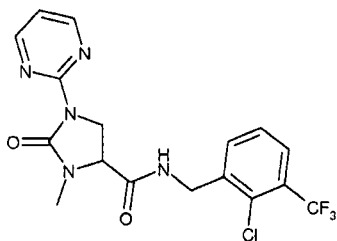
- A mixture of crude 3-methyl-2-oxo-1-(2-pyridinylmethyl)-4-imidazolidinecarboxylic acid (~0.7 mmol), 1-hydroxybenzotriazole hydrate (113 mg, 0.84 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (161 mg, 0.84 mmol), and N-ethyl morpholine (0.27 ml, 2.1 mmol) in dichloromethane (20 ml) / N,N-dimethylformamide (2 ml) was stirred at room temperature for 10 minutes. A solution of [(2-chloro-3,4-difluorophenyl)methyl]amine (150 mg, 0.84 mmol) in dichloromethane (5 ml) was added and the reaction stirred at room temperature for 18 hours. The mixture was diluted with dichloromethane and the solution was washed with saturated sodium hydrogen carbonate solution, water and brine, dried and evaporated. The residue

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- was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane. The residue was triturated with ether/hexanes and the solid was dried. The residue was dissolved in dichloromethane (2 ml), hydrogen chloride (1M in ether, 0.1 ml) was added and the solvent was evaporated. The solid was co-
- 5 evaporated with ethyl acetate and ether and then triturated with ether. The solid was collected and dried to give *N*-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyridinylmethyl)-4-imidazolidinecarboxamide hydrochloride (40 mg). LC/MS $[M+H]^+ = 395$, retention time = 1.85 minutes.
- 10 The 3-methyl-2-oxo-1-(2-pyridinylmethyl)-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:
- (i) A suspension of sodium hydride (240 mg, 6 mmol, 60% dispersion in oil) in *N*-methyl-2-pyrrolidinone (6 ml) was stirred at 0°C under argon. A solution of methyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (474 mg, 3 mmol) (prepared as described in
- 15 step (ii) of Example 8) in *N*-methyl-2-pyrrolidinone (3 ml) was added dropwise over 10 minutes. The reaction was stirred at 0°C for 15 minutes and 2-(bromomethyl)pyridine hydrobromide (835 mg, 3.3 mmol) was added portionwise over 5 minutes. The mixture was stirred at 0°C for 30 minutes and then at room temperature for 20 hours. The reaction was treated with ice water and extracted with
- 20 dichloromethane. The mixture was applied to a SCX ion exchange cartridge and washed with methanol and then 2M ammonia in methanol. The basic fractions were combined and evaporated. The residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to give methyl 3-methyl-2-oxo-1-(2-pyridinylmethyl)-4-imidazolidinecarboxylate (190 mg), LC/MS $[M+H]^+ = 250$.
- 25 (ii) A stirred solution of methyl 3-methyl-2-oxo-1-(2-pyridinylmethyl)-4-imidazolidinecarboxylate (190 mg, 0.76 mmol) in tetrahydrofuran (1.5 ml) / water (1 ml) at 0°C was treated with lithium hydroxide (55 mg, 2.28 mmol) and the reaction mixture was stirred at 0-5°C for 3 hours. The reaction was acidified to pH 2 with 2N hydrochloric acid and the solvent was evaporated. The residue was dried to give 3-
- 30 methyl-2-oxo-1-(2-pyridinylmethyl)-4-imidazolidinecarboxylic acid which was used crude in the next step.

Example 10 *N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide (E10)

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- A suspension of crude 3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxylic acid (0.6 mmol) in dichloromethane (10 ml) was treated with 1-hydroxybenzotriazole hydrate (98 mg, 0.72 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (138 mg, 0.72 mmol) and N-ethyl morpholine (0.3 ml, 2.4 mmol) was stirred at room temperature for 10 minutes. {[2-Chloro-3-(trifluoromethyl)phenyl]methyl}amine (126 mg, 0.6 mmol) was added. The reaction was diluted with dichloromethane (10 ml) and N,N-dimethylformamide (1 ml) and stirred at room temperature for 18 hours. Additional 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (138 mg, 0.72 mmol) was added and the suspension was stirred at room temperature for 5 days. The mixture was diluted with dichloromethane and the solution was washed with saturated sodium hydrogen carbonate solution, water, citric acid solution, water and brine, dried and evaporated. The residue was purified by mass-directed automated HPLC. The solid was triturated with ether/hexanes, collected and dried to give *N*-{[2-chloro-3-(trifluoromethyl)phenyl]methyl}-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide (42 mg), LC/MS $[M+H]^+ = 414$, retention time = 2.30 minutes.
- The 3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:
- (i) A suspension of methyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (316 mg, 2 mmol) (prepared as described in step (ii) of Example 8) in THF (10 ml) was stirred at -40°C. Lithium hexamethyldisilazide (2 ml, 1M solution in THF) was added dropwise and the mixture was stirred at -40°C for 15 minutes and then at -70°C for 1 hour. A solution of 2-bromopyrimidine (318 mg, 2 mmol) in THF (1 ml) was added dropwise and the reaction was stirred at -70°C for 1 hour and then warmed to 0°C over 1 hour and then stirred at room temperature overnight. The reaction mixture was diluted with citric acid solution and dichloromethane. The organic layer was separated, washed with water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to give

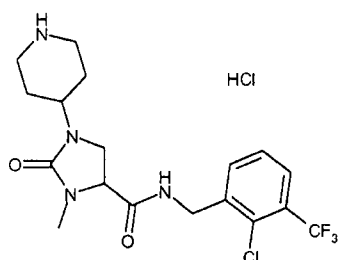
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crude methyl 3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxylate (144 mg) which was used in the next step, LC/MS $[M+H]^+ = 237$.

- (ii) A stirred solution of methyl 3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxylate (144 mg, 0.6 mmol) in THF (1.5 ml) at 0°C was treated with lithium hydroxide (72 mg, 3 mmol) in water (1 ml) and the reaction mixture was stirred at 0-5°C for 1 hours. The reaction was acidified to pH 2 with 2N hydrochloric acid and the solvent was evaporated. The residue dried to give 3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxylic acid which was used crude in the next step, LC/MS $[M+H]^+ = 223$.

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Example 11 *N*-{[2-Chloro-3-(trifluoromethyl)phenyl]methyl}-3-methyl-2-oxo-1-(4-piperidinyl)-4-imidazolidinecarboxamide hydrochloride (**E11**)



- 15 A solution of 1,1-dimethylethyl 4-{4-[[[2-chloro-3-(trifluoromethyl)phenyl]methyl]amino]carbonyl}-3-methyl-2-oxo-1-imidazolidinyl}-1-piperidinecarboxylate (218 mg, 0.42 mmol) in 1,4-dioxane (3 ml) was treated with 4M hydrogen chloride in 1,4-dioxane (1 ml) and the reaction was stirred at room temperature for 4 hours. The solvent was evaporated and the gum was dissolved in methanol and the solvent evaporated. The residue was triturated with ether and the solid was collected and dried to give *N*-{[2-chloro-3-(trifluoromethyl)phenyl]methyl}-3-methyl-2-oxo-1-(4-piperidinyl)-4-imidazolidinecarboxamide hydrochloride (153 mg, 80%), LC/MS $[M+H]^+ = 419$, retention time = 1.75 minutes.

- 25 The 1,1-dimethylethyl 4-{4-[[[2-chloro-3-(trifluoromethyl)phenyl]methyl]amino]carbonyl}-3-methyl-2-oxo-1-imidazolidinyl}-1-piperidinecarboxylate used in the method described above was prepared as follows:
- (i) A solution of 1,1-dimethylethyl 4-oxo-1-piperidinecarboxylate (3.0 g, 15 mmol) in THF (45 ml) was stirred at -78°C under argon. Lithium hexamethyldisilazide (15 ml, 15 mmol, 1M solution in THF) was added dropwise and the reaction was stirred at -78°C for 1 hour. A solution of 1,1,1-trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (6.43 g, 18 mmol) in THF (12 ml) was

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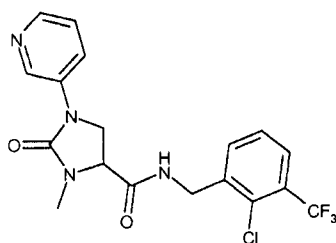
- added dropwise. The reaction was allowed to warm to room temperature over 2 hours. The reaction was quenched by the addition of water and the THF was evaporated. The residue was extracted with ether. The ether layer was separated and washed with water, 2N sodium hydroxide solution, water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 5-25% ethyl acetate in hexanes to give 1,1-dimethylethyl 4-
5 {{{(trifluoromethyl)sulfonyl}oxy}-3,6-dihydro-1(2*H*)-pyridinecarboxylate (2.91 g, 59%).
- (ii) A solution of 1,1-dimethylethyl 4-{{{(trifluoromethyl)sulfonyl}oxy}-3,6-dihydro-1(2*H*)-pyridinecarboxylate (2.65 g, 8 mmol), methyl 3-methyl-2-oxo-4-
10 imidazolidinecarboxylate (1.26 g, 8 mmol) (prepared as described in step (ii) of Example 8) in 1,4-dioxane (50 ml) was treated with cesium carbonate (3.91 g, 12 mmol), XantphosTM (348 mg, 0.6 mmol) and tris(dibenzylideneacetone)dipalladium(0) (183 mg, 0.2 mmol). The mixture was flushed with argon and the reaction was heated at reflux for 1 hour. After cooling to room temperature, the reaction mixture
15 was diluted with water and extracted with ethyl acetate. The organic layers were washed with water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 0-100% ethyl acetate in hexanes to give 1,1-dimethylethyl 4-{3-methyl-4-[(methyloxy)carbonyl]-2-oxo-1-imidazolidinyl}-3,6-dihydro-1(2*H*)-pyridinecarboxylate (1.7 g, 63%), LC/MS [M+H]⁺ = 340.
- (iii) A solution of 1,1-dimethylethyl 4-{3-methyl-4-[(methyloxy)carbonyl]-2-oxo-1-imidazolidinyl}-3,6-dihydro-1(2*H*)-pyridinecarboxylate (1.36 g, 4 mmol) in ethyl acetate (30 ml) containing palladium on charcoal (100 mg, 10% paste) was hydrogenated at room temperature and pressure for 24 hours. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by
25 silica gel chromatography eluting with 50-100% ethyl acetate in hexanes to give 1,1-dimethylethyl 4-{3-methyl-4-[(methyloxy)carbonyl]-2-oxo-1-imidazolidinyl}-1-piperidinecarboxylate (205 mg, 15%), LC/MS [M+H]⁺ = 342.
- (iv) A solution of 1,1-dimethylethyl 4-{3-methyl-4-[(methyloxy)carbonyl]-2-oxo-1-imidazolidinyl}-1-piperidinecarboxylate (200 mg, 0.58 mmol) in THF (3 ml) was stirred at 0°C. A solution of lithium hydroxide (15 mg, 0.64 mmol) in water (2 ml) was added and the reaction was stirred at 0°C under argon for 90 minutes. The solution was acidified to pH 4 with 2N hydrochloric acid and the solvent was evaporated. The residue was co-evaporated with toluene and the residue dried over phosphorous pentoxide under high vacuum to give crude 1-(1-{{{(1,1-dimethylethyl)oxy}carbonyl}-4-piperidinyl}-3-methyl-2-oxo-4-imidazolidinecarboxylic acid which was used in the next
35 step, LC/MS [M+H]⁺ = 328.

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(v) To a stirred suspension of 1-(1-[[[1,1-dimethylethyl]oxy]carbonyl]-4-piperidinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid (0.55 mmol) in dichloromethane (10 ml) was added 1-hydroxybenzotriazole hydrate (89 mg, 0.66 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (127 mg, 0.66 mmol) and N-ethylmorpholine (0.21 ml, 1.65 mmol) and the mixture was stirred at room temperature for 15 minutes. A solution of [[2-chloro-3-(trifluoromethyl)phenyl]methyl]amine (115 mg, 0.55 mmol) was added and the reaction was stirred at room temperature for 3 hours. The reaction was diluted with dichloromethane and the solution was washed with saturated sodium hydrogen carbonate solution, water, citric acid solution, water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 5-10% methanol in dichloromethane to give 1,1-dimethylethyl 4-{4-[[[2-chloro-3-(trifluoromethyl)phenyl]methyl]amino]carbonyl]-3-methyl-2-oxo-1-imidazolidinyl}-1-piperidinecarboxylate (243 mg, 85%), LC/MS $[M+H]^+ = 519$, retention time = 2.89 minutes.

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Example 12 *N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-(3-pyridinyl)-4-imidazolidinecarboxamide (**E12**)



A mixture of crude 3-methyl-2-oxo-1-(3-pyridinyl)-4-imidazolidinecarboxylic acid (0.8 mmol), 1-hydroxybenzotriazole hydrate (147 mg, 0.96 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (184 mg, 0.96 mmol), and N-ethylmorpholine (0.307 ml, 2.4 mmol) in dichloromethane (15 ml) was stirred at room temperature for 10 minutes. A solution of [[2-chloro-3-(trifluoromethyl)phenyl]methyl]amine (168 mg, 0.8 mmol) in dichloromethane (1 ml) was added and the reaction stirred at room temperature for 4 hours. The mixture was partitioned between dichloromethane and saturated sodium hydrogen carbonate solution. The organic phase was separated, washed with water and brine, dried and evaporated. The residue was purified by mass-directed automated HPLC. The solid was dissolved in methanol (5 ml) and anhydrous HCl in ether (1M, 0.5 ml) was added and the solution was evaporated. The resulting solid was collected, washed with ether and dried to give a pale yellow solid. The solid was dissolved in methanol and applied to a SCX ion exchange cartridge and washed with methanol and then 2M

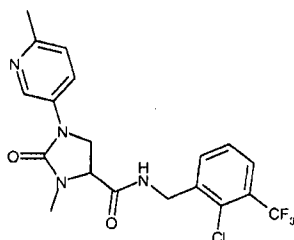
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ammonia in methanol. The basic fractions were combined and evaporated and the resulting residue was triturated with ether, collected and dried to give *N*-{[2-Chloro-3-(trifluoromethyl)phenyl]methyl}-3-methyl-2-oxo-1-(3-pyridinyl)-4-imidazolidinecarboxamide (27 mg, 8%). LC/MS $[M+H]^+ = 413$, retention time = 1.96 minutes.

The 3-methyl-2-oxo-1-(3-pyridinyl)-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

- (i) A solution of 3-bromopyridine (316 mg, 2. mmol) and methyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (316 mg, 2 mmol) (prepared as described in step (ii) of Example 8) in 1,4-dioxane (10 ml) was treated with cesium carbonate (977 mg, 3 mmol), XantphosTM (87 mg, 0.15 mmol) (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, e.g. available from Aldrich, CAS no. 161265-03-8) and tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol) and the mixture was heated under reflux under argon for 22 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate (x3). The organic layers were combined, washed with water and brine and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to give methyl 3-methyl-2-oxo-1-(3-pyridinyl)-4-imidazolidinecarboxylate (273 mg, 58%). LC/MS $[M+H]^+ = 236$.
- (ii) A solution of methyl 3-methyl-2-oxo-1-(3-pyridinyl)-4-imidazolidinecarboxylate (0.27 g, 1.15 mmol) in tetrahydrofuran (3 ml) at 0°C was treated with a solution of lithium hydroxide (0.030 g, 1.26 mmol) in water (2 ml) and the mixture was stirred at 0°C for 90 minutes. Hydrochloric acid (2M) was added to adjust the pH of the reaction mixture to pH 2 and the solvent was evaporated. The residue was dried over phosphorus pentoxide to give crude 3-methyl-2-oxo-1-(3-pyridinyl)-4-imidazolidinecarboxylic acid which was used in the next step. LC/MS $[M+H]^+ = 222$.

Example 13 *N*-{[2-Chloro-3-(trifluoromethyl)phenyl]methyl}-3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (**E13**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



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A mixture of 3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt (175 mg, 0.5 mmol), 1-hydroxybenzotriazole hydrate (115 mg, 0.75 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg, 0.75 mmol) and N-ethyl morpholine (0.319 ml, 2.5 mmol) in dichloromethane (8 ml) was stirred at
5 room temperature for 10 minutes. A solution of {[2-chloro-3-(trifluoromethyl)phenyl]methyl}amine (105 mg, 0.5 mmol) in dichloromethane (2 ml) was added and the reaction stirred at room temperature for 4 hours. The mixture was partitioned between dichloromethane and saturated sodium hydrogen carbonate solution. The organic phase was separated, washed with water and brine, dried and
10 evaporated. The residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to give N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (95 mg, 44%). LC/MS $[M+H]^+$ = 427, retention time = 1.98 minutes.

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The 3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt used in the method described above was prepared as follows:

Step (i) Phosphorus oxychloride (2.2 ml, 24 mmol) was added dropwise to a stirred solution of (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid
20 (5.28 g, 20 mmol) in pyridine (10 ml), tert-butanol (15 ml) and chloroform (25 ml) at -10 °C. The mixture was stirred at -5 to 0°C for 30 minutes and then at room temperature for 4 hours. The solution was added dropwise to stirred ice water (200 ml) containing sodium acetate (~ 40 g). The mixture was diluted with chloroform (100 ml) and the mixture was stirred for 30 minutes. The organic layer was separated,
25 washed with cold 0.1M hydrochloric acid, water, saturated sodium hydrogen carbonate solution, water and brine, dried (MgSO₄) and evaporated. The residue was dried to give 5-(1,1-dimethylethyl) 1-(phenylmethyl) 2-oxo-1,5-imidazolidinedicarboxylate (5.65 g, 88%) as a colourless solid. LC/MS $[M+H]^+$ = 321.

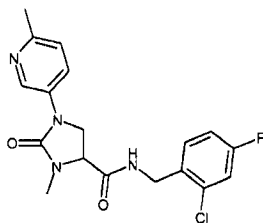
30 [For a method similar to this step (i), see: K. Hayashi et al., *J. Med. Chem.*, 1989, 32(2), 289-297; e.g. see Scheme 1 and compounds (5) and (6a) on p.289 therein and synthesis of compound (6a) in p.293 experimental section therein, incorporated herein by reference.]

Step (ii) To a stirred solution of 5-(1,1-dimethylethyl) 1-(phenylmethyl) 2-oxo-1,5-
35 imidazolidinedicarboxylate (4.16 g, 13 mmol) in DMF (60 ml) at 0°C was added sodium hydride (60% dispersion in oil) (0.546 g, 13.65 mmol). After 40 minutes at

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- 0°C iodomethane (4.06 ml, 65.0 mmol) was added and the reaction was allowed to warm to room temperature. After 6 hours the solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was separated, washed with water and brine, dried (MgSO₄) and evaporated. The residue was purified by silica gel chromatography eluting with 30-100% ethyl acetate in hexanes to give 4-(1,1-dimethylethyl) 1-(phenylmethyl) 3-methyl-2-oxo-1,4-imidazolidinedicarboxylate (3.12 g, 9.33 mmol, 72 %) (LC/MS [M+H]⁺ = 335) and 5-(1,1-dimethylethyl) 1-(phenylmethyl) 3-methyl-2-oxo-1,5-imidazolidinedicarboxylate (560 mg, 1.675 mmol, 12 %) (LC/MS [M+H]⁺ = 335).
- Step (iii) A solution of 4-(1,1-dimethylethyl) 1-(phenylmethyl) 3-methyl-2-oxo-1,4-imidazolidinedicarboxylate (3.12 g, 9.33 mmol) in methanol (40 ml) containing Pd/C (10% paste, 400 mg) was hydrogenated at room temperature and pressure for 18 hours. The mixture was filtered through a filter pad and the pad washed with methanol. The filtrates were combined, evaporated and dried to give 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (1.76g, 94%). LC/MS [M+H]⁺ = 201.
- Step (iv) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (300 mg, 1.5 mmol) and 5-bromo-2-methylpyridine (258 mg, 1.5 mmol) in 1,4-dioxane (10 ml) was treated with cesium carbonate (733 mg, 2.25 mmol), XantphosTM (65.1 mg, 0.113 mmol) and tris(dibenzylideneacetone)dipalladium(0) (34.3 mg, 0.038 mmol) and the mixture was heated under reflux under argon for 18 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water and brine and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to give 1,1-dimethylethyl 3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxylate (352 mg, 81%). LC/MS [M+H]⁺ = 292.
- Step (v) A solution of 1,1-dimethylethyl 3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxylate (352 mg, 1.2 mmol) in TFA/DCM (1:2, 6ml) was stirred at room temperature for 6 hours. The solution was evaporated and the residue was dried to give crude acid (assume ~ 1.2 mmol, TFA salt) which was used in the next step. LC/MS [M+H]⁺ = 236.

- Example 14** N-[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (**E14**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

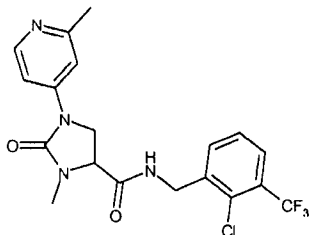


In a manner analogous to that described in Example 13 above N-[(2-chloro-4-fluorophenyl)methyl]-3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-

imidazolidinecarboxamide was prepared substituting [(2-chloro-4-

5 fluorophenyl)methyl]amine for the [(2-chloro-3-(trifluoromethyl)phenyl)methyl]amine used in the above procedure. LC/MS $[M+H]^+ = 377$, retention time = 1.71 minutes.

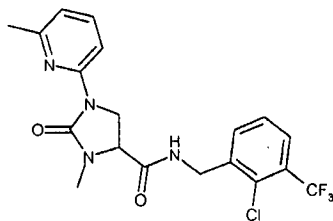
Example 15 N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(2-methyl-4-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (**E15**) (in a form obtainable or
10 prepared from (4S)-2-oxo-3-[(phenylmethyl)oxy]carbonyl-4-imidazolidinecarboxylic acid)



In a manner analogous to that described in Example 13 above N-[(2-chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(2-methyl-4-pyridinyl)-2-oxo-4-

15 imidazolidinecarboxamide was prepared substituting 4-bromo-2-methylpyridine for 5-bromo-2-methylpyridine used in Step (iv) of the above procedure. LC/MS $[M+H]^+ = 427$, retention time = 1.91 minutes.

Example 16 N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(6-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (**E16**) (in a form obtainable or prepared
20 from (4S)-2-oxo-3-[(phenylmethyl)oxy]carbonyl-4-imidazolidinecarboxylic acid)



A mixture of 3-methyl-1-(6-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt (147 mg, 0.42 mmol), 1-hydroxybenzotriazole hydrate (96 mg, 0.63 mmol),

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (121 mg, 0.63 mmol) and N-ethyl morpholine (0.27 ml, 2.1 mmol) in dichloromethane (8 ml) was stirred at room temperature for 10 minutes. A solution of {[2-chloro-3-(trifluoromethyl)phenyl]methyl}amine (88 mg, 0.42 mmol) in dichloromethane (2 ml) was added and the reaction stirred at room temperature for 4 hours. The mixture was partitioned between dichloromethane and saturated sodium hydrogen carbonate solution. The organic phase was separated, washed with water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to give N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(6-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (110 mg, 61%). LC/MS $[M+H]^+$ = 427, retention time = 2.66 minutes.

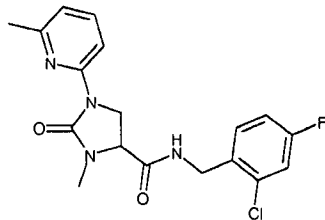
The 3-methyl-1-(6-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt used in the method described above was prepared as follows:

(i) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (300 mg, 1.5 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 2-bromo-6-methylpyridine (258 mg, 1.5 mmol) in 1,4-dioxane (10 ml) was treated with cesium carbonate (733 mg, 2.25 mmol), XantphosTM (65.1 mg, 0.113 mmol) and tris(dibenzylideneacetone)dipalladium(0) (34.3 mg, 0.038 mmol) and the mixture was heated under reflux under argon for 18 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water and brine and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with 0-100% ethyl acetate in isohexane to give 1,1-dimethylethyl 3-methyl-1-(6-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxylate (246 mg, 56%). LC/MS $[M+H]^+$ = 292.

(ii) A solution of 1,1-dimethylethyl 3-methyl-1-(6-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxylate (246 mg, 0.84 mmol) in TFA/DCM (1:2, 6ml) was stirred at room temperature for 6 hours. The solution was evaporated and the residue was dried to give 3-methyl-1-(6-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt (assume ~ 0.84 mmol) which was used in the next step. LC/MS $[M+H]^+$ = 236.

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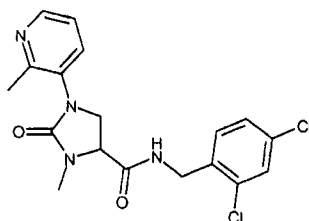
Example 17 N-[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-1-(6-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (**E17**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



- 5 In a manner analogous to that described in Example 16 above N-[(2-chloro-4-fluorophenyl)methyl]-3-methyl-1-(6-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxamide was prepared substituting [(2-chloro-4-fluorophenyl)methyl]amine for the [(2-chloro-3-(trifluoromethyl)phenyl)methyl]amine used in the above procedure. LC/MS $[M+H]^+$ = 377, retention time = 2.33 minutes.

10

Example 18 N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (**E18**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



- 15 A mixture of 3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt (279 mg, 0.8 mmol), 1-hydroxybenzotriazole hydrate (147 mg, 0.96 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (184 mg, 0.96 mmol) and N-ethyl morpholine (0.613 ml, 4.8 mmol) in dichloromethane (18 ml) was stirred at room temperature for 10 minutes. A solution of [1-(2,4-
- 20 dichlorophenyl)methyl]amine (141 mg, 0.8 mmol) in dichloromethane (2 ml) was added and the reaction stirred at room temperature for 4 hours. The mixture was partitioned between dichloromethane and saturated sodium hydrogen carbonate solution. The organic phase was separated, washed with water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 0-
- 25 10% methanol in dichloromethane to give N-[(2,4-dichlorophenyl)methyl]-3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (147 mg, 47%). LC/MS $[M+H]^+$ = 393, retention time = 1.76 minutes.

b4

Enantiomeric excess = 95.7%, as determined by chiral chromatography Method (C), indicative of (4*S*)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide, retention time = 8.06 minutes.

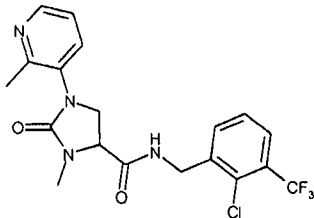
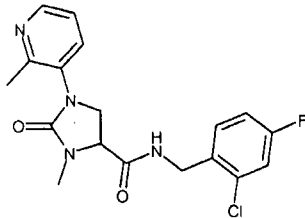
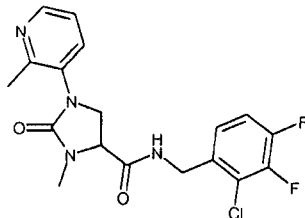
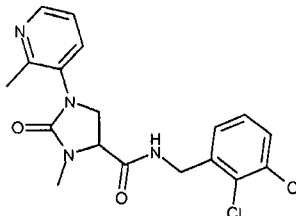
- 5 The 3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt used in the method described above was prepared as follows:
- (i) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (600 mg, 3.00 mmol) (prepared as described in step (iii) of Example 13) and 3-bromo-2-methylpyridine (515 mg, 3.00 mmol) in 1,4-dioxane (20 ml) was treated with cesium carbonate (1464 mg, 4.49 mmol), XantphosTM (130 mg, 0.225 mmol) and
- 10 tris(dibenzylideneacetone)dipalladium(0) (68.6 mg, 0.075 mmol) and the mixture was heated under reflux under argon for 18 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water and brine and evaporated in vacuo. The
- 15 residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to give 1,1-dimethylethyl 3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxylate (738 mg, 85%). LC/MS [M+H]⁺ = 292.
- (ii) A solution of 1,1-dimethylethyl 3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxylate (738 mg, 2.53 mmol) in TFA/DCM (1:2, 12ml) was stirred at
- 20 room temperature for 6 hours. The solution was evaporated and the residue was co-evaporated with toluene and dried to give crude 3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt (assume ~ 2.5 mmol) which was used in the next step.
- 25 Examples 19-22 (in forms obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

In a manner analogous to that described for Example 18 above the compounds tabulated below (Table 2) were prepared by substituting the appropriate amine (or

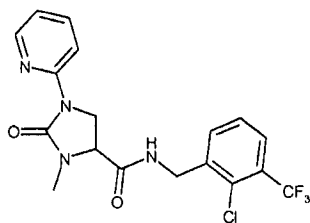
30 salt thereof) for the [(2,4-dichlorophenyl)methyl]amine used in the above procedure. All of the amines used to make the amines shown in Table 2 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

35 Table 2

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Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E19	 <i>N</i>-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(2-methyl-4-pyridinyl)-2-oxo-4-imidazolidinecarboxamide	427	1.97
E20	 <i>N</i>-[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide	377	1.69
E21	 <i>N</i>-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide	395	1.65
E22	 <i>N</i>-[(2,3-Dichlorophenyl)methyl]-3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide	393	1.73

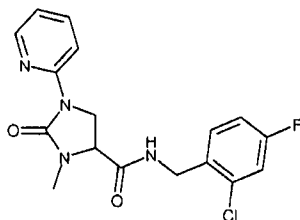
Example 23 N-{{2-Chloro-3-(trifluoromethyl)phenyl}methyl}-3-methyl-2-oxo-1-(2-pyridinyl)-4-imidazolidinecarboxamide (**E23**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[{(phenylmethyl)oxy}carbonyl]-4-imidazolidinecarboxylic acid)



- 5 A mixture of 3-methyl-2-oxo-1-(2-pyridinyl)-4-imidazolidinecarboxylic acid TFA salt (117 mg, 0.35 mmol), 1-hydroxybenzotriazole hydrate (80 mg, 0.525 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (101 mg, 0.525 mmol) and N-ethyl morpholine (0.224 ml, 1.75 mmol) in dichloromethane (8 ml) was stirred at room temperature for 10 minutes. A solution of {{2-chloro-3-
- 10 (trifluoromethyl)phenyl}methyl}amine (73.4 mg, 0.35 mmol) in dichloromethane (2 ml) was added and the reaction stirred at room temperature for 18 hours. The mixture was partitioned between dichloromethane and saturated sodium hydrogen carbonate solution. The organic phase was separated, washed with water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 0-
- 15 10% methanol in dichloromethane to give N-{{2-chloro-3-(trifluoromethyl)phenyl}methyl}-3-methyl-2-oxo-1-(2-pyridinyl)-4-imidazolidinecarboxamide (90 mg, 62%). LC/MS $[M+H]^+$ = 413, retention time = 2.55 minutes.
- 20 The 3-methyl-2-oxo-1-(2-pyridinyl)-4-imidazolidinecarboxylic acid TFA salt used in the method described above was prepared as follows:
- (i) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (400 mg, 2 mmol) (prepared as described in step (iii) of Example 13) and 2-bromopyridine (316 mg, 2 mmol) in 1,4-dioxane (10 ml) was treated with cesium carbonate (977 mg, 3 mmol), XantphosTM (87 mg, 0.15 mmol) and
- 25 tris(dibenzylideneacetone)dipalladium(0) (45.8 mg, 0.05 mmol) and the mixture was heated under reflux under argon for 18 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water and brine and evaporated in vacuo. The
- 30 residue was purified by silica gel chromatography eluting with 0-100% ethyl acetate in isohexane (2 columns required) to give 1,1-dimethylethyl 3-methyl-2-oxo-1-(2-pyridinyl)-4-imidazolidinecarboxylate (198 mg, 36%). LC/MS $[M+H]^+$ = 278.

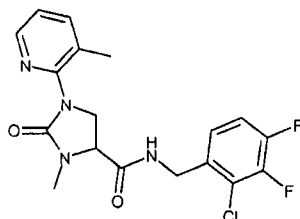
(ii) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-1-(2-pyridinyl)-4-imidazolidinecarboxylate (198 mg, 0.71 mmol) in TFA/DCM (1:2, 4.5 ml) was stirred at room temperature for 8 hours. The solution was evaporated and the residue was dried to give 3-methyl-2-oxo-1-(2-pyridinyl)-4-imidazolidinecarboxylic acid TFA salt (assume ~ 0.71 mmol)) which was used in the next step. LC/MS $[M+H]^+ = 222$.

Example 24 *N*-[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyridinyl)-4-imidazolidinecarboxamide (**E24**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



In a manner analogous to that described in Example 23 above *N*-[(2-chloro-4-fluorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyridinyl)-4-imidazolidinecarboxamide was prepared substituting [(2-chloro-4-fluorophenyl)methyl]amine for the [(2-chloro-3-(trifluoromethyl)phenyl)methyl]amine used in the above procedure. LC/MS $[M+H]^+ = 363$, retention time = 2.21 minutes.

Example 25 *N*-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (**E25**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



A mixture of 3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt (279 mg, 0.8 mmol), 1-hydroxybenzotriazole hydrate (147 mg, 0.96 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (184 mg, 0.96 mmol) and *N*-ethyl morpholine (0.613 ml, 4.8 mmol) in dichloromethane (20 ml) was stirred at room temperature for 10 minutes. [(2-Chloro-3,4-difluorophenyl)methyl]amine hydrochloride (171 mg, 0.8 mmol) was added and the reaction stirred at room temperature for 18 hours. The mixture was diluted with dichloromethane and was washed with 3N citric acid solution. The organic phase was separated, washed with

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brine, dried and evaporated. The residue was purified by mass-directed automated HPLC to give N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (145 mg, 46%). LC/MS $[M+H]^+$ = 395, retention time = 2.36 minutes.

5

The 3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt used in the method described above was prepared as follows:

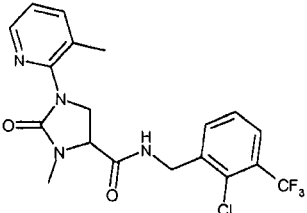
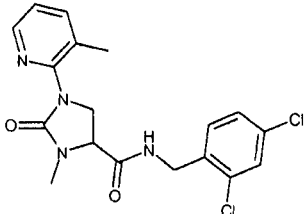
- (i) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (600 mg, 3 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 2-bromo-3-methylpyridine (515 mg, 3 mmol) in 1,4-dioxane (20 ml) was treated with cesium carbonate (1464 mg, 4.5 mmol), XantphosTM (130 mg, 0.225 mmol) and tris(dibenzylideneacetone)dipalladium(0) (68.6 mg, 0.075 mmol) and the mixture was heated under reflux under argon for 18 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water and brine and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with 0-100% ethyl acetate in isohexane to give 1,1-dimethylethyl 3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxylate (700 mg, 80%). LC/MS $[M+H]^+$ = 292.
- (ii) A solution of 1,1-dimethylethyl 3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxylate (700 mg, 2.4 mmol) in TFA/DCM (1:2, 12ml) was stirred at room temperature for 6 hours. The solution was evaporated and the residue was co-evaporated with toluene and dried to give 3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt (assume ~ 2.4 mmol) which was used in the next step. LC/MS $[M+H]^+$ = 236.

Examples 26-27 (in forms obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

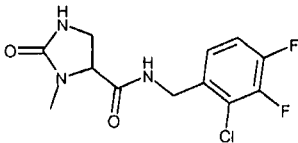
- In a manner analogous to that described for Example 25 above the compounds tabulated below (Table 3) were prepared by substituting the appropriate amine (or salt thereof) for the [(2-chloro-3,4-difluorophenyl)methyl]amine hydrochloride used in the above procedure. All of the amines used to make the amines shown in Table 3 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

6d

Table 3

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E26	 N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxamide	427	2.54
E27	 N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxamide	393	2.47

Example 28 N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E28**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



A mixture of 3-methyl-2-oxo-4-imidazolidinecarboxylic acid (115 mg, 0.8 mmol), 1-hydroxybenzotriazole hydrate (147 mg, 0.96 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (184 mg, 0.96 mmol) and N-ethyl morpholine (0.613 ml, 4.8 mmol) in dichloromethane (18 ml) was stirred at room temperature for 10 minutes. A solution of [(2-chloro-3,4-difluorophenyl)methyl]amine (142 mg, 0.8 mmol) in dichloromethane (2 ml) was added and the reaction stirred at room temperature for 18 hours. The mixture was diluted with dichloromethane (60



ml) and the mixture was washed with 3N citric acid solution (30 ml). The organic phase was separated, washed with brine, dried and evaporated. The residue was purified by mass-directed automated HPLC to give N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (95mg, 39%).

5 LC/MS [M+H]⁺ = 304, retention time = 1.99 minutes.

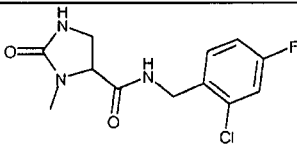
The 3-methyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

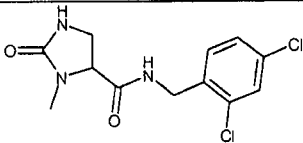
10 A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (801 mg, 4 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-
15 {[(phenylmethyl)oxy]carbonyl}-4-imidazolidinecarboxylic acid) in TFA/DCM (trifluoroacetic acid / dichloromethane) (1:2, 9 ml) was stirred at room temperature for 6 hours. The solution was evaporated, the residue was co-evaporated with toluene and dried to give crude 3-methyl-2-oxo-4-imidazolidinecarboxylic acid (assume ~ 4 mmol) which was used in the next step. LC/MS [M+H]⁺ = 145.

Examples 29-30 (in forms obtainable or prepared from (4S)-2-oxo-3-
{[(phenylmethyl)oxy]carbonyl}-4-imidazolidinecarboxylic acid)

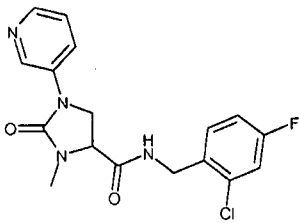
20 In a manner analogous to that described for Example 28 above the compounds tabulated below (Table 4) were prepared by substituting the appropriate amine (or salt thereof) for the [(2-chloro-3,4-difluorophenyl)methyl]amine used in the above procedure. All of the amines used to make the amines shown in Table 4 are available from commercial sources or can be prepared using routes described previously in the
25 chemical literature or analogous methods.

Table 4

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E29	 N-[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide	286	1.89

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E30	 <i>N</i> -[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide	302	2.10

Example 31 *N*-[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-2-oxo-1-(3-pyridinyl)-4-imidazolidinecarboxamide (**E31**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

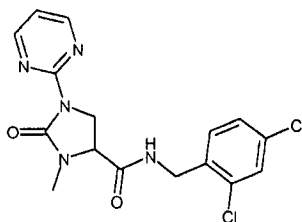


5 A solution of *N*-[(2-chloro-4-fluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (28.6 mg, 0.1 mmol) (prepared as described in Example 29) and 3-bromopyridine (15.8 mg, 0.1 mmol) in 1,4-dioxane (3 ml) was treated with cesium carbonate (81 mg, 0.25 mmol), XantphosTM (4.3 mg, 0.075 mmol) and

10 tris(dibenzylideneacetone)dipalladium(0) (2.3 mg, 0.025 mmol) and the mixture was heated under reflux under argon for 18 hours. After cooling to room temperature, the reaction mixture was diluted with saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The organic layers were combined, washed with water and brine and evaporated in vacuo. The residue was purified by silica gel

15 chromatography eluting with 0-10% methanol in dichloromethane. The resulting residue was triturated with ether, the solid collected and dried to give *N*-[(2-chloro-4-fluorophenyl)methyl]-3-methyl-2-oxo-1-(3-pyridinyl)-4-imidazolidinecarboxamide (18 mg, 50%). LC/MS [M+H]⁺ = 363 , retention time 1.68 minutes.

20 **Example 32** *N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide (**E32**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



A mixture of 3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxylic acid TFA salt (168 mg, 0.5 mmol), 1-hydroxybenzotriazole hydrate (101 mg, 0.75 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg, 0.75 mmol) and N-ethyl morpholine (0.316 ml, 2.5 mmol) in dichloromethane (8 ml) was stirred at room temperature for 10 minutes. A solution of [1-(2,4-dichlorophenyl)methyl]amine (0.067 ml, 0.5 mmol) in dichloromethane (2 ml) was added and the reaction stirred at room temp for 4 hours. The mixture was partitioned between dichloromethane and saturated sodium hydrogen carbonate, The organic phase was separated, washed with water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane to give N-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide (20 mg, 10.5 % yield). LC/MS $[M+H]^+$ = 380, retention time = 2.22 minutes.

15

The 3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxylic acid TFA salt used in the method described above was prepared as follows:

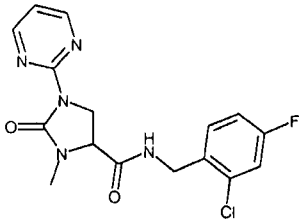
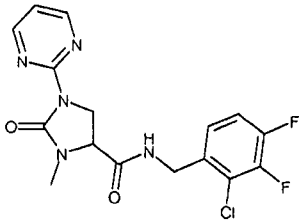
- (i) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (801 mg, 4 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 2-bromopyrimidine (636 mg, 4 mmol) in 1,4-dioxane (20 ml) was treated with cesium carbonate (1955 mg, 6 mmol), XantphosTM (174 mg, 0.3 mmol) and tris(dibenzylideneacetone)dipalladium(0) (92 mg, 0.1 mmol) and the mixture was heated under reflux under argon for 1 hour. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water and brine and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with 0-20% methanol in ethyl acetate to 1,1-dimethylethyl 3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxylate (360 mg, 32%). LC/MS $[M+H]^+$ = 279.
- (ii) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxylate (0.557 g, 2 mmol) in TFA/DCM (1:2, 7.5 ml) was stirred at room temperature for 6 hours. The solution was evaporated and the residue was

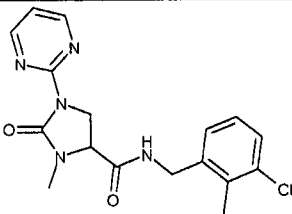
dried to give crude (4S)-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxylic acid TFA salt (assume ~ 2 mmol) which was used in the next step. LC/MS [M+H]⁺ = 223.

5 Examples 33-35 (in forms obtainable or prepared from (4S)-2-oxo-3-
 {[(phenylmethyl)oxy]carbonyl}-4-imidazolidinecarboxylic acid)

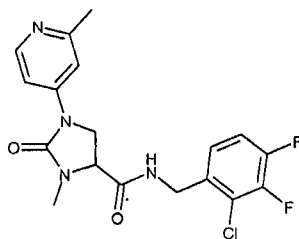
10 In a manner analogous to that described for Example 32 above the compounds
 tabulated below (Table 5) were prepared by substituting the appropriate amine (or
 salt thereof) for the [1-(2,4-dichlorophenyl)methyl]amine used in the above
 procedure. All of the amines used to make the amines shown in Table 5 are available
 from commercial sources or can be prepared using routes described previously in the
 chemical literature or analogous methods.

15 Table 5

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E33	 N-[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide	366	2.03
E34	 N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide	382	2.11

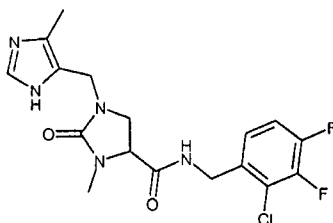
Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E35	 <i>N</i> -[(3-Chloro-2-methylphenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide	360	2.18

Example 36 *N*-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(2-methyl-4-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (**E36**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



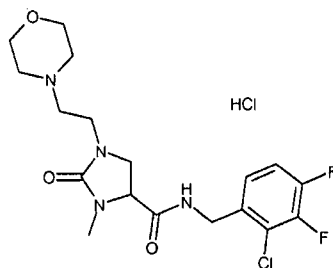
A solution of *N*-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (152 mg, 0.5 mmol) (prepared as described in Example 28) and 4-bromo-2-methylpyridine (86 mg, 0.5 mmol) in 1,4-dioxane (3 ml) was treated with cesium carbonate (244 mg, 0.75 mmol), XantphosTM (21.7 mg, 0.038 mmol) and tris(dibenzylideneacetone)dipalladium(0) (11.5 mg, 0.013 mmol) and the mixture was heated under reflux under argon for 3 hours. After cooling to room temperature, the reaction mixture was diluted with saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The organic layers were combined, washed with water and brine and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane. The resulting residue was triturated with ether, the solid was collected and dried to give *N*-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(2-methyl-4-pyridinyl)-2-oxo-4-imidazolidinecarboxamide (123 mg, 62%). LC/MS [M+H]⁺ = 395, retention time = 1.68 minutes.

Example 37 N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-[(4-methyl-1H-imidazol-5-yl)methyl]-2-oxo-4-imidazolidinecarboxamide (**E37**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



5 A solution of N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (152 mg, 0.5 mmol) (prepared as described in Example 28), (4-methyl-1H-imidazol-5-yl)methanol hydrochloride (93 mg, 0.625 mmol) and p-toluene sulfonic acid monohydrate (19 mg, 0.100 mmol) in N-methyl-2-pyrrolidone (1 ml) was heated at 130 °C under argon for 3 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane. The solution was washed with saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was purified by mass-directed automated HPLC, followed by trituration with ether to give N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-1-[(4-methyl-1H-imidazol-5-yl)methyl]-2-oxo-4-imidazolidinecarboxamide (147 mg, 74%). LC/MS [M+H]⁺ = 398, retention time = 1.57 minutes.

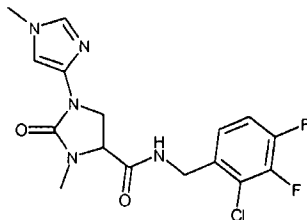
Example 38 N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxamide hydrochloride (**E38**)



20 A mixture of N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (100 mg, 0.33 mmol) (prepared as described in Example 28) and potassium carbonate (91 mg, 0.66 mmol) in DMF (1 ml) was stirred at room temperature for 10 minutes and 4-(2-chloroethyl)morpholine hydrochloride (61 mg, 0.33 mmol) was added. The mixture was stirred for 30 minutes and then heated at 60°C for 3h and 80°C for 2h. The mixture was cooled to room temperature and sodium hydride (40 mg, 60% dispersion in oil, 1 mmol) was added and the mixture

heated at 50°C for 16h. The reaction mixture was cooled to room temperature and diluted with dichloromethane. The solution was washed with saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was purified by mass-directed automated HPLC to give two components with same molecular ion. Each component was converted to the corresponding HCl salt by dissolving the product from mass-directed automated HPLC in methanol/dichloromethane, adding an excess of 1M HCl in ether, evaporating the solvent, co-evaporating the residue with methanol and ether. The residue was triturated with ether/heptane and the solid collected and dried to give N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxamide hydrochloride (22 mg, 15%) (LC/MS [M+H]⁺ = 417, retention time = 1.40 minutes) and N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxamide hydrochloride (6 mg, 4%) (LC/MS [M+H]⁺ = 417, retention time = 1.55 minutes).

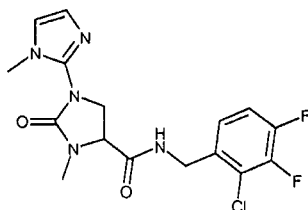
Example 39 N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxamide (**E39**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



To a stirred mixture of N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (100 mg, 0.33 mmol) (prepared as described in Example 28), 4-bromo-1-methyl-1H-imidazole (63.8 mg, 0.396 mmol) in 1,4-dioxane (6 ml) was added potassium phosphate (350 mg, 1.65 mmol), copper (I) iodide (62.8 mg, 0.33 mmol) and trans-N,N-dimethylcyclohexane-1,2-diamine (0.052 ml, 0.33 mmol) and the mixture was heated at reflux under argon for 1h. The mixture was cooled to room temperature and partitioned between saturated sodium hydrogen carbonate solution and dichloromethane. The organic extracts were separated, washed with water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 0-20% methanol in dichloromethane, followed by mass-directed automated HPLC to give N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-1-

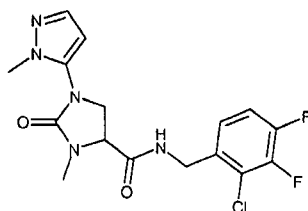
(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxamide (15 mg, 12%).
LC/MS $[M+H]^+ = 384$, retention time = 1.71 minutes.

- Example 40** N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-2-yl)-2-oxo-4-imidazolidinecarboxamide (**E40**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



- To a stirred mixture of N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (91 mg, 0.3 mmol) (prepared as described in Example 28) and 2-bromo-1-methyl-1H-imidazole (48.3 mg, 0.3 mmol) in 1,4-dioxane (6 ml) was added potassium phosphate (318 mg, 1.5 mmol), copper (I) iodide (57.1 mg, 0.3 mmol) and trans-N,N-dimethylcyclohexane-1,2-diamine (0.047 ml, 0.3 mmol) and the mixture was heated at reflux under argon for 3 hours. The mixture was cooled to room temperature and partitioned between saturated sodium hydrogen carbonate solution and dichloromethane. The organic extracts were separated, washed with water and brine, dried and evaporated. The residue was purified by mass-directed automated HPLC to give N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-2-yl)-2-oxo-4-imidazolidinecarboxamide (22 mg, 19%). LC/MS $[M+H]^+ = 384$, retention time = 1.69 minutes.

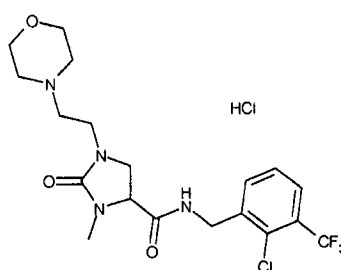
- Example 41** N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(1-methyl-1H-pyrazol-5-yl)-2-oxo-4-imidazolidinecarboxamide (**E41**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



To a stirred mixture of N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (60.7 mg, 0.2 mmol) (prepared as described in Example

28), 5-iodo-1-methyl-1H-pyrazole (41.6 mg, 0.2 mmol) in 1,4-dioxane (4 ml) was added potassium phosphate (212 mg, 1 mmol), copper (I) iodide (38.1 mg, 0.2 mmol) and trans-N,N-dimethylcyclohexane-1,2-diamine (0.032 ml, 0.2 mmol) and the mixture was heated at reflux under argon for 1h. The mixture was cooled to room temperature and partitioned between saturated sodium hydrogen carbonate solution and dichloromethane. The organic extracts were separated, washed with water and brine, dried and evaporated. The residue was purified by mass-directed automated HPLC to give N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(1-methyl-1H-pyrazol-5-yl)-2-oxo-4-imidazolidinecarboxamide (18 mg, 23%). LC/MS [M+H]⁺ = 384, retention time = 2.22 minutes.

Example 42 N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxamide hydrochloride (**E42**)



A mixture of 3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxylic acid TFA salt (186 mg, 0.5 mmol), N-ethyl morpholine (0.383 ml, 3 mmol), 1-hydroxybenzotriazole hydrate (92 mg, 0.6 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg, 0.6 mmol) in dichloromethane (9 ml) was stirred at room temperature for 10 minutes. A solution of [[2-chloro-3-(trifluoromethyl)phenyl]methyl]amine (105 mg, 0.5 mmol) in dichloromethane (1 ml) was added and the reaction stirred at room temperature for 18 hours. The mixture was diluted with dichloromethane and was washed with saturated sodium hydrogen carbonate solution. The organic phase was separated, washed with brine, dried and evaporated. The residue was purified by mass-directed automated HPLC. The product from mass-directed automated HPLC was dissolved in methanol (2 ml) and an excess of 1M hydrogen chloride in ether (0.5 ml) was added. The solvent was evaporated, the residue was triturated with ether and the solid collected and dried to give N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxamide hydrochloride (73 mg, 30%). LC/MS [M+H]⁺ = 449, retention time = 1.80 minutes.

The 3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxylic acid TFA salt used in the method described above was prepared as follows:

(i) To a stirred solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (1.0 g, 5 mmol) (prepared as described in step (iii) of

5 Example 13) in N,N-dimethylformamide (20 ml) at 0°C was added sodium hydride (60% dispersion in oil) (220 mg, 5.5 mmol). After 10 minutes a solution of 4-(2-chloroethyl)morpholine (898 mg, 6 mmol) in N,N-dimethylformamide (2 ml) and potassium iodide (166 mg, 1 mmol) was added and the mixture was heated at 70°C for 2 hours. After cooling to room temperature water was added and the mixture was
10 partitioned between saturated sodium hydrogen carbonate solution and dichloromethane. The organic extracts were separated, washed with water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 5-10% 2M ammonia in methanol and dichloromethane to give 1,1-dimethylethyl-3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxylate
15 (740 mg, 47%) as an oil. LC/MS [M+H]⁺ = 314.

(ii) A solution of 1,1-dimethylethyl-3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxylate (740 mg, 2.361 mmol) in TFA/DCM (1:2, 6ml) was stirred at room temperature for 5 hours. The solution was evaporated and the residue was co-evaporated with DCM and dried to give crude 3-methyl-1-[2-(4-morpholinyl)ethyl]-
20 2-oxo-4-imidazolidinecarboxylic acid TFA salt (assume ~ 2.3 mmol) which was used in the next step. LC/MS [M+H]⁺ = 258.

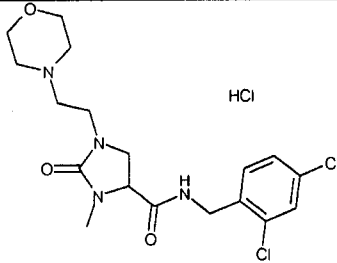
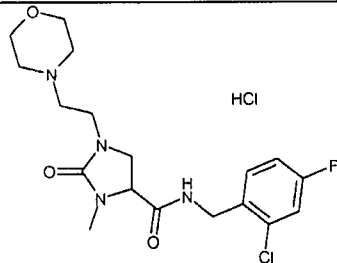
Examples 43-44

In a manner analogous to that described for Example 42 above the compounds
25 tabulated below (Table 6) were prepared by substituting the appropriate amine (or salt thereof) for the {[2-chloro-3-(trifluoromethyl)phenyl]methyl}amine used in the above procedure. All of the amines used to make the amines shown in Table 6 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

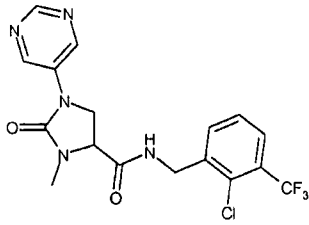
30

Table 6

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
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Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E43	 <i>N</i>-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxamide hydrochloride	415	1.71
E44	 <i>N</i>-[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxamide hydrochloride	399	1.51

Example 45 *N*-{[2-Chloro-3-(trifluoromethyl)phenyl]methyl}-3-methyl-2-oxo-1-(5-pyrimidinyl)-4-imidazolidinecarboxamide (**E45**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



5

A solution of 3-methyl-2-oxo-1-(5-pyrimidinyl)-4-imidazolidinecarboxylic acid (0.6 mmol) in dichloromethane (6 ml) was treated with *N*-ethyl morpholine (0.460 ml, 3.60 mmol), 1-hydroxybenzotriazole hydrate (110 mg, 0.720 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (138 mg, 0.720 mmol) and the mixture was stirred at room temperature for 10 minutes. A solution of {2-chloro-3-

(trifluoromethyl)phenyl)methyl}amine (126 mg, 0.600 mmol) in dichloromethane (1 ml) was added and the reaction stirred at room temperature for 3 hours. The mixture was diluted with dichloromethane and the solution was washed with 3N citric acid, water, saturated sodium bicarbonate solution and brine, dried and evaporated. The residue was purified by mass-directed automated HPLC to give *N*-[2-chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-2-oxo-1-(5-pyrimidinyl)-4-imidazolidinecarboxamide (54 mg, 22%). LC/MS $[M+H]^+$ = 414, retention time 2.37 minutes.

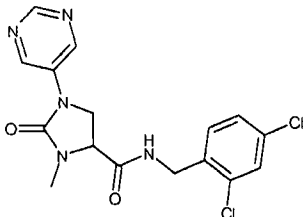
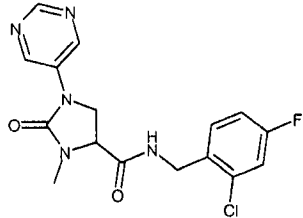
- 10 The 3-methyl-2-oxo-1-(5-pyrimidinyl)-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:
- (i) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (601 mg, 3 mmol) (prepared as described in step (iii) of Example 13, starting from (4*S*)-2-oxo-3-[[{(phenylmethyl)oxy}carbonyl]-4-imidazolidinecarboxylic acid) and 5-bromopyrimidine (477 mg, 3.00 mmol) in 1,4-dioxane (20 ml) was treated with cesium carbonate (1466 mg, 4.50 mmol), XantphosTM (130 mg, 0.225 mmol) and tris(dibenzylideneacetone)dipalladium(0) (68.7 mg, 0.075 mmol) and the mixture was heated under reflux under argon for 3 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water and brine and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with 0-100% ethyl acetate in isohexane to give 1,1-dimethylethyl 3-methyl-2-oxo-1-(5-pyrimidinyl)-4-imidazolidinecarboxylate (349 mg, 42%). LC/MS $[M+H]^+$ = 279.
- (ii) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-1-(5-pyrimidinyl)-4-imidazolidinecarboxylate (630 mg, 2.264 mmol) in TFA/DCM (1:2, 9 ml) was stirred at room temperature for 8 hours. The solution was evaporated and the residue was co-evaporated with toluene and dried to give crude 3-methyl-2-oxo-1-(5-pyrimidinyl)-4-imidazolidinecarboxylic acid (assume ~ 2.2 mmol) which was used in the next step. LC/MS $[M+H]^+$ = 223.

30 Examples 46-47 (in forms obtainable or prepared from (4*S*)-2-oxo-3-[[{(phenylmethyl)oxy}carbonyl]-4-imidazolidinecarboxylic acid)

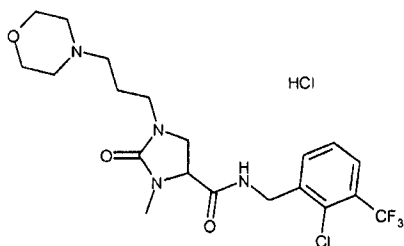
In a manner analogous to that described for Example 45 above the compounds tabulated below (Table 6) were prepared by substituting the appropriate amine (or salt thereof) for the {[2-chloro-3-(trifluoromethyl)phenyl)methyl}amine used in the

above procedure. All of the amines used to make the amines shown in Table 7 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

5 Table 7

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E46	 <i>N</i> -[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-1-(5-pyrimidinyl)-4-imidazolidinecarboxamide	380	2.28
E47	 <i>N</i> -[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-2-oxo-1-(5-pyrimidinyl)-4-imidazolidinecarboxamide	364	2.08

Example 48 *N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-[3-(4-morpholinyl)propyl]-2-oxo-4-imidazolidinecarboxamide hydrochloride (**E48**)

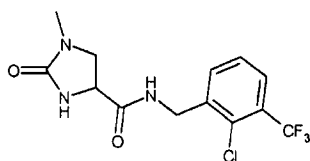


- 10 In a manner analogous to that described in Example 42 above *N*-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-[3-(4-morpholinyl)propyl]-2-oxo-4-imidazolidinecarboxamide hydrochloride was prepared substituting 4-(3-

63

chloropropyl)morpholine for 4-(2-chloroethyl)morpholine used in Step (i) of the Example 42 procedure. LC/MS $[M+H]^+ = 463$, retention time = 1.82 minutes.

- Example 49** N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-1-methyl-2-oxo-4-imidazolidinecarboxamide (**E49**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



- A mixture of 1-methyl-2-oxo-4-imidazolidinecarboxylic acid (144 mg, 1 mmol), N-ethyl morpholine (0.767 ml, 6.00 mmol), 1-hydroxybenzotriazole hydrate (184 mg, 1.200 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (230 mg, 1.200 mmol) in dichloromethane (18 ml) was stirred at room temperature for 10 minutes. A solution of [[2-chloro-3-(trifluoromethyl)phenyl]methyl]amine (210 mg, 1.000 mmol) in dichloromethane (2 ml) was added and the reaction stirred at room temperature for hours. The mixture was diluted with dichloromethane and the mixture was washed with 3N citric acid solution. The organic phase was separated, washed with brine, dried and evaporated. The residue was purified by mass-directed automated HPLC to give the N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-1-methyl-2-oxo-4-imidazolidinecarboxamide (150 mg, 55%). LC/MS $[M+H]^+ = 336$, retention time = 2.22 minutes.

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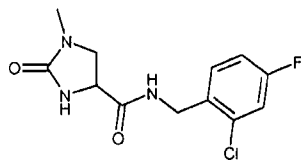
The 1-methyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

- (i) A solution of 5-(1,1-dimethylethyl) 1-(phenylmethyl) 3-methyl-2-oxo-1,5-imidazolidinedicarboxylate (3.8 g, 11.36 mmol) (prepared as described in step (ii) of Example 13, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) in methanol (50 ml) containing Pd/C (10% paste, 400 mg) was hydrogenated at room temperature and pressure for 18 hours. The mixture was filtered through a filter pad and the pad washed with methanol. The filtrates were combined, evaporated and dried to give 1,1-dimethylethyl 1-methyl-2-oxo-4-imidazolidinecarboxylate (1.001 g, 5 mmol) (2.17 g, 95%); LC/MS $[M+H]^+ = 201$.
- (ii) A solution of 1,1-dimethylethyl 1-methyl-2-oxo-4-imidazolidinecarboxylate (1.001 g, 5 mmol) in TFA/DCM (1:2, 7.5 ml) was stirred at room temperature for 6 hours. The solution was evaporated and the residue was dried to give crude 1-methyl-2-

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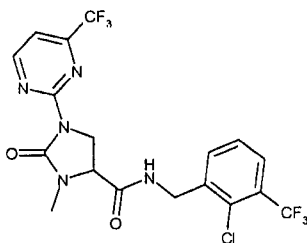
oxo-4-imidazolidinecarboxylic acid (assume 5 mmol), which was used in the next step. LC/MS $[M+H]^+ = 145$.

- Example 50 N-[(2-Chloro-4-fluorophenyl)methyl]-1-methyl-2-oxo-4-imidazolidinecarboxamide (**E50**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



- In a manner analogous to that described in Example 49 above N-[(2-chloro-4-fluorophenyl)methyl]-1-methyl-2-oxo-4-imidazolidinecarboxamide was prepared substituting [(2-chloro-4-fluorophenyl)methyl]amine for the {[2-chloro-3-(trifluoromethyl)phenyl]methyl}amine used in the above procedure. LC/MS $[M+H]^+ = 286$, retention time = 1.90 minutes.

Example 51 N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxamide (**E51**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



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A mixture of crude 3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxylic acid (10 ml of 0.05M solution in DCM, 0.5 mmol), N-ethylmorpholine (0.383 ml, 3.00 mmol), 1-hydroxybenzotriazole hydrate (92 mg, 0.600 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg, 0.600 mmol) was stirred at room temperature for 10 minutes. A solution of [[2-chloro-3-(trifluoromethyl)phenyl]methyl]amine (105 mg, 0.5 mmol) in dichloromethane (1 ml) was added and the reaction stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane and the solution was washed with saturated sodium hydrogen carbonate solution, water, aqueous citric acid, water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane. The residue was triturated with ether and the resulting solid was collected and dried to give N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxamide (150 mg, 62%). LC/MS [M+H]⁺ = 482, retention time 2.81 minutes.

The 3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

(i) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (600 mg, 3 mmol) (prepared as described in step (iii) of Example 13, starting from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 2-chloro-4-(trifluoromethyl)pyrimidine (547 mg, 3.00 mmol) in 1,4-dioxane (20 ml) was treated with cesium carbonate (1464 mg, 4.49 mmol), XantphosTM (130 mg, 0.225 mmol) and tris(dibenzylideneacetone)dipalladium(0) (68.6 mg, 0.075 mmol) and the mixture was heated at reflux under argon for 6 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic

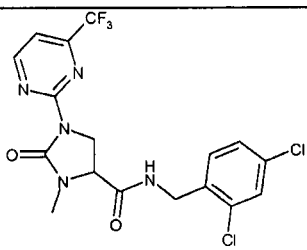
layers were combined, washed with water and brine and evaporated. The residue was purified by silica gel chromatography eluting with 0-100% ethyl acetate in isohexane to give 1,1-dimethylethyl 3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxylate (506 mg, 49%). LC/MS $[M+H]^+ = 347$.

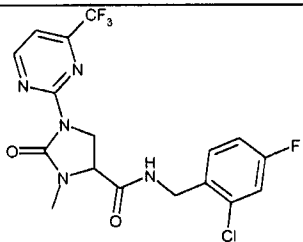
- 5 (ii) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxylate (506 mg, 1.46 mmol) in TFA/DCM (1:2, 9 ml) was stirred at room temperature for 16 hours. The solution was evaporated and the residue was co-evaporated with toluene and dried to give crude 3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxylic acid (assume ~ 1.5 mmol)
- 10 which was used in the next step. LC/MS $[M+H]^+ = 291$.

Examples 52-53 (in forms obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

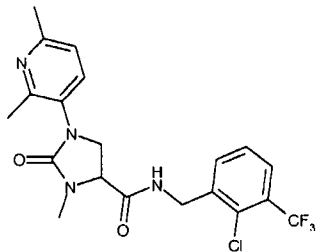
- 15 In a manner analogous to that described for Example 51 above the compounds tabulated below (Table 8) were prepared by substituting the appropriate amine (or salt thereof) for the {[2-chloro-3-(trifluoromethyl)phenyl]methyl}amine used in the above procedure. All of the amines used in Table 8 are available from commercial
- 20 literature or analogous methods.

Table 8

Example no.	Chemical name	$[M+H]^+$	Retention time (mins)
E52	 N-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxamide	448	2.77

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E53	 N-[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxamide	432	2.60

Example 54 N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E54**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



A mixture of crude 1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid TFA salt (10 ml of 0.05M solution in DCM, 0.5 mmol), N-ethylmorpholine (0.383 ml, 3.00 mmol), 1-hydroxybenzotriazole hydrate (92 mg, 0.600 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg, 0.600 mmol) was stirred at room temperature for 10 minutes. A solution of {2-chloro-3-(trifluoromethyl)phenyl)methyl}amine (105 mg, 0.5 mmol) in dichloromethane (1 ml) was added and the reaction stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane and the solution was washed with saturated sodium hydrogen carbonate solution, water and brine, dried and evaporated. The residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane. The residue was triturated with ether and the resulting solid was collected and dried to give N-[(2-chloro-3-(trifluoromethyl)phenyl)methyl]-1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-

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imidazolidinecarboxamide (104 mg, 47%). LC/MS $[M+H]^+$ = 441, retention time = 1.86 minutes.

5 The 1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid TFA salt used in the method described above was prepared as follows:

(i) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (600 mg, 3.00 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 3-bromo-2,6-dimethylpyridine (557 mg, 3.00 mmol) in 1,4-dioxane (20 ml) was treated with
10 cesium carbonate (1464 mg, 4.49 mmol), XantphosTM (130 mg, 0.225 mmol) and tris(dibenzylideneacetone)dipalladium(0) (68.6 mg, 0.075 mmol) and the mixture was heated at reflux under argon for 3 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water and brine and evaporated in vacuo. The
15 residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane. The residue was dissolved in methanol and applied to a SCX ion exchange cartridge and washed with methanol and then 2M ammonia in methanol. The basic fractions were combined and evaporated to give 1,1-dimethylethyl 1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylate (493 mg, 54%).
20 LC/MS $[M+H]^+$ = 306.

(ii) A solution of 1,1-dimethylethyl 1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylate (0.489 g, 1.6 mmol) in TFA/DCM (1:2, 9 ml) was stirred at room temperature for 16 hours. The solution was evaporated and the residue was co-evaporated with toluene and dried to give crude 1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid TFA salt, (assume ~ 1.6 mmol) which
25 was used in the next step. LC/MS $[M+H]^+$ = 250.

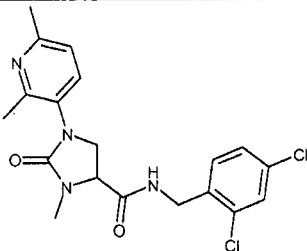
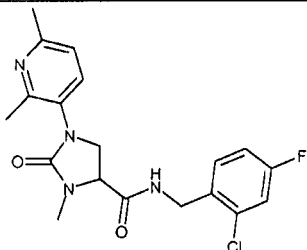
Examples 55-56 (in forms obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

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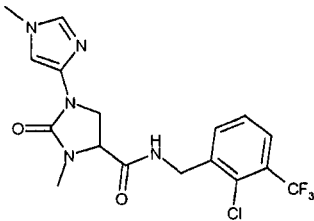
In a manner analogous to that described for Example 54 above the compounds tabulated below (Table 9) were prepared by substituting the appropriate amine (or salt thereof) for the [[2-chloro-3-(trifluoromethyl)phenyl]methyl]amine used in the above procedure. All of the amines used in Table 9 are available from commercial
35 sources or can be prepared using routes described previously in the chemical literature or analogous methods.

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Table 9

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E55	 N-[(2,4-Dichlorophenyl)methyl]-1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide	407	1.77
56	 N-[(2-Chloro-4-fluorophenyl)methyl]-1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide	391	1.61

Example 57 N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxamide (**E57**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



10 A solution of 3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxylic acid trifluoroacetate salt (145 mg, 0.647 mmol) in dichloromethane (4 ml) was treated with 1-hydroxyorthobenzotriazole hydrate (119 mg, 0.776 mmol), 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride (149 mg, 0.776 mmol) & N-ethylmorpholine (0.491 ml, 3.88 mmol) and the mixture stirred at room temp for 10 minutes. 1-([2-Chloro-3-(trifluoromethyl)phenyl]methyl)amine (136 mg, 0.647 mmol) was then added and the reaction stirred at room temp over the weekend. The
5 reaction was diluted with dichloromethane and washed with 3N citric acid, saturated sodium hydrogen carbonate solution, water and brine, separated through a hydrophobic frit and the organic layer reduced under vacuum. The residue was purified by mass-directed automated HPLC and freeze dried to give N-([2-chloro-3-(trifluoromethyl)phenyl]methyl)-3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-
10 imidazolidinecarboxamide (30 mg, 10.6 % yield). LC/MS $[M+H]^+$ = 416, retention time = 1.92 minutes.

The 3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxylic acid trifluoroacetate salt used in the method described above was prepared as follows:

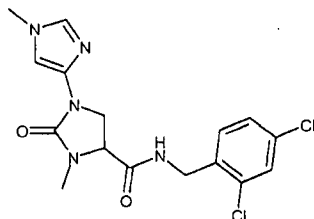
15 (i) To a stirred mixture of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (200 mg, 0.999 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-([(phenylmethyl)oxy]carbonyl)-4-imidazolidinecarboxylic acid) and 4-bromo-1-methyl-1H-imidazole (193 mg, 1.199 mmol) in 1,4-dioxane (8 ml) was added potassium phosphate (1060 mg, 4.99 mmol),
20 copper(I) iodide (190 mg, 0.999 mmol) and trans-N,N-dimethylcyclohexane-1,2-diamine (0.158 ml, 0.999 mmol) and the reaction mixture was stirred at reflux under argon for 3 hours. The mixture was cooled to room temperature and diluted with dichloromethane (20mL) and filtered and washed through with dichloromethane. The filtrate was concentrated under vacuum and taken up in dichloromethane. The
25 solution was washed with 0.880 ammonia (x3), water then brine and separated by hydrophobic frit and the organic layer was reduced under vacuum. The residue was purified by Flashmaster automated silica gel chromatography eluting with 0-20% methanol in dichloromethane to leave an oil which crystallised on standing. The residue was dried under vacuum overnight to give 1,1-dimethylethyl 3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxylate (285 mg, 87 % yield).
30 LC/MS $[M+H]^+$ = 281.

(ii) Trifluoroacetic acid (1.0 ml, 12.98 mmol) was added to a solution of 1,1-dimethylethyl 3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxylate (220 mg, 0.785 mmol) in DCM (2 ml) and the reaction
35 mixture was stirred at room temperature for 5 hours. The solvent was evaporated under vacuum, azeotroping with toluene and the residue was dried under vacuum over the weekend to give crude 3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-

imidazolidinecarboxylic acid trifluoroacetate salt which was taken through to next step without further purification. LC/MS $[M+H]^+ = 225$.

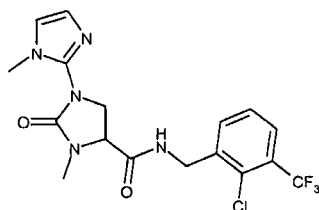
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- Example 58** N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxamide (**E58**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



- A solution of 3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxylic acid trifluoroacetate salt (0.105 g, 0.47 mmol) (prepared as described in step (ii) of Example 57) and N-ethyl morpholine (0.361 ml, 2.82 mmol) in dichloromethane (5 ml) was treated with 1-hydroxybenzotriazole hydrate (0.086 g, 0.564 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.090 g, 0.470 mmol) and stirred at room temperature for 10 minutes. 1-(2,4-Dichlorophenyl)methanamine (0.063 ml, 0.470 mmol) was added and the reaction mixture was stirred over the weekend. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solution, water and brine and separated using a hydrophobic frit. The filtrate was concentrated under vacuum and purified by mass-directed automated HPLC to give N-[(2,4-dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxamide (26 mg, 13.75 % yield). LC/MS $[M+H]^+ = 382$, retention time = 1.83 minutes.

- Example 59** N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(1-methyl-1H-imidazol-2-yl)-2-oxo-4-imidazolidinecarboxamide (**E59**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



A solution of 3-methyl-1-(1-methyl-1H-imidazol-2-yl)-2-oxo-4-imidazolidinecarboxylic acid (166 mg, 0.517 mmol) and N-ethyl morpholine (0.397 ml, 3.10 mmol) in dichloromethane (5 ml) was treated with 1-hydroxybenzotriazole hydrate (95 mg, 0.620 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (99 mg, 0.517 mmol) and stirred at room temperature for 10 minutes. 1-[2-Chloro-3-(trifluoromethyl)phenyl]methanamine (108 mg, 0.517 mmol) was then added and the reaction stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solution, water and brine, separated through a hydrophobic frit and the organic layer was reduced under vacuum. The residue was purified by mass-directed automated HPLC to give N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(1-methyl-1H-imidazol-2-yl)-2-oxo-4-imidazolidinecarboxamide (67 mg, 29.6 % yield). LC/MS $[M+H]^+ = 416$, retention time = 1.89 minutes.

15 The 3-methyl-1-(1-methyl-1H-imidazol-2-yl)-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

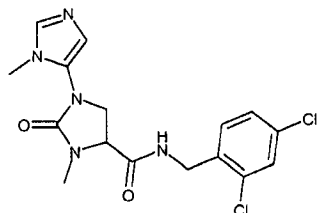
(i) To a stirred solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (0.200 g, 1.00 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 2-bromo-1-methyl-1H-imidazole (0.146 ml, 1.500 mmol) in 1,4-dioxane (8 ml) was added potassium phosphate (1.062 g, 5.00 mmol), copper(I) iodide (0.190 g, 1.000 mmol) and trans-N,N-dimethylcyclohexane-1,2-diamine (0.155 ml, 1.000 mmol) and the mixture heated at reflux under argon overnight. The mixture was cooled to room temperature and diluted with dichloromethane. The solid was filtered off, washed with dichloromethane and the filtrate reduced under vacuum. The residue was re-dissolved in dichloromethane and washed with 0.880 ammonia solution (x2), water then brine and passed through a hydrophobic frit and the organic layer reduced under vacuum. The residue was purified by Flashmaster automated silica gel chromatography eluting with 0-10% methanol in dichloromethane to give 1,1-dimethylethyl 3-methyl-1-(1-methyl-1H-imidazol-2-yl)-2-oxo-4-imidazolidinecarboxylate (145 mg, 37.8 % yield). LC/MS $[M+H]^+ = 281$.

(ii) Trifluoroacetic acid (0.059 ml, 0.517 mmol) was added to a solution of 1,1-dimethylethyl 3-methyl-1-(1-methyl-1H-imidazol-2-yl)-2-oxo-4-imidazolidinecarboxylate (145 mg, 0.517 mmol) in DCM (2 ml) and the reaction stirred at room temperature overnight. The reaction mixture was co-evaporated with toluene and dried to give 3-methyl-1-(1-methyl-1H-imidazol-2-yl)-2-oxo-4-

imidazolidinecarboxylic acid (assume ~ 0.517 mmol) which was used which was used in the next step. LC/MS $[M+H]^+ = 225$.

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Example 60 N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxamide (**E60**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



A solution of 3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxylic acid (155 mg, 0.458 mmol) and N-ethylmorpholine (0.348 ml, 2.75 mmol) in dichloromethane (5 ml) was treated with 1-hydroxybenzotriazole hydrate (84 mg, 0.550 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (88 mg, 0.458 mmol) and stirred at room temperature for 10 minutes. 1-(2,4-Dichlorophenyl)methanamine (81 mg, 0.458 mmol) was then added and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solution, water and brine, separated through a hydrophobic frit and the organic layer reduced under vacuum. The residue was purified by mass-directed automated HPLC to give N-[(2,4-dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxamide (63 mg, 34.2 % yield). LC/MS $[M+H]^+ = 382$, retention time = 1.71 minutes.

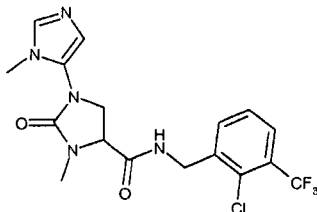
The 3-methyl-1-(1-methyl-1H-imidazol-2-yl)-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

(i) To a stirred solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (801 mg, 4.00 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 5-bromo-1-methylimidazole (644 mg, 4.00 mmol) in 1,4-dioxane (30 ml) was added potassium phosphate (4246 mg, 20.00 mmol), trans-N,N-dimethylcyclohexane-1,2-diamine (0.631 ml, 4.00 mmol) and copper(I) iodide (762 mg, 4.00 mmol) and the mixture stirred at reflux overnight. The reaction mixture was diluted with dichloromethane and filtered through celite. The filter pad was

washed with dichloromethane and the filtrate was reduced under vacuum. The residue was re-dissolved in dichloromethane, washed with 0.880 ammonia (x2), water then brine and passed through a hydrophobic frit and the solution was concentrated under vacuum. The residue was purified by Flashmaster automated silica gel chromatography eluting with 0-10% methanol in dichloromethane to give 1,1-dimethylethyl 3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxylate (393 mg, 32.6 % yield). LC/MS $[M+H]^+ = 281$.

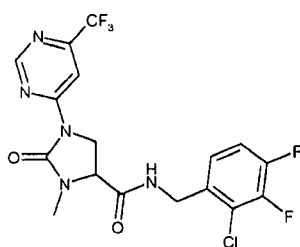
(ii) Trifluoroacetic acid (2 ml) was added to a solution of 1,1-dimethylethyl (4S)-3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxylate (390 mg, 1.391 mmol) in dichloromethane (4 ml) and stirred at room temperature for 2 hours, then allowed to stand overnight. The solvent was evaporated and the residue was co-evaporated with toluene and dried under heated vacuum (40°C) overnight to give 3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxylic acid TFA salt (assume ~ 1.4 mmol) which was used which was used in the next step. LC/MS $[M+H]^+ = 225$.

Example 61 N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxamide (**E61**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



In a manner analogous to that described in Example 60 above N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxamide was prepared substituting 1-(2,4-dichlorophenyl)methanamine for the [[2-chloro-3-(trifluoromethyl)phenyl]methyl]amine used in the above procedure. LC/MS $[M+H]^+ = 416$, retention time = 1.75 minutes.

Example 62 N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-1-[6-(trifluoromethyl)-4-pyrimidinyl]-4-imidazolidinecarboxamide (**E62**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



To a suspension of 3-methyl-2-oxo-1-[6-(trifluoromethyl)-4-pyrimidinyl]-4-imidazolidinecarboxylic acid (200 mg, 0.612 mmol) and N-ethylmorpholine (0.465 ml, 3.67 mmol) in dichloromethane (10 ml)/DMF (1 ml) was added 1-hydroxybenzotriazole hydrate (113 mg, 0.735 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (117 mg, 0.612 mmol) and the reaction mixture was stirred for 1 hour at room temperature. 1-(2-Chloro-3,4-difluorophenyl)methanamine (131 mg, 0.612 mmol) was then added and the reaction stirred overnight. Additional 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (117 mg, 0.612 mmol) was added and the reaction mixture was stirred for 3 hours. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solution, water, 3N citric acid solution, water then brine and separated through a hydrophobic frit and the organic layer concentrated under vacuum. The residue was purified by SP4 automated silica gel chromatography eluting with 10-100% ethyl acetate in isohexane to give N-[(2-chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-1-[6-(trifluoromethyl)-4-pyrimidinyl]-4-imidazolidinecarboxamide (95 mg, 33.8 % yield). LC/MS [M+H]⁺ = 450, retention time = 2.93 minutes.

The 3-methyl-2-oxo-1-[6-(trifluoromethyl)-4-pyrimidinyl]-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

(i) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (800 mg, 4.00 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 4-chloro-6-(trifluoromethyl)pyrimidine (729 mg, 4.00 mmol) in 1,4-dioxane (40 ml) was treated with cesium carbonate (1953 mg, 5.99 mmol), XantphosTM (173 mg, 0.300 mmol) and tris(dibenzylideneacetone)dipalladium(0) (91 mg, 0.100 mmol) and the reaction mixture was heated at reflux under argon overnight. After cooling the reaction was diluted with water and extracted with ethyl acetate (x2). The organic layers were combined and washed with water and brine, dried over anhydrous sodium sulfate

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and reduced under vacuum. The residue was purified by Flashmaster automated silica gel chromatography eluting with 0-30% ethyl acetate in isohexane to give 1,1-dimethylethyl 3-methyl-2-oxo-1-[6-(trifluoromethyl)-4-pyrimidinyl]-4-imidazolidinecarboxylate (983 mg, 67.5 % yield). LC/MS $[M+H]^+ = 347$.

- 5 (ii) Trifluoroacetic acid (4 ml, 51.9 mmol) was added to a solution of 1,1-dimethylethyl 3-methyl-2-oxo-1-[6-(trifluoromethyl)-4-pyrimidinyl]-4-imidazolidinecarboxylate (980 mg, 2.83 mmol) in dichloromethane (8 ml) and the solution was stirred at room temperature for 6 hours. The solvent was evaporated and the residue was co-evaporated with toluene. The residue was dissolved in
- 10 saturated sodium hydrogen carbonate solution and the solution was loaded onto an amino column eluting with 10% 2N hydrochloric acid in methanol. Product-containing fractions were combined and reduced under vacuum and the residue was triturated with methanol and the solid was filtered off. The filtrate was reduced under vacuum to give 3-methyl-2-oxo-1-[6-(trifluoromethyl)-4-pyrimidinyl]-4-imidazolidinecarboxylic
- 15 acid hydrochloride salt (893 mg, assume ~2.8 mmol) which was used in the next step. LC/MS $[M+H]^+ = 291$.

Examples 63-64 (in forms obtainable or prepared from (4S)-2-oxo-3-
{[(phenylmethyl)oxy]carbonyl}-4-imidazolidinecarboxylic acid)

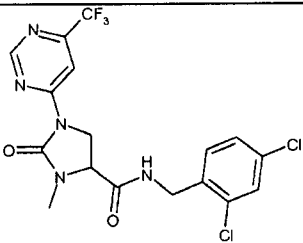
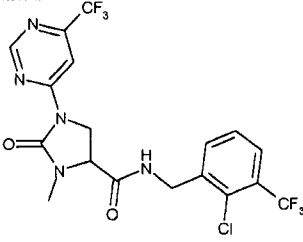
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In a manner analogous to that described for Example 62 above the compounds tabulated below (Table 10) were prepared by substituting the appropriate amine (or salt thereof) for the 1-(2-chloro-3,4-difluorophenyl)methanamine used in the above procedure. All of the amines used in Table 10 are available from commercial sources

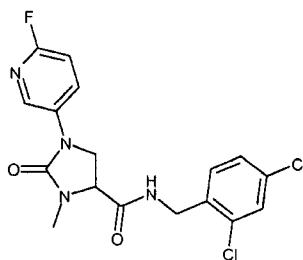
25 or can be prepared using routes described previously in the chemical literature or analogous methods.

Table 10

Example no.	Chemical name	$[M+H]^+$	Retention time (mins)
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Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E63	 N-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-1-[6-(trifluoromethyl)-4-pyrimidinyl]-4-imidazolidinecarboxamide	448	3.04
E64	 N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-[6-(trifluoromethyl)-4-pyrimidinyl]-4-imidazolidinecarboxamide	482	3.08

Example 65 N-[(2,4-Dichlorophenyl)methyl]-1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E65**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



To a solution of 1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid TFA salt (200 mg, 0.836 mmol) and N-ethylmorpholine (0.635 ml, 5.02 mmol) in dichloromethane (10 ml) was added 1-hydroxybenzotriazole hydrate (128 mg, 0.836 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (160 mg,

0.836 mmol) and the mixture was stirred for 10 minutes. 1-(2,4-Dichlorophenyl)methanamine (147 mg, 0.836 mmol) was added and the reaction stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solution, water and brine, separated through a hydrophobic frit and the organic layer was reduced under vacuum. The residue was purified by FFlashmaster automated silica gel chromatography eluting with 10-100% ethyl acetate in isohexane to give N-[(2,4-dichlorophenyl)methyl]-1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (60 mg, 18 % yield). LC/MS $[M+H]^+$ = 397, retention time = 2.63 minutes.

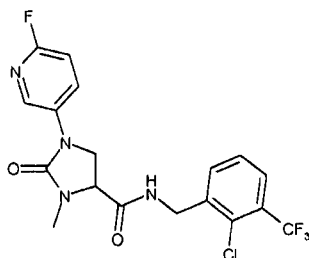
The 1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid TFA salt used in the method described above was prepared as follows:

(i) To a solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (400 mg, 1.998 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 5-bromo-2-fluoropyridine (352 mg, 1.998 mmol) in 1,4-dioxane (20 ml) was added trans-N,N-dimethylcyclohexane-1,2-diamine (0.062 ml, 0.400 mmol), potassium phosphate (1272 mg, 5.99 mmol) and copper(I) iodide (38.0 mg, 0.200 mmol) and the reaction mixture was heated at reflux under argon overnight. The reaction mixture was allowed to cool and the solvent was evaporated. The residue was partitioned between dichloromethane and water. The organic layer was separated and washed with water (~ 50 ml) containing 0.880 ammonia solution (~ 5 ml), then brine and passed through a hydrophobic frit and the organic layer was reduced under vacuum. The residue was purified by SP4 automated silica gel chromatography eluting with 10-80% ethyl acetate in isohexane to give 1,1-dimethylethyl 1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylate (422 mg, 68.7 % yield). LC/MS $[M+H]^+$ = 296.

(ii) Trifluoroacetic acid (2 ml) was added to a solution of 1,1-dimethylethyl 1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylate (420 mg, 1.422 mmol) in dichloromethane (5 ml) and the mixture was stirred at room temperature for 36 hours. The reaction mixture was reduced under vacuum and the residue was azeotroped with toluene and dried under heated vacuum to give 1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid TFA salt (assume ~1.4 mmol) which was used in the next step. LC/MS $[M+H]^+$ = 240.

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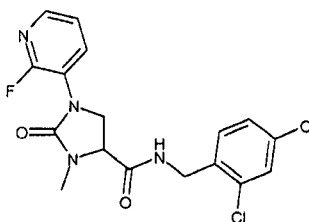
Example 66 N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E66**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



5 In a manner analogous to that described in Example 65 above N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide was prepared substituting [[2-chloro-3-(trifluoromethyl)phenyl]methyl]amine for the 1-(2,4-dichlorophenyl)methanamine used in the above procedure. LC/MS $[M+H]^+$ = 431, retention time = 2.69 minutes.

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Example 67 N-[(2,4-Dichlorophenyl)methyl]-1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E67**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



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To a solution of 1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid TFA salt (182 mg, 0.761 mmol) and N-ethylmorpholine (0.578 ml, 4.57 mmol) in dichloromethane (5 ml) was added 1-hydroxybenzotriazole hydrate (117 mg, 0.761 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (146 mg, 0.761 mmol) and the reaction mixture was stirred for 10 minutes at room temperature. 1-(2,4-Dichlorophenyl)methanamine (134 mg, 0.761 mmol) was added and the reaction was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and the solution was washed with saturated sodium hydrogen carbonate solution, water and brine, separated through a hydrophobic frit and the organic layer was reduced under vacuum. The residue was purified by SP4 automated silica gel chromatography eluting with 10-100% ethyl acetate in isohexane

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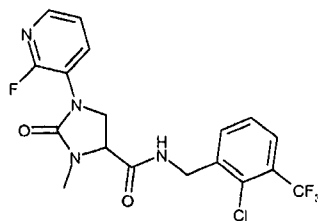
100

to give N-[(2,4-dichlorophenyl)methyl]-1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (125 mg, 40.5 % yield)

LC/MS $[M+H]^+ = 397$, retention time = 2.51 minutes.

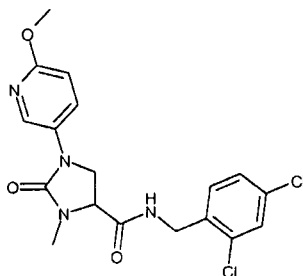
- 5 The 1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid TFA salt used in the method described above was prepared as follows:
- (i) To a solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (400 mg, 1.998 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 2-
- 10 fluoro-3-iodopyridine (352 mg, 1.998 mmol) in 1,4-dioxane (20 ml) was added trans-N,N-dimethylcyclohexane-1,2-diamine (0.062 ml, 0.400 mmol), potassium phosphate (1272 mg, 5.99 mmol) and copper(I) iodide (38.0 mg, 0.200 mmol) and the reaction mixture was heated at reflux under argon overnight. The reaction mixture was allowed to cool and the solvent was evaporated. The residue was partitioned
- 15 between dichloromethane and water. The organic layer was separated and washed with water (~ 50 ml) containing 0.880 ammonia solution (~ 5 ml), then brine and passed through a hydrophobic frit and the organic layer was reduced under vacuum. The residue was purified by SP4 automated silica gel chromatography eluting with 10-80% ethyl acetate in isohexane to give 1,1-dimethylethyl 1-(2-fluoro-3-pyridinyl)-3-
- 20 methyl-2-oxo-4-imidazolidinecarboxylate (405 mg, 67.3 % yield). LC/MS $[M+H]^+ = 296$.
- (ii) Trifluoroacetic acid (2 ml) was added to a solution of 1,1-dimethylethyl (4S)-1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylate (400 mg, 1.355 mmol) in dichloromethane (5 ml) and the solution was stirred at room temperature for 36
- 25 hours. The reaction mixture was reduced under vacuum and the residue was azeotroped with toluene and dried under heated vacuum to give 1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid TFA salt (assume ~1.35 mmol) which was used in the next step. LC/MS $[M+H]^+ = 240$.

- 30 Example 68 N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E68**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



In a manner analogous to that described in Example 65 above N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide was prepared substituting [[2-chloro-3-(trifluoromethyl)phenyl]methyl]amine for the 1-(2,4-dichlorophenyl)methanamine used in the above procedure. LC/MS [M+H]⁺ = 431, retention time = 2.56 minutes.

Example 69 N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxamide (**E69**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



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To a solution of 3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxylic acid TFA salt (145 mg, 0.404 mmol) and N-ethylmorpholine (0.307 ml, 2.424 mmol) in dichloromethane (5 ml) was added 1-hydroxybenzotriazole hydrate (61.9 mg, 0.404 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (77 mg, 0.404 mmol) and the reaction mixture was stirred for 10 minutes at room temperature. 1-(2,4-Dichlorophenyl)methanamine (71.1 mg, 0.404 mmol) was added and the reaction was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and the solution was washed with saturated sodium hydrogen carbonate solution, water and brine, separated through a hydrophobic frit and the organic layer was reduced under vacuum. The residue was purified by SP4 automated silica gel chromatography eluting with 10-100% ethyl acetate in isohexane to give N-[(2,4-dichlorophenyl)methyl]-3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxamide (101 mg, 59.9 % yield). LC/MS [M+H]⁺ = 409, retention time = 2.34 minutes.

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The 1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid TFA salt used in the method described above was prepared as follows:

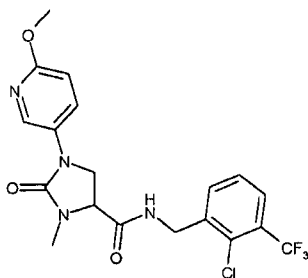
(i) To a solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (400 mg, 1.998 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 5-

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- bromo-2-(methyloxy)pyridine (0.259 ml, 1.998 mmol) in 1,4-dioxane (20 ml) was added cesium carbonate (2604 mg, 7.99 mmol), XantphosTM (87 mg, 0.150 mmol) and tris(dibenzylideneacetone)dipalladium(0) (91 mg, 0.100 mmol) and the reaction was stirred at reflux overnight. After cooling the solvent was removed under vacuum and the residue was partitioned between dichloromethane and water. The organic layer was separated, washed with saturated sodium hydrogen carbonate solution, water and then brine and passed through a hydrophobic frit. The organic layer was reduced under vacuum and the residue was purified by Flashmaster automated silica gel chromatography eluting with 0-30% ethyl acetate in isohexane to give 1,1-dimethylethyl 3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxylate (272 mg, 43.4 % yield). LC/MS $[M+H]^+ = 308$.
- (ii) Trifluoroacetic acid (1 ml) was added to a solution of 1,1-dimethylethyl 3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxylate (270 mg, 0.878 mmol) in dichloromethane (2 ml) and the solution was stirred at room temperature overnight. The reaction mixture reduced to dryness under vacuum azeotroping with toluene and then dried under heated vacuum overnight to give 3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxylic acid TFA salt (assume ~ 0.88 mmol). LC/MS $[M+H]^+ = 252$.

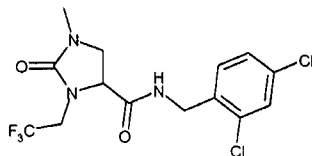
- Example 70** N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxamide (**E70**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



- In a manner analogous to that described in Example 69 above N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxamide was prepared substituting {[2-chloro-3-(trifluoromethyl)phenyl]methyl}amine for the 1-(2,4-dichlorophenyl)methanamine used in the above procedure. LC/MS $[M+H]^+ = 443$, retention time = 2.41 minutes.

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Example 72 N-[(2,4-Dichlorophenyl)methyl]-1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxamide (**E72**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



5 A mixture of 1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxylic acid (84 mg, 0.37 mmol), 1-hydroxybenzotriazole hydrate (68.0 mg, 0.444 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (85 mg, 0.444 mmol) and N-ethyl morpholine (0.189 ml, 1.480 mmol) in dichloromethane (9 ml) was stirred at room temperature for 10 minutes. A solution of [1-(2,4-dichlorophenyl)methyl]amine (65.1 mg, 0.37 mmol) in dichloromethane (1 ml) was added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (10 ml) and the solution was washed with saturated sodium hydrogen carbonate solution (10 ml), water (10 ml), citric acid solution (10 ml) and
10 15 brine (10 ml), dried and evaporated. The residue was purified by mass-directed automated HPLC. The residue was triturated with ether and the resulting solid was collected and dried to give N-[(2,4-dichlorophenyl)methyl]-1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxamide (60 mg, 42%). LC/MS $[M+H]^+ = 384$, retention time = 2.64 minutes.

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The 1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

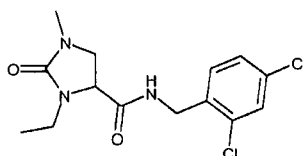
(i) A solution of 1,1-dimethylethyl 1-methyl-2-oxo-4-imidazolidinecarboxylate (180 mg, 0.9 mmol) (prepared as described in step (i) of Example 49 from 5-(1,1-dimethylethyl) 1-(phenylmethyl) 3-methyl-2-oxo-1,5-imidazolidinedicarboxylate, itself prepared as described in step (ii) of Example 13, starting originally from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) in N,N-dimethylformamide (10 ml), under argon at -35 °C, was treated with sodium hydride (60% dispersion in oil) (36.0 mg, 0.900 mmol). The mixture was stirred at -35 °C for
25 30 15 minutes and then 2,2,2-trifluoroethyl trichloromethanesulfonate (507 mg, 1.800 mmol) was added and the reaction mixture was stirred at -35 °C for 2 hours (the temperature increased slowly to -15°C). The reaction was quenched with water (5ml) and allowed to warm to room temperature and the reaction mixture was extracted

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with ethyl acetate (2 x 20 ml). The organic layer was separated, washed with saturated sodium hydrogen carbonate solution (10 ml), water (2 x 10ml) and brine (20 ml) and evaporated. The residue was purified by silica gel chromatography eluting with 10-100% ethyl acetate in isohexane to give 1,1-dimethylethyl 1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxylate (107 mg, 42%). LC/MS $[M+H]^+ = 283$.

(ii) A solution of 1,1-dimethylethyl 1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxylate (107 mg, 0.379 mmol) in TFA/DCM (1:2, 3 ml) was stirred at room temperature for 4 hours. The solution was evaporated and the residue was co-evaporated with dichloromethane and dried to give crude 1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxylic acid (assume ~ 0.38 mmol) which was used in the next reaction. LC/MS $[M+H]^+ = 227$.

Example 73 N-[(2,4-Dichlorophenyl)methyl]-3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxamide (**E73**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



A mixture of 3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxylic acid (138 mg, 0.800 mmol), 1-hydroxybenzotriazole hydrate (147 mg, 0.960 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (184 mg, 0.960 mmol) and N-ethylmorpholine (0.409 ml, 3.20 mmol) in dichloromethane (9 ml) was stirred at room temperature for 10 minutes. A solution of [1-(2,4-dichlorophenyl)methyl]amine (141 mg, 0.8 mmol) in dichloromethane (1 ml) was added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (10 ml) and the solution was washed with saturated sodium hydrogen carbonate solution (10 ml), water (10 ml), citric acid solution (10 ml) and brine (10 ml), dried and evaporated. The residue was purified by mass-directed automated HPLC. The residue was triturated with ether and the resulting solid was collected and dried to give N-[(2,4-dichlorophenyl)methyl]-3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxamide (141 mg, 53%). LC/MS $[M+H]^+ = 330$, retention time = 2.36 minutes.

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The 3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

- (i) A stirred solution of 1,1-dimethylethyl 1-methyl-2-oxo-4-imidazolidinecarboxylate (0.501 g, 2.5 mmol) (prepared as described in step (i) of Example 49 from 5-(1,1-dimethylethyl) 1-(phenylmethyl) 3-methyl-2-oxo-1,5-imidazolidinedicarboxylate, itself prepared as described in step (ii) of Example 13, starting originally from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) in N,N-dimethylformamide (10 ml) was cooled to -10°C under argon and treated with iodoethane (0.404 ml, 5.00 mmol). Sodium hydride (60% dispersion in oil) (0.100 g, 2.500 mmol) was added portion wise. The mixture was allowed stirred warm to room temperature over 3 hours. The solvent was evaporated in vacuo and the residue was partitioned between ethyl acetate (20 ml) and brine (10 ml). The aqueous layer was re-extracted with ethyl acetate (20 ml) and the organic extracts were combined, washed with saturated sodium hydrogen carbonate solution (20 ml), water (2 x 20 ml) and brine (20 ml), dried and evaporated. The residue was purified by silica gel chromatography eluting with 25-100% ethyl acetate in isohexane to give 1,1-dimethylethyl 3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxylate (433 mg, 76%).

LC/MS $[M+H]^+ = 229$.

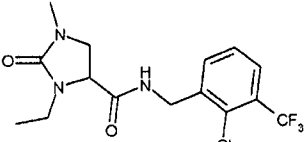
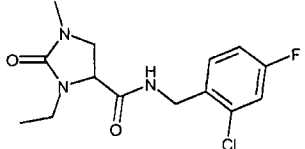
- (ii) A solution of 1,1-dimethylethyl 3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxylate (433 mg, 1.897 mmol) in TFA/DCM (1:2, 6 ml) was stirred at room temperature for 18 hours. The solution was evaporated and the residue was co-evaporated with dichloromethane and dried to give crude 3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxylic acid, (assume ~ 1.9 mmol). LC/MS $[M+H]^+ = 173$.

- 25 Examples 74-75 (in forms obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

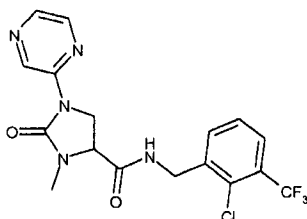
- In a manner analogous to that described for Example 73 above the compounds tabulated below (Table 11) were prepared by substituting the appropriate amine (or salt thereof) for the [1-(2,4-dichlorophenyl)methyl]amine used in the above procedure. All of the amines used in Table 11 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

- 35 Table 11



Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E74	 N-([2-chloro-3-(trifluoromethyl)phenyl]methyl)-3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxamide	364	2.44
E75	 N-([2-chloro-4-fluorophenyl]methyl)-3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxamide	314	2.15

Example 76 N-([2-chloro-3-(trifluoromethyl)phenyl]methyl)-3-methyl-2-oxo-1-(2-pyrazinyl)-4-imidazolidinecarboxamide (**E76**) (in a form obtainable or prepared from (4S)-2-oxo-3-([(phenylmethyl)oxy]carbonyl)-4-imidazolidinecarboxylic acid)



To a solution of 3-methyl-2-oxo-1-(2-pyrazinyl)-4-imidazolidinecarboxylic acid (145 mg, 0.561 mmol) and N-ethylmorpholine (0.426 ml, 3.36 mmol) in dichloromethane (5 ml) was added 1-hydroxybenzotriazole hydrate (86 mg, 0.561 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (107 mg, 0.561 mmol) and the reaction mixture was stirred for 10 minutes at room temperature. 1-[2-chloro-3-(trifluoromethyl)phenyl]methanamine (141 mg, 0.673 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen

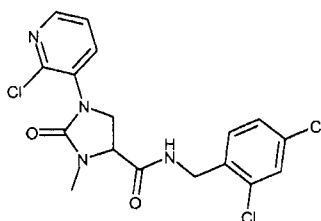
carbonate solution, water and brine and separated by hydrophobic frit and the organic layer reduced under vacuum. The residue was purified by SP4 automated silica gel chromatography eluting with 10-100% ethyl acetate in isohexane to give N-
5 {2-chloro-3-(trifluoromethyl)phenyl)methyl}-3-methyl-2-oxo-1-(2-pyrazinyl)-4-imidazolidinecarboxamide (45 mg, 19 % yield). LC/MS $[M+H]^+$ = 413, retention time = 2.21 minutes.

The 3-methyl-2-oxo-1-(2-pyrazinyl)-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

- 10 (i) To a solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (400 mg, 1.998 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-([(phenylmethyl)oxy]carbonyl)-4-imidazolidinecarboxylic acid) and 2-chloropyrazine (0.179 ml, 1.998 mmol) in 1,4-dioxane (20 ml) was added cesium carbonate (2604 mg, 7.99 mmol), tris(dibenzylideneacetone)dipalladium(0) (91 mg, 15 0.100 mmol) and XantphosTM (87 mg, 0.150 mmol) and the reaction mixture was stirred at reflux overnight. The reaction mixture was allowed to cool to room temperature and the solvent was removed under vacuum and the residue was partitioned between dichloromethane and water. The organic layer was washed with saturated sodium hydrogen carbonate solution, water and brine and separated by
20 hydrophobic frit. The solution was reduced under vacuum and the residue purified by silica gel chromatography eluting with 10-75% ethyl acetate in isohexane to give the crude 1,1-dimethylethyl 3-methyl-2-oxo-1-(2-pyrazinyl)-4-imidazolidinecarboxylate (322 mg, 38.2 % yield) which was used in the next step. LC/MS $[M+H]^+$ = 279.
- 25 (ii) Trifluoroacetic acid (1 ml) was added to a solution of 1,1-dimethylethyl 3-methyl-2-oxo-1-(2-pyrazinyl)-4-imidazolidinecarboxylate (290 mg, 0.709 mmol) in dichloromethane and the solution was stirred at room temperature overnight. The reaction mixture was reduced to dryness azeotroping with toluene and dried under heated vacuum. The residue was taken up in dichloromethane and extracted with
30 saturated sodium hydrogen carbonate solution (x3) and aqueous layer reduced under vacuum. The residue was taken up in water and the solution acidified to pH 4 by the slow addition of 2N hydrochloric acid. The solution was washed with dichloromethane (x2) and the solvent was reduced under vacuum. The residue was triturated with the minimal amount of methanol, the solid was filtered off and the
35 filtrate reduced under vacuum to leave a white solid which was dried under heated vacuum to give 3-methyl-2-oxo-1-(2-pyrazinyl)-4-imidazolidinecarboxylic acid (242 mg, ~ 0.7 mmol) which was used in the next step. LC/MS $[M+H]^+$ = 223.

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Example 77 1-(2-Chloro-3-pyridinyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E77**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



5

To a solution of 1-(2-chloro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid (179 mg, 0.484 mmol) and *N*-ethylmorpholine (0.368 ml, 2.91 mmol) in dichloromethane (5 ml) was added 1-hydroxybenzotriazole hydrate (111 mg, 0.726 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (139 mg, 0.726 mmol) and the mixture was stirred for 10 minutes at room temperature. 1-(2,4-Dichlorophenyl)methanamine (128 mg, 0.726 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solution, water and brine and separated by hydrophobic frit and the solution was reduced under vacuum. The residue was purified by SP4 automated silica gel chromatography eluting with 10-100% ethyl acetate in isohexane to give 1-(2-chloro-3-pyridinyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (60 mg, 27.6 % yield). LC/MS $[M+H]^+$ = 413, retention time = 2.21 minutes

The 1-(2-chloro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

(i) To a solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (650 mg, 3.25 mmol) (prepared as described in step (iii) of Example 13, starting from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and 3-bromo-2-chloropyridine (625 mg, 3.25 mmol) in 1,4-dioxane (30 ml) was added cesium carbonate (4231 mg, 12.98 mmol), tris(dibenzylideneacetone)dipalladium(0) (149 mg, 0.162 mmol) and XantphosTM (141 mg, 0.243 mmol) and the reaction stirred at reflux overnight. The reaction mixture was allowed to cool and solvent was removed under vacuum and the residue partitioned between ethyl acetate and water. The organic layer was separated and washed with saturated sodium hydrogen carbonate

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solution, water and brine and separated by hydrophobic frit. The organic solution was reduced under vacuum and the residue purified by SP4 automated silica gel chromatography eluting with 10-80% ethyl acetate in iso-hexane to give 1,1-dimethylethyl 1-(2-chloro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylate (579 mg, 51.5 % yield)

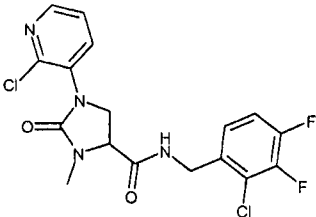
LC/MS [M+H]⁺ = 312.

(ii) Trifluoroacetic acid (2.5 ml) was added to a solution of 1,1-dimethylethyl 1-(2-chloro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylate (579 mg, 1.857 mmol) in dichloromethane (10 ml) and the solution was stirred at room temperature for 36 hours. The solvent was evaporated under vacuum azeotroping with toluene and the residue dried under heated vacuum overnight 1-(2-chloro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid (537 mg, 70.4 % yield) which was used crude in the next step. LC/MS MH⁺ = 256.

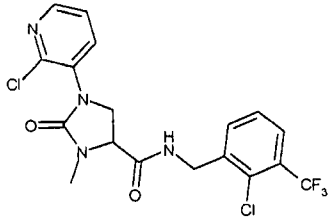
Examples 78-79 (in forms obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

In a manner analogous to that described for Example 77 above the compounds tabulated below (Table 12) were prepared by substituting the appropriate amine (or salt thereof) for the [1-(2,4-dichlorophenyl)methyl]amine used in the above procedure. All of the amines used in Table 12 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

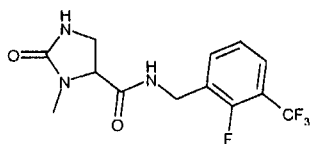
Table 12

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E78	 N-[(2-Chloro-3,4-difluorophenyl)methyl]-1-(2-chloro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide	415	2.07

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Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E79	 1-(2-Chloro-3-pyridinyl)-N-([2-chloro-3-(trifluoromethyl)phenyl]methyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide	447	2.29

Example 80 N-([2-Fluoro-3-(trifluoromethyl)phenyl]methyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E80**) (in a form obtainable or prepared from (4S)-2-oxo-3-([(phenylmethyl)oxy]carbonyl)-4-imidazolidinecarboxylic acid)



A mixture of 3-methyl-2-oxo-4-imidazolidinecarboxylic acid (86 mg, 0.6 mmol) (prepared as described in Example 28 from 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate, itself prepared as described in step (iii) of Example 13, starting originally from (4S)-2-oxo-3-([(phenylmethyl)oxy]carbonyl)-4-imidazolidinecarboxylic acid), N-ethyl morpholine (0.380 ml, 3.00 mmol), 1-hydroxybenzotriazole hydrate (110 mg, 0.720 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (138 mg, 0.720 mmol) in dichloromethane (9 ml) was stirred at room temperature for 10 minutes, under an argon atmosphere. { [2-Fluoro-3-(trifluoromethyl)phenyl]methyl}amine (0.1 ml, 0.684 mmol) was added and the reaction was stirred overnight under an argon atmosphere. The reaction mixture was diluted with dichloromethane (10ml) and the solution was washed with saturated sodium hydrogen carbonate solution (10ml), water (10ml), citric acid solution (10ml) and brine (10ml). The citric acid layer was re-extracted with dichloromethane and the dichloromethane extracts were combined, dried and evaporated. The residue was purified by mass-directed automated HPLC. Fractions containing product were collected and the solvent was evaporated in vacuo to give

MM

N-[[2-fluoro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (16 mg, 8% yield) as a white solid. LC/MS [M+H]⁺ = 320, retention time = 1.85 minutes.

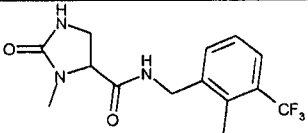
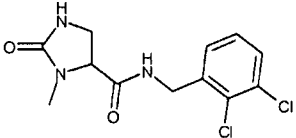
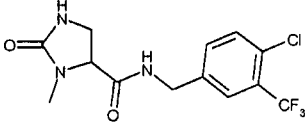
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Examples 81-83 (in forms obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

10 In a manner analogous to that described for Example 80 above the compounds tabulated below (Table 13) were prepared by substituting the appropriate amine (or salt thereof) for the {[2-fluoro-3-(trifluoromethyl)phenyl]methyl}amine used in the above procedure. All of the amines used in Table 13 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

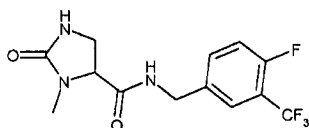
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Table 13

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E81	 3-Methyl-N-[[2-methyl-3-(trifluoromethyl)phenyl]methyl]-2-oxo-4-imidazolidinecarboxamide	316	1.94
E82	 N-[(2,3-Dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide	302	1.78
E83	 N-[[4-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide	336	2.00

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Example 84 N-[[4-Fluoro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E84**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



5

A mixture of 3-methyl-2-oxo-4-imidazolidinecarboxylic acid (86 mg, 0.6 mmol) (prepared as described in Example 28 from 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate, itself prepared as described in step (iii) of Example 13, starting originally from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid), N-ethyl morpholine (0.380 ml, 3.00 mmol), 1-hydroxybenzotriazole hydrate (110 mg, 0.720 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (138 mg, 0.720 mmol) in dichloromethane (9 ml) was stirred at room temperature for 10 minutes, under an argon atmosphere. [[4-Fluoro-3-(trifluoromethyl)phenyl]methyl]amine (127 mg, 0.660 mmol) was added and the reaction was stirred overnight under an argon atmosphere. The reaction mixture was diluted with dichloromethane (10ml) and the solution was washed with saturated sodium hydrogen carbonate solution (10ml), water (10ml) and brine (10ml). The organic solution was dried and the solvent was evaporated in vacuo. The residue was purified by mass-directed automated HPLC. Fractions containing product were collected and the solvent was evaporated in vacuo to give N-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (8 mg, 4% yield) as a white solid. LC/MS [M+H]⁺ = 320, retention time = 1.87 minutes.

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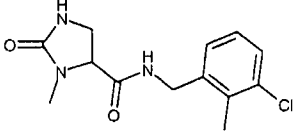
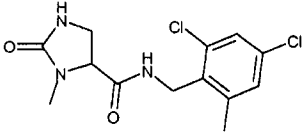
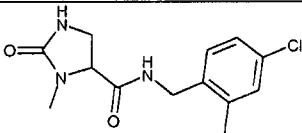
Examples 85-87 (in forms obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

In a manner analogous to that described for Example 84 above the compounds tabulated below (Table 14) were prepared by substituting the appropriate amine (or salt thereof) for the [[4-fluoro-3-(trifluoromethyl)phenyl]methyl]amine used in the above procedure. All of the amines used in Table 14 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

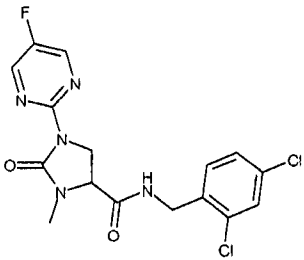
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Table 14

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E85	 N-[(3-Chloro-2-methylphenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide	282	1.78
E86	 N-[(2,4-Dichloro-6-methylphenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide	316	1.97
E87	 N-[(4-Chloro-2-methylphenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide	282	1.87

5 Example 88 N-[(2,4-Dichlorophenyl)methyl]-1-(5-fluoro-2-pyrimidinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E88**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[{(phenylmethyl)oxy]carbonyl}-4-imidazolidinecarboxylic acid)



10 1-(5-Fluoro-2-pyrimidinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid (211 mg, 0.878 mmol) was suspended in dichloromethane (5 ml) under argon and treated with

N-ethylmorpholine (0.667 ml, 5.27 mmol), 1-hydroxybenzotriazole hydrate (161 mg, 1.054 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (202 mg, 1.054 mmol) and stirred at room temperature for ~5 minutes. The mixture was then treated with 1-(2,4-dichlorophenyl)methanamine (0.117 ml, 0.878 mmol) and left to stir overnight at room temperature. The mixture was diluted with dichloromethane (~10 ml) and washed with saturated sodium hydrogen carbonate solution, water, 10% aqueous citric acid, water, and brine, then filtered through a hydrophobic frit and evaporated. Trituration of the resulting oil with diethyl ether gave N-[(2,4-dichlorophenyl)methyl]-1-(5-fluoro-2-pyrimidinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (187 mg, 53.5 % yield) as a white solid which was collected by filtration and dried *in vacuo*. LC/MS [M+H]⁺ = 398, retention time = 2.12 minutes.

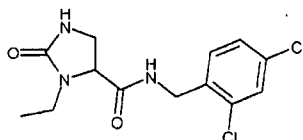
The 1-(5-fluoro-2-pyrimidinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

(i) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (300 mg, 1.498 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[(phenylmethyl)oxy]carbonyl-4-imidazolidinecarboxylic acid) and 2-chloro-5-fluoropyrimidine (0.194 ml, 1.573 mmol) in 1,4-dioxane (10 ml) was treated with cesium carbonate (732 mg, 2.247 mmol), XantphosTM (65.0 mg, 0.112 mmol), and tris(dibenzylideneacetone)dipalladium(0) (34.3 mg, 0.037 mmol) and then heated at reflux for ~3 hrs. The mixture was cooled to room temperature, diluted with water (~25 ml) and extracted with ethyl acetate (3 x). The combined ethyl acetate layers were washed with water and then with brine and evaporated to give a yellow/brown residue. This was purified by automated silica-gel column chromatography (Biotage SP-4), eluting with a 0-100% gradient of ethyl acetate in isohexane (8 column volumes), to give 1,1-dimethylethyl 1-(5-fluoro-2-pyrimidinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylate (232 mg, 52.3 % yield) as a white solid.

(ii) 1,1-Dimethylethyl 1-(5-fluoro-2-pyrimidinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylate (232 mg, 0.783 mmol) was dissolved in a mixture of trifluoroacetic acid (2 ml, 26.0 mmol) and dichloromethane (4ml) at 0°C and then left to warm to room temperature and stirred overnight. The mixture was evaporated (azeotroping with toluene and then with dichloromethane to remove all TFA traces) to give 1-(5-fluoro-2-pyrimidinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid (211 mg) as a white solid which was used without further purification in subsequent chemistry. LC/MS MH⁺ = 240.85.

MS

Example 89 *N*-[(2,4-Dichlorophenyl)methyl]-3-ethyl-2-oxo-4-imidazolidinecarboxamide (**E89**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



5

A mixture of 3-ethyl-2-oxo-4-imidazolidinecarboxylic acid (127 mg, 0.800 mmol), 1-hydroxybenzotriazole hydrate (147 mg, 0.960 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (184 mg, 0.960 mmol) and *N*-ethyl morpholine (0.409 ml, 3.20 mmol) in dichloromethane (9 ml) was stirred at room temperature for 10 minutes. A solution of [1-(2,4-dichlorophenyl)methyl]amine (141 mg, 0.8 mmol) in dichloromethane (1 ml) was added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (20 ml) and the mixture was washed with 3N citric acid solution (10 ml). The organic phase was separated, washed with brine (10 ml) and evaporated.

The residue was purified by mass-directed automated HPLC. The residue was triturated with ether and the resulting solid was collected and dried to give the product as a white solid (45 mg, 18%). LCMS $[M+H]^+ = 316$, retention time 1.93 minutes.

The 3-ethyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

(i) To a stirred solution of 5-(1,1-dimethylethyl) 1-(phenylmethyl) 2-oxo-1,5-imidazolidinedicarboxylate (1602 mg, 5 mmol) (prepared as described in step (ii) of Example 13, starting from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) in tetrahydrofuran (20 ml) under argon at 0°C was added sodium hydride (60% dispersion in oil, 210 mg, 5.25 mmol) (portion wise). The reaction mixture was stirred at 10°C for 1 hour. Acetic acid (1 ml, 17.47 mmol) was added dropwise and the solvent was evaporated. The residue was partitioned between in ethyl acetate (30 ml) and brine (15 ml). The organic extracts were combined, dried and evaporated. The residue was purified by silica gel chromatography eluting with 50-100% ethyl acetate in isohexane to give 4-(1,1-dimethylethyl) 1-(phenylmethyl) 2-oxo-1,4-imidazolidinedicarboxylate (780 mg, 49%). LC/MS $[M+H]^+ = 321$.

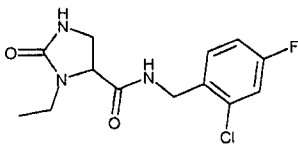
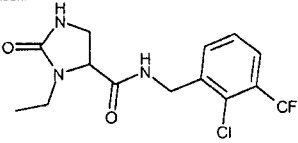
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- (ii) A stirred solution of 4-(1,1-dimethylethyl) 1-(phenylmethyl) 2-oxo-1,4-imidazolidinedicarboxylate (0.769 g, 2.4 mmol) in N,N-dimethylformamide (10 ml) was cooled to -10°C under argon and treated with iodoethane (0.194 ml, 2.400 mmol). Sodium hydride (60% dispersion in oil) (0.096 g, 2.400 mmol) was added portion wise. The mixture was allowed to warm to room temperature over 3 hours and stirred at room temperature for 16 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate (20 ml) and brine (10 ml). The aqueous layer was re-extracted with ethyl acetate (20 ml) and the organic extracts were combined, washed with saturated sodium hydrogen carbonate solution (20 ml), water (2 x 20 ml) and brine (20 ml), dried and evaporated to give 4-(1,1-dimethylethyl) 1-(phenylmethyl) 3-ethyl-2-oxo-1,4-imidazolidinedicarboxylate (1.15 g) which was used crude in the next reaction. LC/MS $[M+H]^+ = 349$.
- (iii) A solution of 4-(1,1-dimethylethyl) 1-(phenylmethyl) 3-ethyl-2-oxo-1,4-imidazolidinedicarboxylate (836 mg, 2.4 mmol) in methanol (15 ml) containing palladium on carbon (10% paste, 200 mg) was hydrogenated at room temperature and pressure for 72 hours. The mixture was filtered through a filter pad and the pad washed with methanol. The filtrates were combined and evaporated to give 1,1-dimethylethyl 3-ethyl-2-oxo-4-imidazolidinecarboxylate which was used in the next reaction (540 mg). LC/MS $[M+H]^+ = 215$.
- (iv) A solution of 1,1-dimethylethyl 3-ethyl-2-oxo-4-imidazolidinecarboxylate (0.514 g, 2.4 mmol) in trifluoroacetic acid/dichloromethane (1:2, 6 ml) was stirred at room temperature for 18 hours. The solution was evaporated and the residue was co-evaporated with dichloromethane and dried to give 3-ethyl-2-oxo-4-imidazolidinecarboxylic acid (assume ~ 2.4 mmol). LC/MS $[M+H]^+ = 159$.

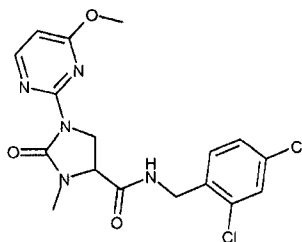
Examples 90-91 (in forms obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

In a manner analogous to that described for Example 89 above the compounds tabulated below (Table 15) were prepared by substituting the appropriate amine (or salt thereof) for the [1-(2,4-dichlorophenyl)methyl]amine used in the above procedure. All of the amines used in Table 15 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

Table 15

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E90	 <i>N</i> -[(2-Chloro-4-fluorophenyl)methyl]-3-ethyl-2-oxo-4-imidazolidinecarboxamide	300	1.74
E91	 <i>N</i> -[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-ethyl-2-oxo-4-imidazolidinecarboxamide	350	2.05

Example 92 *N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-[4-(methoxy)-2-pyrimidinyl]-2-oxo-4-imidazolidinecarboxamide (**E92**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



3-Methyl-1-[4-(methoxy)-2-pyrimidinyl]-2-oxo-4-imidazolidinecarboxylic acid (76 mg, 0.3 mmol) (~ 0.3mmol) in dichloromethane (4 ml) was treated with the 4A molecular sieves (200mg, 0.300 mmol), and the mixture stirred at RT for 5 minutes. *N*-Ethylmorpholine (0.190 ml, 1.500 mmol), 1-hydroxybenzotriazole hydrate (55.1 mg, 0.360 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (82 mg, 0.360 mmol) were then added and the reaction stirred at RT under argon for 10 minutes. [(2,4-Dichlorophenyl)methyl]amine (58.1 mg, 0.330 mmol) was added and

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the reaction left to stir at RT under argon for 4 hours. The reaction mixture was diluted with dichloromethane (15ml) and saturated sodium hydrogen carbonate solution (20ml), and the product was extracted into dichloromethane (x2). The combined organic extracts were washed with water (20 ml), brine (20 ml) and then dried over magnesium sulphate. The solvent was evaporated *in vacuo* to give a yellow solid, which was purified by mass-directed automated HPLC. Fractions containing product were combined and solvent evaporated *in vacuo*, co-evaporated with diethyl ether to give N-[(2,4-dichlorophenyl)methyl]-3-methyl-1-[4-(methyloxy)-2-pyrimidinyl]-2-oxo-4-imidazolidinecarboxamide as a white solid (60 mg, 46.3 % yield).

LC/MS $[M+H]^+ = 410$, retention time 1.73 = minutes.

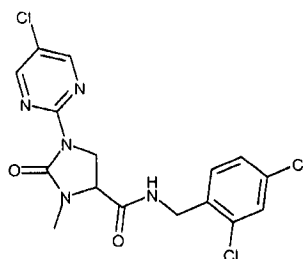
The 3-methyl-1-[4-(methyloxy)-2-pyrimidinyl]-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

- (i) A solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (500 mg, 2.497 mmol) (prepared as described in step (iii) of Example 13, starting from (4S)-2-oxo-3-[(phenylmethyl)oxy]carbonyl-4-imidazolidinecarboxylic acid) and 2-chloro-4-(methyloxy)pyrimidine (361 mg, 2.497 mmol) in 1,4-dioxane (20 ml) was treated with cesium carbonate (1220 mg, 3.75 mmol), XantphosTM (108 mg, 0.187 mmol) and tris(dibenzylideneacetone)dipalladium(0) (57.2 mg, 0.062 mmol) and the mixture was heated at reflux under argon for 3 hours. After cooling to room temperature, the reaction mixture was diluted with water (15 ml) and extracted with ethyl acetate (x2, 20 ml). The organic layers were combined, washed with water (20 ml) and brine (20 ml), dried over magnesium sulphate and then evaporated *in vacuo*. The residue was purified by flash-silica gel chromatography eluting with 0-10% methanol in dichloromethane. The fractions containing product were combined and solvent evaporated *in vacuo* to give a yellow oil. The residue was purified again by flash-silica gel chromatography, eluting with 0-100% ethyl acetate in isohexane to give 1,1-dimethylethyl 3-methyl-1-[4-(methyloxy)-2-pyrimidinyl]-2-oxo-4-imidazolidinecarboxylate as a yellow oil (100 mg, 13 % yield). LC/MS $[M+H]^+ 309$.
- (ii) A solution of 1,1-dimethylethyl 3-methyl-1-[4-(methyloxy)-2-pyrimidinyl]-2-oxo-4-imidazolidinecarboxylate (100 mg, 0.324 mmol) in dichloromethane (0.6 ml)/trifluoroacetic acid (0.300 ml) was stirred at room temperature for 24 hours. The solution was evaporated and the residue was co-evaporated with toluene (x3) and then dichloromethane (x4). The product was then dried in a vacuum oven (50°C) to give crude 3-methyl-1-[4-(methyloxy)-2-pyrimidinyl]-2-oxo-4-imidazolidinecarboxylic

acid as a yellow gum (95 mg, ~0.3 mmol) which was used in the next reaction.

LC/MS $[M+H]^+$ 253.

- 5 Example 93 1-(5-Chloro-2-pyrimidinyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E93**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



- 10 In a manner analogous to that described in Example 88 above 1-(5-chloro-2-pyrimidinyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide was prepared substituting 2,5-dichloropyrimidine for 2-chloro-5-fluoropyrimidine used in step (i) of the above procedure. LC/MS $[M+H]^+$ = 412, retention time = 2.34 minutes.

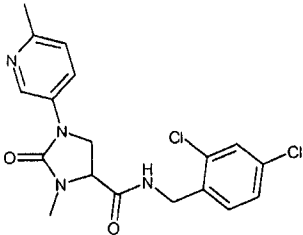
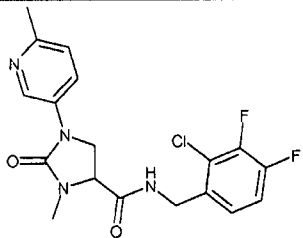
- 15 Examples 94-95 (in forms obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

- 20 In a manner analogous to that described for Example 13 above the compounds tabulated below (Table 16) were prepared by substituting the appropriate amine (or salt thereof) for the {[2-chloro-3-(trifluoromethyl)phenyl]methyl}amine used in the above procedure. All of the amines used in Table 16 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

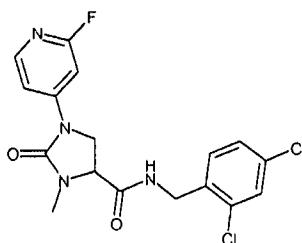
- 25 Table 16

Example no.	Chemical name	$[M+H]^+$	Retention time (mins)

NO

Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
94	 <i>N</i> -[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide	393	2.27
95	 <i>N</i> -[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide	395	2.11

Example 96 *N*-[(2,4-Dichlorophenyl)methyl]-1-(2-fluoro-4-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E96**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



A solution of 1-(2-fluoro-4-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid (200 mg, 0.521 mmol) and *N*-ethyl morpholine (0.400 ml, 3.13 mmol) in dichloromethane (10 ml) was treated with 1-hydroxybenzotriazole hydrate (80 mg, 0.521 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (100 mg, 0.521 mmol) and the reaction mixture was stirred at room temperature for 10 minutes. [(2,4-Dichlorophenyl)methyl]amine (0.084 ml, 0.521 mmol) was then added

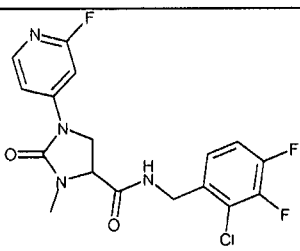
and the reaction stirred overnight. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solution, water and brine and separated through a hydrophobic frit. The organic layer was reduced under vacuum. The residue was purified mass-directed automated HPLC to give N-[(2,4-dichlorophenyl)methyl]-1-(2-fluoro-4-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (64 mg, 30.3 % yield). LC/MS $[M+H]^+$ = 397, retention time = 2.45 minutes.

The 1-(2-fluoro-4-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid used in the above procedure was prepared in a manner analogous to that described in Example 67 above substituting 4-bromo-2-fluoropyridine for 2-fluoro-3-iodopyridine used in step (i) of the Example 67 procedure.

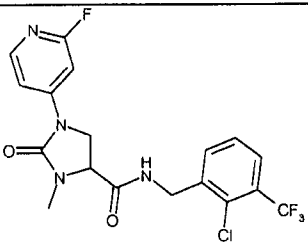
Examples 97-98 (in forms obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

In a manner analogous to that described for Example 96 above the compounds tabulated below (Table 17) were prepared by substituting the appropriate amine (or salt thereof) for the [(2,4-dichlorophenyl)methyl]amine used in the above procedure. All of the amines used in Table 17 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

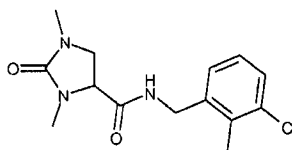
Table 17

Example no.	Chemical name	$[M+H]^+$	Retention time (mins)
97	 N-[(2-Chloro-3,4-difluorophenyl)methyl]-1-(2-fluoro-4-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide	399	2.33

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Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
98	 <i>N</i> -([2-Chloro-3-(trifluoromethyl)phenyl]methyl)-1-(2-fluoro-4-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide	431	2.28

Example 99 *N*-[(3-Chloro-2-methylphenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide (**E99**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



To 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylic acid (6.000 ml, 0.600 mmol) (0.1M solution in dichloromethane) was added the *N*-ethylmorpholine (0.380 ml, 3.00 mmol), 1-hydroxybenzotriazole hydrate (110 mg, 0.720 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (138 mg, 0.720 mmol), and the reaction stirred at RT under argon for 10 minutes. [(3-Chloro-2-methylphenyl)methyl]amine (103 mg, 0.660 mmol) was then added and the reaction left to stir at RT under argon overnight. The reaction mixture was diluted with dichloromethane (15ml) and then the solution was washed with saturated sodium hydrogen carbonate solution (20ml), water (20ml), 3N citric acid solution (20ml), brine (20ml) and then dried over magnesium sulphate. The solvent was evaporated *in vacuo*. The residue was purified by mass-directed automated HPLC. Fractions containing product were combined and solvent evaporated in *vacuo*, co-evaporated with diethyl ether to give the *N*-[(3-chloro-2-methylphenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide as a white solid (50mg, 26.8 % yield). LC/MS [M+H]⁺ = 296, retention time = 1.96 minutes

The 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

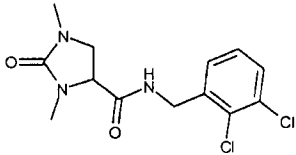
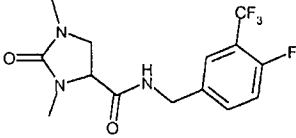
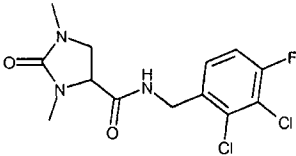
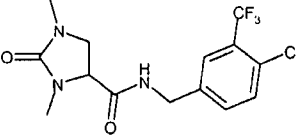
- (i) A stirred solution of 1,1-dimethylethyl 1-methyl-2-oxo-4-imidazolidinecarboxylate (1.75g, 8.74 mmol) (prepared as described in step (i) of Example 49 from 5-(1,1-dimethylethyl) 1-(phenylmethyl) 3-methyl-2-oxo-1,5-imidazolidinedicarboxylate, itself prepared as described in step (ii) of Example 13, starting originally from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) in N,N-dimethylformamide (22 ml) was cooled to -10 °C under argon, and then the methyl iodide (2.186 ml, 35.0 mmol) was added. Sodium hydride (60% dispersion in oil) (0.329 g, 8.22 mmol) was then added portion wise. The reaction mixture was allowed to warm to RT while stirring under argon overnight. The solvent was evaporated *in vacuo* and then the residue partitioned between ethyl acetate (40ml) and brine (30ml). The aqueous layer was re-extracted with ethyl acetate (x2) and then the combined organic extracts were washed with water (x2, 50ml), brine (50ml) and dried over magnesium sulphate. The solvent was evaporated *in vacuo*. The crude product was purified by flash-silica gel chromatography, eluting with 25-100% ethyl acetate / iso-hexane. The fractions containing product were combined and solvent evaporated *in vacuo* to give a yellow oil, 1,1-dimethylethyl 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylate (1.48 g, 79 % yield).
- (ii) A solution of 1,1-dimethylethyl 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylate (1.92 g, 8.96 mmol) in dichloromethane (12 ml)/ trifluoroacetic acid (6.00 ml) was stirred at room temperature for 24 hours. The solution was evaporated and the residue was co-evaporated with toluene (x 3) and then dichloromethane (x2). The product was then dried to give crude 1,3-dimethyl-2-oxo-4-imidazolidinecarboxylic acid (1.65 g) which was dissolved in dichloromethane (90 ml) to give a ~0.1M solution in dichloromethane which was used in subsequent reactions. LC/MS [M+H]⁺ = 159.

- 30 Examples 100-108 (in forms obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

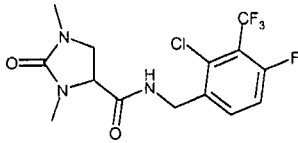
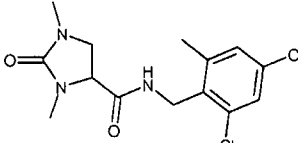
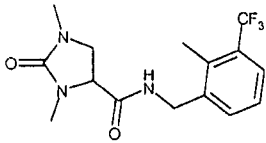
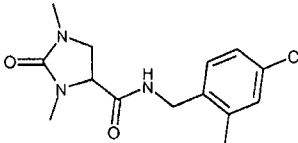
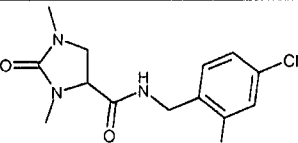
In a manner analogous to that described for Example 99 above the compounds tabulated below (Table 18) were prepared by substituting the appropriate amine (or salt thereof) for the [(3-chloro-2-methylphenyl)methyl]amine used in the above procedure. All of the amines used in Table 18 are available from commercial

sources or can be prepared using routes described previously in the chemical literature or analogous methods.

Table 18

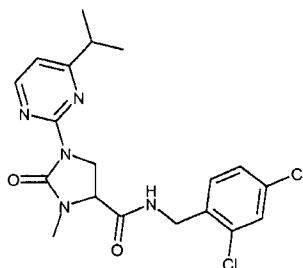
Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E100	 <i>N</i>-[(2,3-Dichlorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide	316	1.97
E101	 <i>N</i>-[[4-Fluoro-3-(trifluoromethyl)phenyl]methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide	334	2.06
E102	 <i>N</i>-[(2,3-Dichloro-4-fluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide	334	2.05
E103	 <i>N</i>-[[4-Chloro-3-(trifluoromethyl)phenyl]methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide	350	2.19

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Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E104	 <i>N</i> -([2-chloro-4-fluoro-3-(trifluoromethyl)phenyl]methyl)-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide	369	2.20
E105	 <i>N</i> -([2,4-dichloro-6-methylphenyl]methyl)-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide	330	2.17
E106	 1,3-Dimethyl- <i>N</i> -([2-methyl-3-(trifluoromethyl)phenyl]methyl)-2-oxo-4-imidazolidinecarboxamide	330	2.17
E107	 <i>N</i> -([4-chloro-2-methylphenyl]methyl)-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide	296	2.00
E108	 <i>N</i> -([2-chloro-4-cyanophenyl]methyl)-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide	307	1.68

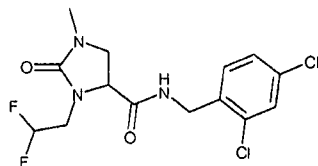
nb

Example 109 *N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-[4-(1-methylethyl)-2-pyrimidinyl]-2-oxo-4-imidazolidinecarboxamide (**E109**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



In a manner analogous to that described in Example 92 above *N*-[(2,4-dichlorophenyl)methyl]-3-methyl-1-[4-(1-methylethyl)-2-pyrimidinyl]-2-oxo-4-imidazolidinecarboxamide was prepared substituting 2-chloro-4-(1-methylethyl)pyrimidine for the 2-chloro-4-(methyloxy)pyrimidine used in step (i) of the Example 92 procedure. LC/MS $[M+H]^+ = 422$, retention time = 2.42 minutes.

Example 110 *N*-[(2,4-Dichlorophenyl)methyl]-3-(2,2-difluoroethyl)-1-methyl-2-oxo-4-imidazolidinecarboxamide (**E110**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



A mixture of 3-(2,2-difluoroethyl)-1-methyl-2-oxo-4-imidazolidinecarboxylic acid (105 mg, 0.505 mmol), 1-hydroxybenzotriazole hydrate (93 mg, 0.606 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (116 mg, 0.606 mmol) and *N*-ethyl morpholine (0.258 ml, 2.020 mmol) in dichloromethane (7 ml) was stirred at room temperature for 10 minutes. [1-(2,4Dichlorophenyl)methyl]amine (89 mg, 0.505 mmol) was added, a solid precipitated and DMF (1ml) was added. The reaction mixture was stirred at room temperature for 18 hours, it was then diluted with dichloromethane (10 ml), washed with saturated sodium hydrogen carbonate solution (10 ml), water (10 ml), citric acid solution (10 ml) and brine (10 ml). The organic phase was dried (magnesium sulfate) and evaporated. The residue was purified by

silica gel chromatography using 0-20 % of methanol in dichloromethane followed by mass-directed automated HPLC. The fraction containing the desired product was evaporated and the residue was triturated with diethyl ether and dried to give a white solid (10mg). LC/MS $[M+H]^+$ = 366, retention time 2.29 minutes.

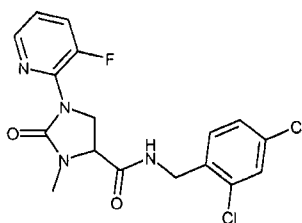
5

The 3-(2,2-difluoroethyl)-1-methyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

- (i) To a solution of 1,1-dimethylethyl 1-methyl-2-oxo-4-imidazolidinecarboxylate (200 mg, 0.999 mmol) (prepared as described in step (i) of Example 49 from 5-(1,1-dimethylethyl) 1-(phenylmethyl) 3-methyl-2-oxo-1,5-imidazolidinedicarboxylate, itself prepared as described in step (ii) of Example 13, starting originally from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) in N,N-dimethylformamide (10 ml) at -35 °C under argon was added sodium hydride (39.9 mg, 0.999 mmol). The mixture was stirred for 15 minutes, 2,2-difluoroethyl trifluoromethanesulfonate (428 mg, 1.998 mmol) was added and the reaction mixture was stirred at -35 °C for 30 minutes then slowly warmed to -15°C. After 1 hour the reaction mixture was quenched with water (10ml), warmed to room temperature and extracted with ethyl acetate (20ml x2). The combined organic layers were washed with sodium hydrogen carbonate saturated solution (15ml), water (10ml x2) and brine (15ml). The organic layer was then dried (magnesium sulfate), filtered and evaporated. The crude residue was purified by silica gel chromatography eluting with 10-100% of ethyl acetate in isohexane to give 1,1-dimethylethyl 3-(2,2-difluoroethyl)-1-methyl-2-oxo-4-imidazolidinecarboxylate (178mg). LC/MS $[M+H]^+$ = 265.
- (ii) 1,1-Dimethylethyl 3-(2,2-difluoroethyl)-1-methyl-2-oxo-4-imidazolidinecarboxylate (178 mg, 0.674 mmol) was dissolved in dichloromethane (3.00 ml) and trifluoroacetic acid (1 ml) was added. The solution was stirred at room temperature for 2 hours. The solvent was evaporated and the residue co-evaporated with dichloromethane and toluene to give a crude 3-(2,2-difluoroethyl)-1-methyl-2-oxo-4-imidazolidinecarboxylic acid (assume 0.674mmol) which was used for the next reaction. LC/MS $[M+H]^+$ = 209.

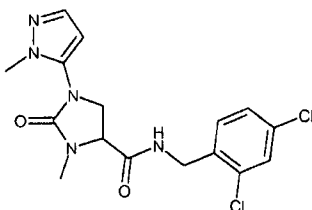
Example 111 N-[(2,4-Dichlorophenyl)methyl]-1-(3-fluoro-2-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E111**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

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In a manner analogous to that described in Example 67 above *N*-[(2,4-dichlorophenyl)methyl]-1-(3-fluoro-2-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide was prepared substituting 2-bromo-3-fluoropyridine for 2-fluoro-3-iodopyridine used in step (i) of the Example 67 procedure. LC/MS $[M+H]^+ = 397$, retention time = 2.32 minutes.

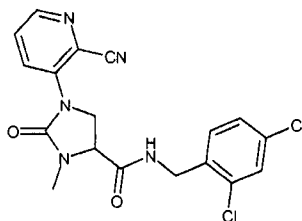
Example 112 *N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1*H*-pyrazol-5-yl)-2-oxo-4-imidazolidinecarboxamide (**E112**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



To a stirred mixture of *N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (200 mg, 0.662 mmol) (prepared as described in Example 30), 5-iodo-1-methyl-1*H*-pyrazole (165 mg, 0.794 mmol) in 1,4-dioxane (20 ml) was added potassium phosphate (703 mg, 3.31 mmol), copper (I) iodide (126 mg, 0.662 mmol) and trans-*N,N*-dimethylcyclohexane-1,2-diamine (0.104 ml, 0.662 mmol) and the reaction mixture was heated at reflux under argon for 18 hours. After cooling to room temperature, ethyl acetate (20 ml), water (10 ml) and 0.880 ammonia solution (5 ml) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 20 ml). The organic extracts were combined, washed with citric acid solution (20 ml), water (10 ml) and brine (10 ml), dried and evaporated. The residue was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane followed by mass-directed automated HPLC to give *N*-[(2,4-dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1*H*-pyrazol-5-yl)-2-oxo-4-imidazolidinecarboxamide (40 mg, 16%). LC/MS $[M+H]^+ = 382$, retention time = 2.12 minutes.

mg

Example 113 1-(2-Cyano-3-pyridinyl)-N-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E113**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

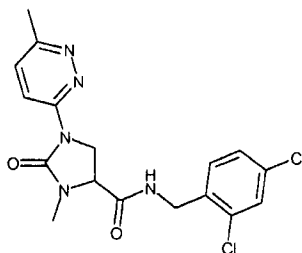


5

A suspension of N-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (200 mg, 0.662 mmol) (prepared as described in Example 30) and 3-bromo-2-pyridinecarbonitrile (121 mg, 0.662 mmol) in 1,4-dioxane (5 ml) was treated with cesium carbonate (323 mg, 0.993 mmol), XantphosTM (28.7 mg, 0.050 mmol) and tris(dibenzylideneacetone)dipalladium(0) (15.15 mg, 0.017 mmol) and the mixture was heated at reflux under argon for overnight. After cooling to room temperature, the reaction mixture was diluted with saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The organic layers were combined, washed with water and brine and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with 10-100% ethyl acetate in isohexane to give 1-(2-cyano-3-pyridinyl)-N-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (212 mg, 78 % yield). LC/MS [M+H]⁺ = 404, retention time = 2.32 minutes.

20

Example 114 N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(6-methyl-3-pyridazinyl)-2-oxo-4-imidazolidinecarboxamide (**E114**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



25

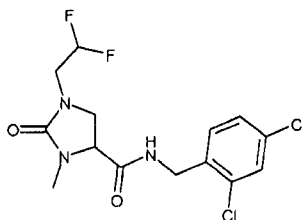
In a manner analogous to that described in Example 92 above N-[(2,4-dichlorophenyl)methyl]-3-methyl-1-(6-methyl-3-pyridazinyl)-2-oxo-4-

130

imidazolidinecarboxamide was prepared substituting 3-chloro-6-methylpyridazine for 2-chloro-4-(methyloxy)pyrimidine used in step (i) of the Example 92 procedure.

LC/MS $[M+H]^+ = 394$, retention time = 1.96 minutes.

- 5 **Example 115** *N*-[(2,4-Dichlorophenyl)methyl]-1-(2,2-difluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E115**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



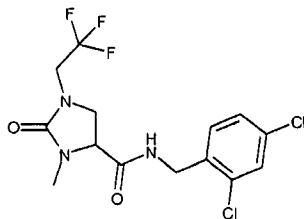
- 10 A mixture of 1-(2,2-difluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid (125 mg, 0.6mmol), 1-hydroxybenzotriazole hydrate (110 mg, 0.720 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (138 mg, 0.720 mmol) and *N*-ethylmorpholine (0.305 ml, 2.400 mmol) in dichloromethane (5 ml) was stirred for 10 minutes. [(2,4-Dichlorophenyl)methyl]amine (106 mg, 0.600 mmol) was added and
- 15 the solution was stirred at room temperature for 3 days. The reaction mixture was diluted with dichloromethane (10ml), washed with saturated sodium hydrogen carbonate solution (10ml), water (10ml) and brine (10ml). The organic phase was dried (magnesium sulphate) and evaporated. The residue was purified by the mass-directed automated HPLC. The fraction containing the desired product was
- 20 evaporated and the residue was triturated with diethyl ether and dried to give *N*-[(2,4-dichlorophenyl)methyl]-1-(2,2-difluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (25mg). LC/MS $[M+H]^+ = 366$, retention time = 2.09 minutes.
- 25 The 1-(2,2-difluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:
- (i) To a solution of 1,1-dimethylethyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (200 mg, 0.999 mmol) (prepared as described in step (iii) of Example 13, starting from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid) and
- 30 2,2-difluoroethyl trifluoromethanesulfonate (428 mg, 1.998 mmol) in *N,N*-dimethylformamide (4 ml) at -35°C under argon was added sodium hydride (80 mg, 1.998 mmol). The reaction mixture was warmed to 0°C over 2 hours, quenched with

B1

water (10ml) and extracted with ethyl acetate (20ml x2). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (15 ml), water (10ml x2) and brine (15ml). The organic layer was dried (magnesium sulfate), filtered and evaporated. The residue was purified by silica gel chromatography eluting with 10-100% ethyl acetate in isohexane to give 1,1-dimethylethyl 1-(2,2-difluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxylate (200mg). LC/MS $[M+H]^+ = 265$.

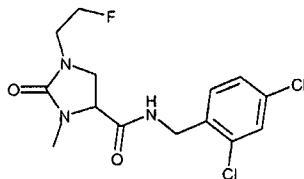
(ii) 1,1-dimethylethyl 1-(2,2-difluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxylate (200 mg, 0.757 mmol) was dissolved in dichloromethane (3 ml) and trifluoroacetic acid (1 ml) added. The solution was stirred at room temperature for 2 hours. The solvent was evaporated and the residue co-evaporated with toluene (x2) to give 1-(2,2-difluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxylic acid (0.757 mmol) which was used in the next step. LC/MS $[M+H]^+ = 209$.

Example 116 N-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxamide (**E116**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



In a manner analogous to that described in Example 115 above N-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxamide was prepared substituting 2,2,2-trifluoroethyl trichloromethanesulfonate for 2,2-difluoroethyl trifluoromethanesulfonate used in step (i) of the Example 115 procedure. LC/MS $[M+H]^+ = 384$, retention time = 2.41 minutes.

Example 117 N-[(2,4-Dichlorophenyl)methyl]-1-(2-fluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E117**) (in a form obtainable or prepared from (4S)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)



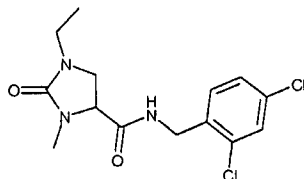
132

In a manner analogous to that described in Example 115 above *N*-[(2,4-dichlorophenyl)methyl]-1-(2-fluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide was prepared substituting 1-fluoro-2-iodoethane for 2,2-difluoroethyl trifluoromethanesulfonate used in step (i) of the Example 115 procedure. LC/MS

5 $[M+H]^+ = 348$, retention time = 2.11 minutes.

Example 118 *N*-[(2,4-Dichlorophenyl)methyl]-1-ethyl-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E118**) (in a form obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

10



In a manner analogous to that described in Example 115 above *N*-[(2,4-dichlorophenyl)methyl]-1-ethyl-3-methyl-2-oxo-4-imidazolidinecarboxamide was prepared substituting iodoethane for 2,2-difluoroethyl trifluoromethanesulfonate used in step (i) of the Example 115 procedure. LC/MS $[M+H]^+ = 330$, retention time = 2.17 minutes.

15

Examples 119-121 (in forms obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

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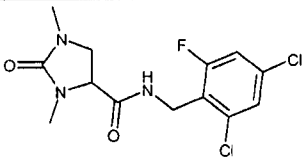
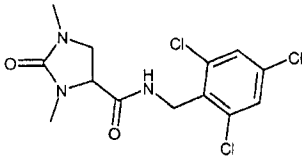
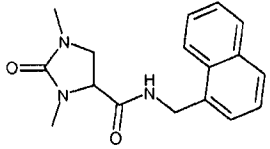
In a manner analogous to that described for Example 99 above the compounds tabulated below (Table 19) were prepared by substituting the appropriate amine (or salt thereof) for the [(3-chloro-2-methylphenyl)methyl]amine used in the above procedure. All of the amines used in Table 19 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

25

Table 19

Example no.	Chemical name	$[M+H]^+$	Retention time (mins)
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123

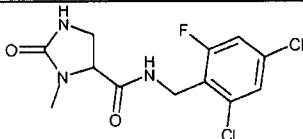
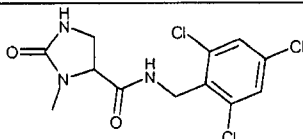
Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E119	 <chem>CN1C(=O)N(C)C(=O)N1CCc2cc(F)c(Cl)c(Cl)c2</chem> <i>N</i> -[(2,4-Dichloro-6-fluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide	334	2.01
E120	 <chem>CN1C(=O)N(C)C(=O)N1CCc2cc(Cl)c(Cl)c(Cl)c2</chem> 1,3-Dimethyl-2-oxo- <i>N</i> -[(2,4,6-trichlorophenyl)methyl]-4-imidazolidinecarboxamide	352	2.16
E121	 <chem>CN1C(=O)N(C)C(=O)N1CCc2c3ccccc3ccc2</chem> 1,3-Dimethyl- <i>N</i> -(1-naphthalenylmethyl)-2-oxo-4-imidazolidinecarboxamide	298	1.95

Examples 122 and 123. (in forms obtainable or prepared from (4*S*)-2-oxo-3-[[[(phenylmethyl)oxy]carbonyl]-4-imidazolidinecarboxylic acid)

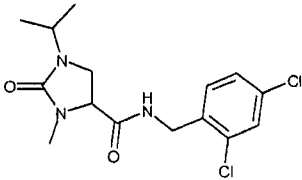
- 5 In a manner analogous to that described for Example 84 above the compounds tabulated below (Table 20) were prepared by substituting the appropriate amine (or salt thereof) for the {[4-fluoro-3-(trifluoromethyl)phenyl]methyl}amine used in the above procedure. All of the amines used in Table 20 are available from commercial
- 10 literature or analogous methods.

Table 20

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Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
E122	 <chem>CN1C(=O)N(C(=O)NCC2=CC(=C(C(=C2)Cl)Cl)F)C1=O</chem> <i>N</i> -[(2,4-Dichloro-6-fluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide	320	1.88
E123	 <chem>CN1C(=O)N(C(=O)NCC2=CC(=C(C(=C2)Cl)Cl)Cl)C1=O</chem> 3-Methyl-2-oxo- <i>N</i> -[(2,4,6-trichlorophenyl)methyl]-4-imidazolidinecarboxamide	338	1.97

Example 124 *N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methylethyl)-2-oxo-4-imidazolidinecarboxamide (**E124**)



5

A mixture of 3-methyl-1-(1-methylethyl)-2-oxo-4-imidazolidinecarboxylic acid (100 mg, 0.537 mmol), *N*-ethylmorpholine (0.274 ml, 2.148 mmol), 1-hydroxybenzotriazole hydrate (99 mg, 0.644 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (124 mg, 0.644 mmol) in dichloromethane (9 ml) was stirred at room temperature for 10 minutes. A solution of [1-(2,4-dichlorophenyl)methyl]amine (95 mg, 0.537 mmol) in dichloromethane (1 ml) was added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (10 ml) and the mixture was washed with saturated sodium hydrogen carbonate solution (10 ml) and brine (10 ml), dried and evaporated. The residue was purified by mass-directed automated HPLC. The residue was triturated with ether and the resulting solid was collected and dried to give *N*-[(2,4-

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dichlorophenyl)methyl]-3-methyl-1-(1-methylethyl)-2-oxo-4-imidazolidinecarboxamide (124 mg, 67%). LCMS $[M+H]^+ = 344$, retention time = 2.32 minutes.

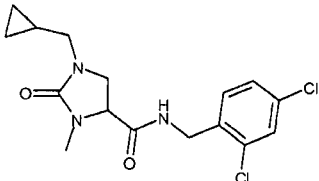
The 3-methyl-1-(1-methylethyl)-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

A stirred solution of methyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (316 mg, 2 mmol) (prepared as described in step (ii) of Example 8) in N,N-dimethylformamide (5 ml) was cooled to 0°C under argon and treated with sodium hydride (60% dispersion in oil) (120 mg, 3.00 mmol). After 10 minutes 2-iodopropane (0.400 ml, 4.00 mmol) was added and the reaction mixture was stirred at room temperature for 18 hours. A solution of lithium hydroxide (57.5 mg, 2.400 mmol) in water (1 ml) was added and the reaction mixture was stirred at room temperature for 30 minutes. Hydrochloric acid (2M) was added to adjust the pH of the mixture to pH 2 and the solvent was evaporated. Dimethylsulfoxide (3 ml) was added to the residue and the suspension was filtered. The filtrate was purified by mass-directed automated HPLC to give 3-methyl-1-(1-methylethyl)-2-oxo-4-imidazolidinecarboxylic acid (100 mg, 27%, over 2 steps). LC/MS $[M+H]^+ = 187$.

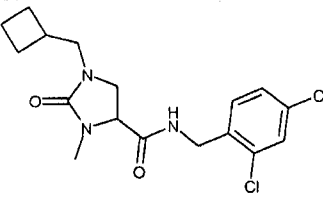
Examples 125 and 126

In a manner analogous to that described for Example 124 above the compounds tabulated below (Table 21) were prepared by substituting the appropriate alkyl bromide for the 2-iodopropane used in the above procedure. All of the alkyl bromides used in Table 21 are available from commercial sources or can be prepared using routes described previously in the chemical literature or analogous methods.

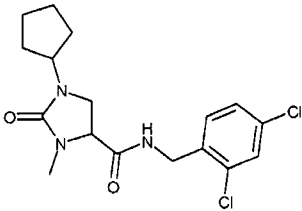
Table 21

Example no.	Chemical name	$[M+H]^+$	Retention time (mins)
E125	 1-(Cyclopropylmethyl)-N-[(2,4-	356	2.41

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Example no.	Chemical name	[M+H] ⁺	Retention time (mins)
	dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide		
E126	 1-(Cyclobutylmethyl)-N-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide	370	2.60

Example 127 1-Cyclopentyl-N-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (**E127**)



5

A mixture of 1-cyclopentyl-3-methyl-2-oxo-4-imidazolidinecarboxylic acid (39 mg, 0.184 mmol), N-ethylmorpholine (0.094 ml, 0.735 mmol), 1-hydroxybenzotriazole hydrate (33.8 mg, 0.220 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (42.3 mg, 0.220 mmol) in dichloromethane (9 ml) was stirred at room temperature for 10 minutes. A solution of [1-(2,4-dichlorophenyl)methyl]amine (32.3 mg, 0.184 mmol) in dichloromethane (1 ml) was added and the reaction mixture was stirred at room temperature for 72 hours. The reaction mixture was diluted with dichloromethane (10 ml) and the mixture was washed with saturated sodium hydrogen carbonate solution (10 ml) and brine (10 ml), dried and evaporated. The residue was purified by mass-directed automated HPLC. The residue was triturated with ether and the resulting solid was collected and dried to give 1-cyclopentyl-N-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide (42 mg, 62%). LCMS [M+H]⁺ = 370, retention time = 2.28 minutes.

20

NS

The 1-cyclopentyl-3-methyl-2-oxo-4-imidazolidinecarboxylic acid used in the method described above was prepared as follows:

A stirred solution of methyl 3-methyl-2-oxo-4-imidazolidinecarboxylate (316 mg, 2.0 mmol) (prepared as described in step (ii) of Example 8) in N,N-dimethylformamide (5

- 5 ml) was cooled to 0°C under argon and treated with sodium hydride (60% dispersion in oil) (80 mg, 2.0 mmol). After 10 minutes bromocyclopentane (298 mg, 2.0 mmol) was added and the reaction mixture was stirred at room temperature for 3 hours and then at 60°C for 18 hours. After cooling to room temperature additional sodium hydride (60% dispersion in oil) (80 mg, 2.0 mmol) was added followed by
- 10 bromocyclopentane (298 mg, 2.0 mmol) and the reaction mixture was heated at 60°C for 48 hours. After cooling to room temperature a solution of lithium hydroxide (0.057 g, 2.400 mmol) in water (1 ml) was added and the reaction mixture was stirred at room temperature for 30 minutes. Hydrochloric acid (2M) was added to adjust the pH of the mixture to pH 2 and the solvent was evaporated. Dimethylsulfoxide (3 ml)
- 15 was added to the residue and the suspension was filtered. The filtrate was purified by mass-directed automated HPLC to give 1-cyclopentyl-3-methyl-2-oxo-4-imidazolidinecarboxylic acid (39 mg, 9%). LC/MS $[M+H]^+ = 213$.

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Mass-directed automated HPLC

Where indicated in the above examples, purification by mass-directed automated HPLC was carried out using the following apparatus and conditions:

5

Hardware

Waters 2525 Binary Gradient Module

Waters 515 Makeup Pump

Waters Pump Control Module

10 Waters 2767 Inject Collect

Waters Column Fluidics Manager

Waters 2996 Photodiode Array Detector

Waters ZQ Mass Spectrometer

Gilson 202 fraction collector

15 Gilson Aspec waste collector

Software

Waters MassLynx version 4 SP2

20 **Column**

The columns used are Waters Atlantis, the dimensions of which are 19mm x 100mm (small scale) and 30mm x 100mm (large scale). The stationary phase particle size is 5µm.

25 **Solvents**

A : Aqueous solvent = Water + 0.1% Formic Acid

B : Organic solvent = Acetonitrile + 0.1% Formic Acid

Make up solvent = Methanol : Water 80:20

Needle rinse solvent = Methanol

30

Methods

There are five methods used depending on the analytical retention time of the compound of interest. They have a 13.5-minute runtime, which comprises a 10-minute gradient followed by a 3.5 minute column flush and re-equilibration step.

35 Large/Small Scale 1.0-1.5 = 5-30% B

Large/Small Scale 1.5-2.2 = 15-55% B

Large/Small Scale 2.2-2.9 = 30-85% B

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

Large/Small Scale 3.6-5.0 = 80-99% B (in 6 minutes followed by 7.5 minutes flush and re-equilibration)

5 Flow rate

All of the above methods have a flow rate of either 20mls/min (Small Scale) or 40mls/min (Large Scale).

Chiral HPLC

- 10 Apparatus and conditions used to characterize enantiomeric purity of selected samples was as follows:

Method (A)

Instrument: Agilent 1100 Series Liquid Chromatogram

- 15 Column: Chiralpak AD (250mm x 4.6mm; 10um particle size)

Mobile phase: Heptane: absolute ethanol (70:30) v/v pump-mixed

Flow rate: 1ml/min

Temperature: Ambient

U.V. Wavelength: 215nm

20

Method (B)

Instrument: Agilent 1100 Series Liquid Chromatogram

Column: Chiralpak AD (250mm x 4.6mm; 10um particle size)

Mobile phase: Heptane: absolute ethanol (50:50) v/v pump-mixed

- 25 Flow rate: 1ml/min

Temperature: Ambient

U.V. Wavelength: 215nm

Method (C)

- 30 Instrument: Agilent 1100 Series Liquid Chromatogram

Column: Chiralpak AD (250mm x 4.6mm; 10um particle size)

Mobile phase: Heptane: absolute ethanol (80:20) v/v pump-mixed

Flow rate: 1ml/min

Temperature: Ambient

- 35 U.V. Wavelength: 215nm

Method (D)

Instrument: Agilent 1100 Series Liquid Chromatogram

Column: Chiralpak AS (250mm x 4.6mm; 10um particle size)

Mobile phase: Heptane: absolute ethanol (80:20) v/v pump-mixed

Flow rate: 1ml/min

5 Temperature: Ambient

U.V. Wavelength: 215nm

Liquid Chromatography / Mass Spectrometry

- 10 Analysis of the above Examples 1-71 and 74-78 by Liquid Chromatography / Mass Spectrometry (LC/MS) was carried out using the following apparatus and conditions:

Hardware

Agilent 1100 Gradient Pump

- 15 Agilent 1100 Autosampler

Agilent 1100 DAD Detector

Agilent 1100 Degasser

Agilent 1100 Oven

Agilent 1100 Controller

- 20 Waters ZQ Mass Spectrometer

Sedere Sedex 85

Software

Waters MassLynx version 4.0 SP2

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Column

The column used is a Waters Atlantis, the dimensions of which are 4.6mm x 50mm.

The stationary phase particle size is 3µm.

- 30 Solvents

A : Aqueous solvent = Water + 0.05% Formic Acid

B : Organic solvent = Acetonitrile + 0.05% Formic Acid

Method

- 35 The generic method used has a 5 minute runtime.

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

The above method has a flow rate of 3ml/mins.

The injection volume for the generic method is 5ul.

The column temperature is 30deg.

- 5 The UV detection range is from 220 to 330nm.

Analysis of the above Examples 72, 73 and 79-123 by Liquid Chromatography / Mass Spectrometry (LC/MS) was carried out using the following apparatus and conditions:

10

Hardware

Agilent 1100 Gradient Pump

Agilent 1100 Autosampler

Agilent 1100 DAD Detector

- 15 Agilent 1100 Degasser

Agilent 1100 Oven

Agilent 1100 Controller

Waters ZQ Mass Spectrometer

Sedere Sedex 85

20

Software

Waters MassLynx version 4.1

Column

- 25 The HPLC analysis was conducted on a Sunfire C18 column (30mm x 4.6mm i.d. 3.5µm packing diameter) at 30 degrees centigrade.

Solvents

A = 0.1% v/v solution of Formic Acid in Water.

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B = 0.1% v/v solution of Formic Acid in Acetonitrile.

Method

The generic method used has a 5 minute runtime. The gradient employed was:

5

Time (min)	Flow Rate (ml/min)	% A	% B
0	3	97	3
0.1	3	97	3
4.2	3	0	100
4.8	3	0	100
4.9	3	97	3
5.0	3	97	3

The UV detection was an averaged signal from wavelength of 210nm to 350nm and mass spectra were recorded on a mass spectrometer using alternate-scan positive and negative mode electrospray ionization.

10

MB

PHARMACOLOGICAL DATA

Compounds of the invention may be tested for *in vitro* biological activity at the P2X7 receptor in accordance with the following studies:

5

Ethidium Accumulation Assay

Studies were performed using NaCl assay buffer of the following composition (in mM): 140mM NaCl, HEPES 10, *N*-methyl-D-glucamine 5, KCl 5.6, D-glucose 10, CaCl₂ 0.5 (pH 7.4). HEK293 cells, expressing human recombinant P2X7 receptors, were grown in poly-L-lysine pretreated 96 well plates for 18-24 h. (The cloning of the human P2X7 receptor is described in US 6,133,434). The cells were washed twice with 350µl of assay buffer before addition of 50µl of antagonist. The cells were then incubated at room temperature (19-21°C) for 30 min before addition of ATP and ethidium (100µM final assay concentration). The ATP concentration was chosen to be close to the EC₈₀ for the receptor type and was 1mM for studies on the human P2X7 receptor. Incubations were continued for 8 or 16 min and were terminated by addition of 25µl of 1.3M sucrose containing 5mM of the P2X7 receptor antagonist reactive black 5 (Aldrich). Cellular accumulation of ethidium was determined by measuring fluorescence (excitation wavelength of 530nm and emission wavelength of 620nm) from below the plate with a Canberra Packard Fluorocount (Pangbourne, UK). Antagonist pIC₅₀ values for blocking ATP responses were determined using iterative curve fitting techniques.

Fluorescent Imaging Plate Reader (FLIPR) Ca Assay

Studies were performed using NaCl assay buffer of the following composition (in mM) for human P2X7: 137 NaCl; 20 HEPES; 5.37 KCl; 4.17 NaHCO₃; 1 CaCl₂; 0.5 MgSO₄; and 1g/L of D-glucose (pH 7.4).

HEK293 cells, expressing human recombinant P2X7 receptors, were grown in poly-L-lysine pretreated 384 well plates for 42-48h. (The cloning of the human P2X7 receptor is described in US 6,133,434). The cells were washed three times with 80µl of assay buffer, loaded for 1h at 37°C with 2µM Fluo4 (Teflabs), washed three times again, and left with 30µl buffer before the addition of 10 µl of 4x concentrated antagonist. The cells were then incubated at room temperature for 30 mins before addition (online, by FLIPR384 or FLIPR3 instrument (Molecular Devices)) of Benzoylbenzoyl-ATP (BzATP) 60µM final assay concentration. The BzATP

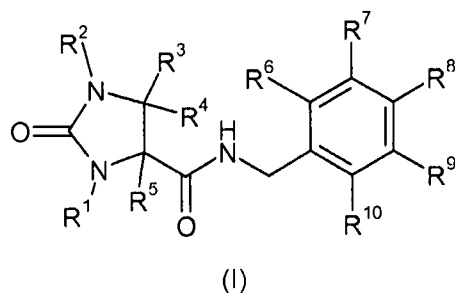
concentration was chosen to be close to the EC_{80} for the receptor type. Incubations and reading were continued for 90sec, and intracellular calcium increase was determined by measuring fluorescence (excitation wavelength of 488nm and emission wavelength of 516nm) from below the plate, with FLIPR CCD camera.

- 5 Antagonist pIC_{50} values for blocking BzATP responses were determined using iterative curve fitting techniques.

- The compounds of Examples 1-127 were tested in the FLIPR Ca Assay and/or the Ethidium Accumulation Assay for human P2X7 receptor antagonist activity and found
- 10 to have pIC_{50} values > 4.7 in the FLIPR Ca Assay and/or pIC_{50} values > 5.5 in the Ethidium Accumulation Assay. The compounds of Examples E1 to E5, E7, E8, E10 to E13, E15, E18, E19, E21, E23, E25 to E28, E30, E32 to E35, E39, E41, E42, E45, E51, E52, E54, E55, E57 to E61, E64 to E70, E72 to E79, E81, E82, E85, E86, E88, E89, E91 to E97, E99, E100, E102, E104 to E108, E110 to E113, E115 to E120, and
- 15 E122 to E127 were found to have pIC_{50} values of about 7.5 or more in the Ethidium Accumulation Assay.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein:

- R^1 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, pyridinylmethyl- or benzyl, and wherein any of said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, pyridinylmethyl- or benzyl is optionally substituted with 1, 2 or 3 halogen atoms; or an unsubstituted phenyl;
- R^2 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, $-(CR^xR^y)_n-NR^{11}R^{12}$, C_{6-10} arylmethyl-, heterocyclyl- $(CR^xR^y)_n$ - or heteroaryl- $(CR^xR^y)_n$; and wherein any of said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, C_{6-10} arylmethyl-, heterocyclyl- $(CR^xR^y)_n$ - or heteroaryl- $(CR^xR^y)_n$ is optionally substituted with 1, 2 or 3 halogen atoms or C_{1-6} alkyl groups, or the heteroaryl- $(CR^xR^y)_n$ is optionally substituted on the heteroaryl ring with one C_{1-3} alkoxy (e.g. methoxy), cyano or trifluoromethyl group;
- R^3 , R^4 and R^5 independently represent hydrogen, fluorine or methyl; and
- R^6 , R^7 , R^8 , R^9 and R^{10} independently represent hydrogen, halogen, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or phenyl, and any of said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or phenyl is optionally substituted with 1, 2 or 3 halogen atoms; or R^9 and R^{10} together with the carbon atoms to which they are attached form a benzene ring which is optionally substituted with 1, 2 or 3 halogen atoms;
- R^x and R^y independently represent hydrogen or C_{1-6} alkyl;
- R^{11} and R^{12} independently represent hydrogen or C_{1-6} alkyl;
- n represents an integer from 0 to 4;
- with the proviso that when R^6 and R^{10} independently represent hydrogen or fluorine, at least one of R^7 , R^8 and R^9 is a halogen atom, or only one of R^7 , R^8 and R^9 is a CF_3 group.

2. A compound or salt as claimed in claim 1, wherein R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, pyridinylmethyl- or benzyl, any of which is optionally substituted with 1, 2 or 3 halogen atoms; or an unsubstituted phenyl.
- 5 3. A compound or salt as claimed in claim 2, wherein R^1 represents methyl, ethyl, or ethyl substituted with 1, 2 or 3 fluorine atoms.
- 10 4. A compound or salt as claimed in claim 2, wherein R^1 represents unsubstituted C_{1-6} alkyl.
5. A compound or salt as claimed in claim 4, wherein R^1 represents methyl.
- 15 6. A compound or salt as claimed in claim 1, 2, 3, 4 or 5, wherein R^2 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, $-(CR^xR^y)_n-NR^{11}R^{12}$, C_{6-10} arylmethyl-, heterocyclyl- $(CR^xR^y)_n-$ or heteroaryl- $(CR^xR^y)_n-$; and wherein any of said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl-, C_{6-10} arylmethyl-, heterocyclyl- $(CR^xR^y)_n-$ or heteroaryl- $(CR^xR^y)_n-$ is optionally substituted with 1, 2 or 3 halogen atoms or C_{1-6} alkyl groups.
- 20 7. A compound or salt as claimed in claim 1, 2, 3, 4 or 5, wherein R^2 represents hydrogen, C_{1-6} alkyl, or heteroaryl- $(CR^xR^y)_n-$ wherein n represents 0; and wherein any of said C_{1-6} alkyl or heteroaryl- $(CR^xR^y)_n-$ is optionally substituted with 1, 2 or 3 halogen atoms or methyl groups; or the heteroaryl- $(CR^xR^y)_n-$ is optionally substituted
- 25 on the heteroaryl ring by one C_{1-3} alkoxy, cyano or trifluoromethyl group.
8. A compound or salt as claimed in claim 7, wherein R^2 represents pyridinyl, pyrimidinyl, imidazolyl or pyrazolyl, wherein any of said groups are optionally substituted with 1 or 2 fluorine or chlorine atoms, with 1 or 2 methyl groups, or with
- 30 one methoxy, cyano or trifluoromethyl group.
9. A compound or salt as claimed in any one of claims 1 to 7, wherein R^2 represents hydrogen or unsubstituted C_{1-6} alkyl.
- 35 10. A compound or salt as claimed in any one of claims 1 to 7, wherein R^2 represents hydrogen, methyl, ethyl, or ethyl substituted with 1, 2 or 3 fluorine atoms.

11. A compound or salt as claimed in any one of the preceding claims, wherein
R¹ and R² do not both represent hydrogen.
12. A compound or salt as claimed in any one of the preceding claims, wherein
5 R¹ and R² both represent methyl, or
R¹ represents methyl and R² represents hydrogen.
13. A compound or salt as claimed in any one of the preceding claims, wherein
10 R³, R⁴ and R⁵ all represent hydrogen.
14. A compound or salt as claimed in any one of the preceding claims, wherein
R⁶, R⁷, R⁸, R⁹ and R¹⁰ independently represent hydrogen, halogen, methyl or
trifluoromethyl.
15. A compound or salt as claimed in any one of the preceding claims, wherein
R⁶ and R⁷ both represent hydrogen,
R⁸ represents hydrogen, chlorine or fluorine,
R⁹ represents hydrogen, chlorine, fluorine or trifluoromethyl, and
R¹⁰ represents chlorine, fluorine, methyl or trifluoromethyl.
- 20 16. A compound or salt as claimed in claim 15, wherein
R⁶ and R⁷ both represent hydrogen,
R⁸ represents hydrogen, chlorine or fluorine,
R⁹ represents hydrogen, chlorine, fluorine or trifluoromethyl, and
25 R¹⁰ represents chlorine or methyl,
wherein one or both of R⁸ and R⁹ is / are other than hydrogen.
17. A compound or salt as claimed in any claim 16, wherein:
R⁶ and R⁷ both represent hydrogen,
30 R⁸ represents hydrogen or fluorine,
R⁹ represents trifluoromethyl, and
R¹⁰ represents chlorine or methyl.
18. A compound or salt as claimed in any one of claims 1 to 14, wherein:
35 R⁶ represents hydrogen, chlorine, fluorine or methyl,
R⁷ represents hydrogen,
R⁸ represents chlorine or fluorine,

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R⁹ represents hydrogen, and
R¹⁰ represents chlorine or methyl.

19. A compound or salt as claimed in claim 18, wherein:

- 5 R⁶ represents hydrogen, chlorine, fluorine or methyl,
R⁷ represents hydrogen,
R⁸ represents chlorine,
R⁹ represents hydrogen, and
R¹⁰ represents chlorine or methyl.

10

20. A compound or salt as claimed in any one of claims 1 to 14, wherein:
R⁶, R⁷ and R⁸ each represent hydrogen, R⁹ represents trifluoromethyl, and R¹⁰
represents chlorine;

R⁶, R⁷ and R⁹ each represent hydrogen and R⁸ and R¹⁰ both represent chlorine;

- 15 R⁶ and R⁷ both represent hydrogen, R⁸ and R⁹ both represent fluorine, and R¹⁰
represents chlorine;

R⁶, R⁷ and R⁸ each represent hydrogen, R⁹ represents trifluoromethyl, and R¹⁰
represents methyl;

R⁶ and R⁷ both represent hydrogen, R⁸ represents fluorine, R⁹ represents

- 20 trifluoromethyl, and R¹⁰ represents chlorine;

R⁶ is methyl, R⁷ and R⁹ both represent hydrogen, and R⁸ and R¹⁰ both represent
chlorine;

R⁶, R⁸ and R¹⁰ each represent chlorine, and R⁷ and R⁹ both represent hydrogen;

R⁶, R⁷ and R⁸ each represent hydrogen, R⁹ represents trifluoromethyl, and R¹⁰

- 25 represents fluorine;

R⁶, R⁷ and R⁹ each represent hydrogen, R⁸ represents fluorine, and R¹⁰ represents
chlorine;

R⁶, R⁷ and R⁹ each represent hydrogen, R⁸ represents chlorine, and R¹⁰ represents
methyl;

- 30 R⁶, R⁷ and R⁸ each represent hydrogen, R⁹ represents chlorine, and R¹⁰ represents
methyl;

R⁶ and R⁷ both represent hydrogen, R⁸ represents fluorine, and R⁹ and R¹⁰ both
represent chlorine;

R⁶, R⁷ and R⁸ each represent hydrogen and R⁹ and R¹⁰ both represent chlorine; or

- 35 R⁶ is fluorine, R⁷ and R⁹ both represent hydrogen, and R⁸ and R¹⁰ both represent
chlorine.

mg

21. A compound or salt as claimed in claim 20, wherein:
R⁶, R⁷ and R⁸ each represent hydrogen, R⁹ represents trifluoromethyl, and R¹⁰ represents chlorine;
R⁶, R⁷ and R⁹ each represent hydrogen and R⁸ and R¹⁰ both represent chlorine;
5 R⁶ and R⁷ both represent hydrogen, R⁸ and R⁹ both represent fluorine, and R¹⁰ represents chlorine;
R⁶, R⁷ and R⁸ each represent hydrogen, R⁹ represents trifluoromethyl, and R¹⁰ represents methyl;
R⁶ and R⁷ both represent hydrogen, R⁸ represents fluorine, R⁹ represents trifluoromethyl, and R¹⁰ represents chlorine;
10 R⁶ is methyl, R⁷ and R⁹ both represent hydrogen, and R⁸ and R¹⁰ both represent chlorine; or
R⁶, R⁸ and R¹⁰ each represent chlorine, and R⁷ and R⁹ both represent hydrogen.
22. A compound or salt as claimed in claim 21, wherein:
R⁶, R⁷ and R⁸ each represent hydrogen, R⁹ represents trifluoromethyl, and R¹⁰ represents chlorine;
R⁶, R⁷ and R⁹ each represent hydrogen and R⁸ and R¹⁰ both represent chlorine; or
R⁶ and R⁷ both represent hydrogen, R⁸ and R⁹ both represent fluorine, and R¹⁰ represents chlorine.
23. A compound or salt as claimed in claim 1, which is a compound selected from examples E1 to E50 or a pharmaceutically acceptable salt thereof.
24. A compound or salt as claimed in claim 1, which is a compound selected from examples E51 to E123 or a pharmaceutically acceptable salt thereof.
25. A compound or a pharmaceutically acceptable salt thereof, which is
- N*-{[2-chloro-3-(trifluoromethyl)phenyl]methyl}-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-dichlorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2-chloro-3,4-difluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
N-{[2-fluoro-3-(trifluoromethyl)phenyl]methyl}-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
1,3-dimethyl-2-oxo-*N*-[(2,3,4-trifluorophenyl)methyl]-4-imidazolidinecarboxamide,

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- N*-[(2-chloro-4-fluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide,
5 *N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-(4-piperidinyl)-4-imidazolidinecarboxamide,
N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-(3-pyridinyl)-4-imidazolidinecarboxamide,
10 *N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(2-methyl-4-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
15 *N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(2-methyl-4-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(2-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
20 *N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-(2-pyridinyl)-4-imidazolidinecarboxamide,
N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
N-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
25 *N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(3-methyl-2-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
30 *N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide,
N-[(2-Chloro-4-fluorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide,
N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide,
35 *N*-[(3-Chloro-2-methylphenyl)methyl]-3-methyl-2-oxo-1-(2-pyrimidinyl)-4-imidazolidinecarboxamide,

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- N*-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxamide,
N-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(1-methyl-1H-pyrazol-5-yl)-2-oxo-4-imidazolidinecarboxamide,
5 *N*-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-[2-(4-morpholinyl)ethyl]-2-oxo-4-imidazolidinecarboxamide, or
N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-2-oxo-1-(5-pyrimidinyl)-4-imidazolidinecarboxamide;
10 or a pharmaceutically acceptable salt thereof.

26. A compound or a pharmaceutically acceptable salt thereof, which is

- N*-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxamide,
15 *N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-imidazolidinecarboxamide,
N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
20 *N*-[(2,4-Dichlorophenyl)methyl]-1-(2,6-dimethyl-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-4-yl)-2-oxo-4-imidazolidinecarboxamide,
25 *N*-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-2-yl)-2-oxo-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxamide,
30 *N*-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-1-(1-methyl-1H-imidazol-5-yl)-2-oxo-4-imidazolidinecarboxamide,
N-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-3-methyl-2-oxo-1-[6-(trifluoromethyl)-4-pyrimidinyl]-4-imidazolidinecarboxamide,
N-[(2,4-Dichlorophenyl)methyl]-1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
35 *N*-[(2-Chloro-3-(trifluoromethyl)phenyl)methyl]-1-(6-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,

- N*-[(2,4-Dichlorophenyl)methyl]-1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-1-(2-fluoro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- 5 *N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxamide,
- N*-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-1-[6-(methyloxy)-3-pyridinyl]-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichlorophenyl)methyl]-1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxamide,
- 10 *N*-[(2,4-Dichlorophenyl)methyl]-3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2-Chloro-4-fluorophenyl)methyl]-3-ethyl-1-methyl-2-oxo-4-imidazolidinecarboxamide,
- 15 *N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-1-(2-pyrazinyl)-4-imidazolidinecarboxamide,
- 1-(2-Chloro-3-pyridinyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- 20 *N*-[(2-Chloro-3,4-difluorophenyl)methyl]-1-(2-chloro-3-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- 1-(2-Chloro-3-pyridinyl)-*N*-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- 3-Methyl-*N*-[[2-methyl-3-(trifluoromethyl)phenyl]methyl]-2-oxo-4-imidazolidinecarboxamide,
- 25 *N*-[(2,3-Dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(3-Chloro-2-methylphenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichloro-6-methylphenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichlorophenyl)methyl]-1-(5-fluoro-2-pyrimidinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- 30 *N*-[(2,4-Dichlorophenyl)methyl]-3-ethyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[[2-Chloro-3-(trifluoromethyl)phenyl]methyl]-3-ethyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-[4-(methyloxy)-2-pyrimidinyl]-2-oxo-4-imidazolidinecarboxamide,
- 35 1-(5-Chloro-2-pyrimidinyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,

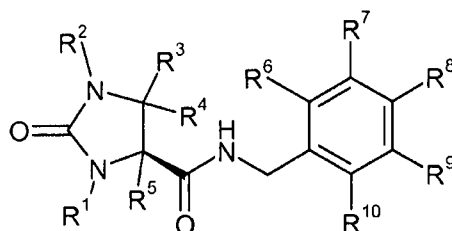
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- N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2-Chloro-3,4-difluorophenyl)methyl]-3-methyl-1-(6-methyl-3-pyridinyl)-2-oxo-4-imidazolidinecarboxamide,
- 5 *N*-[(2,4-Dichlorophenyl)methyl]-1-(2-fluoro-4-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2-Chloro-3,4-difluorophenyl)methyl]-1-(2-fluoro-4-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(3-Chloro-2-methylphenyl)methyl]-1,3-dimethyl-2-oxo-4-
- 10 imidazolidinecarboxamide,
- N*-[(2,3-Dichlorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,3-Dichloro-4-fluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2-Chloro-4-fluoro-3-(trifluoromethyl)phenyl)methyl]-1,3-dimethyl-2-oxo-4-
- 15 imidazolidinecarboxamide,
- N*-[(2,4-Dichloro-6-methylphenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
- 1,3-Dimethyl-*N*-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-2-oxo-4-imidazolidinecarboxamide,
- 20 *N*-[(4-Chloro-2-methylphenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2-Chloro-4-cyanophenyl)methyl]-1,3-dimethyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichlorophenyl)methyl]-3-(2,2-difluoroethyl)-1-methyl-2-oxo-4-imidazolidinecarboxamide,
- 25 *N*-[(2,4-Dichlorophenyl)methyl]-1-(3-fluoro-2-pyridinyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methyl-1*H*-pyrazol-5-yl)-2-oxo-4-imidazolidinecarboxamide,
- 1-(2-Cyano-3-pyridinyl)-*N*-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-
- 30 imidazolidinecarboxamide,
- N*-[(2,4-Dichlorophenyl)methyl]-1-(2,2-difluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichlorophenyl)methyl]-3-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-4-imidazolidinecarboxamide,
- 35 *N*-[(2,4-Dichlorophenyl)methyl]-1-(2-fluoroethyl)-3-methyl-2-oxo-4-imidazolidinecarboxamide,
- N*-[(2,4-Dichlorophenyl)methyl]-1-ethyl-3-methyl-2-oxo-4-imidazolidinecarboxamide,

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- N-[(2,4-Dichloro-6-fluorophenyl)methyl]-1,3-dimethyl-2-oxo-4-
 imidazolidinecarboxamide,
 1,3-Dimethyl-2-oxo-N-[(2,4,6-trichlorophenyl)methyl]-4-imidazolidinecarboxamide,
 N-[(2,4-Dichloro-6-fluorophenyl)methyl]-3-methyl-2-oxo-4-imidazolidinecarboxamide,
 5 3-Methyl-2-oxo-N-[(2,4,6-trichlorophenyl)methyl]-4-imidazolidinecarboxamide,
 N-[(2,4-Dichlorophenyl)methyl]-3-methyl-1-(1-methylethyl)-2-oxo-4-
 imidazolidinecarboxamide,
 1-(Cyclopropylmethyl)-N-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-
 imidazolidinecarboxamide,
 10 1-(Cyclobutylmethyl)-N-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-
 imidazolidinecarboxamide, or
 1-Cyclopentyl-N-[(2,4-dichlorophenyl)methyl]-3-methyl-2-oxo-4-
 imidazolidinecarboxamide;
 15 or a pharmaceutically acceptable salt thereof.

27. A compound or salt as claimed in any one of the preceding claims, which is a compound of formula (IA) or a pharmaceutically acceptable salt thereof:



(IA)

wherein:

- R¹ represents C₁₋₄ alkyl or C₃₋₄ cycloalkyl, any of which is optionally substituted with 1,
 2 or 3 fluorine atoms,
 25 and R², R^x, R^y, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and n are as defined in any
 one of the preceding claims,

- and wherein more than 50% by molarity of the compound of formula (IA) or the
 pharmaceutically acceptable salt thereof has the indicated stereochemistry at the
 30 ring-carbon atom bonded to R⁵.

28. A compound or salt as claimed in claim 27, wherein R¹ represents methyl or ethyl.

29. A pharmaceutical composition which comprises a compound or a
5 pharmaceutically acceptable salt thereof as defined in any one of the preceding claims, and a pharmaceutically acceptable carrier or excipient.

30. A compound or pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 28 for use in therapy.

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31. A method of treating a human or animal subject suffering from pain, inflammation or a neurodegenerative disease, which method comprises administering to said subject an effective amount of a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 28.

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32. Use of a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 28 for the manufacture of a medicament for the treatment or prevention of pain, inflammation or a neurodegenerative disease.

20 33. Use of a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 28 for the manufacture of a medicament for the treatment or prevention of inflammatory pain, neuropathic pain or visceral pain.

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DERIVADOS DE CARBOXAMIDA IMIDAZOLIDINA COMO

MODULADORES DE P2X7

MEMORIA DESCRIPTIVA

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La presente invención se refiere a derivados de amida heterocíclica que modulan la función del receptor P2X7 y son capaces de antagonizar los efectos de ATP en el receptor P2X7 ("antagonistas del receptor P2X7"); a procedimientos para su preparación; a composiciones farmacéuticas que las contienen; y al uso de dichos compuestos en la terapia.

El receptor P2X7 es un canal iónico activado con ligando que se expresa en células del linaje hematopoyético, por ejemplo, macrófagos, microglías, mastocitos, y linfocitos (T y B) (ver, por ejemplo, Collo et al., Neuropharmacology, Vol. 36, pp. 1277-1283 (1997)), y se activa por nucleótidos extracelulares, particularmente adenosina trifosfato (ATP). Activación de receptores P2X7 se ha implicado en la formación de células gigantes, desgranulación, muerte celular citolítica, difusión de CD62L, regulación de proliferación celular, y liberación de citoquinas pro-inflamatorias tales como interleucina 1 ($IL-1\beta$) y factor de necrosis tumoral ($TNF\alpha$) (por ejemplo, Hide et al., Journal of Neurochemistry, Vol. 75., pp. 965-972 (2000)). Los receptores P2X7 también se localizan en células que presentan antígeno, queratinocitos, células parótida, hepatocitos, eritrocitos, células eritroleucémicas, monocitos, fibroblastos, células de médula ósea, neuronas,

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y células mesangiales renales. Además, el receptor P2X7 se expresa por medio de terminales presinápticas en el sistema nervioso central y periférico y ha mostrado que media la liberación de glutamato en células gliales (Anderson, C. et al., Drug. Dev. Res., Vol. 50, página 92 (2000)).

5 La localización del receptor P2X7 a células clave del sistema inmune, acopladas con su capacidad de liberar importantes mediadores inflamatorios de estas células sugiere una función potencial de antagonistas del receptor P2X7 en el tratamiento de un amplio intervalo de enfermedades incluyendo dolor y trastornos neurodegenerativos. Estudios recientes pre-
10 clínicos *in vivo* han implicado directamente el receptor P2X7 en el dolor inflamatorio y dolor neuropático (Dell'Antonio et al., Neurosci. Lett., 327, pp. 87-90, 2002; Chessell, IP. et al., Pain, 114, pp.386-396, 2005) aunque no hay evidencia *in vitro* de que los receptores P2X7 median la muerte de neuronas corticales inducida por células microgliales (Skaper, S.D. et al., Program No.
15 937.7 2005 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2005. Online). Además, la sobre-regulación del receptor P2X7 se ha observado alrededor de placas β -amiloide en un modelo ratón de enfermedad de Alzheimer (Parvathenani, L. et al., J. Biol. Chem., Vol. 278(15), pp. 13309-13317, 2003).

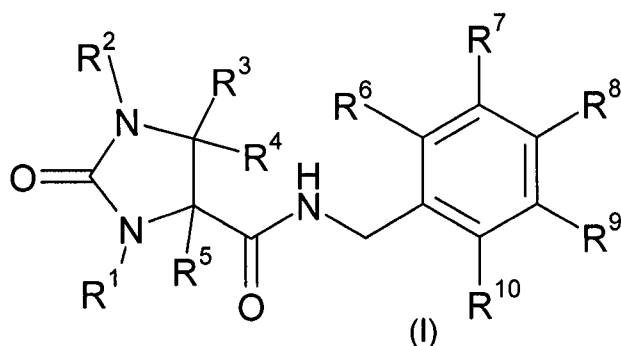
20 WO 01/10799 A1 (Aventis Pharmaceutical Products Inc.) describe métodos para la preparación de N-[(alifático o aromático)carbonil]-2-aminoacetamida y para ciclización de dichos compuestos. JP 50-24287 (Sumitomo Chemical Co., Ltd) describe ciertos compuestos 2-oxo-4-

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imidazolidinacarboxamida 5-sustituida.

La presente invención provee compuestos que modulan la función del receptor P2X7 y son capaces de antagonizar los efectos de ATP en el receptor P2X7 ("antagonistas del receptor P2X7").

5 Un primer aspecto de la invención provee un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo:



en donde:

R^1 representa hidrógeno, alquilo de C_{1-6} (por ejemplo, metilo o etilo), alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} , cicloalquilmetilo-
 15 C_{3-6} , piridinilmetilo- o bencilo, y en donde cualquiera de dichos alquilo de C_{1-6} , alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} , cicloalquilmetilo- C_{3-6} , piridinilmetilo- o bencilo es opcionalmente sustituido con 1, 2 o 3 átomos de halógeno (por ejemplo, 1 o 2) (por ejemplo, flúor o cloro); o un fenilo no sustituido;

20 R^2 representa hidrógeno, alquilo de C_{1-6} (por ejemplo, metilo, etilo, n-propilo o i-propilo), alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} , cicloalquilmetilo- C_{3-6} , $-(CR^xR^y)_n-NR^{11}R^{12}$, arilmetilo- C_{6-10} , heterociclilo- $(CR^xR^y)_n$ - o heteroarilo- $(CR^xR^y)_n$; y en donde cualquiera de dichos alquilo de

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C₁₋₆, alqueno de C₂₋₆, alquino de C₂₋₆, cicloalquilo de C₃₋₆, cicloalquilmetilo-C₃₋₆, arilmetilo-C₆₋₁₀, heterociclilo-(CR^xR^y)_n- o heteroarilo-(CR^xR^y)_n- se sustituye opcionalmente con 1, 2 o 3 (por ejemplo, 1 o 2) átomos de halógeno (por ejemplo, flúor o cloro) o grupos alquilo de C₁₋₆ (por ejemplo, metilo), o el

5 heteroarilo-(CR^xR^y)_n- se sustituye opcionalmente en el anillo heteroarilo con un alcoxi de C₁₋₃ (por ejemplo, metoxi), ciano o grupo trifluorometilo;

R³, R⁴ y R⁵ independientemente representan hidrógeno, flúor o metilo;

R⁶, R⁷, R⁸, R⁹ y R¹⁰ independientemente representan hidrógeno,

10 halógeno, ciano, alquilo de C₁₋₆, alqueno de C₂₋₆, alquino de C₂₋₆, cicloalquilo de C₃₋₆ o fenilo, y en donde cualquiera de dichos alquilo de C₁₋₆, alqueno de C₂₋₆, alquino de C₂₋₆, cicloalquilo de C₃₋₆ o fenilo se sustituye opcionalmente con 1, 2 o 3 átomos de halógeno; o R⁹ y R¹⁰ junto con los átomos de carbono a los cuales se unen forman un anillo de benceno que se sustituye

15 opcionalmente con 1, 2 o 3 átomos de halógeno;

R^x y R^y representan independientemente hidrógeno o alquilo de C₁₋₆;

R¹¹ y R¹² representan independientemente hidrógeno o alquilo de C₁₋₆; y

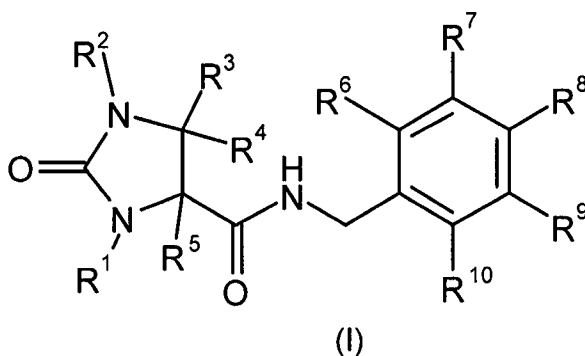
20 n representa un número entero de 0 a 4;

con la condición de que cuando R⁶ y R¹⁰ representan independientemente hidrógeno o flúor, al menos uno de R⁷, R⁸ y R⁹ sea un átomo de halógeno, o solo uno de R⁷, R⁸ y R⁹ sea un grupo CF₃.

En una modalidad particular, R^2 representa hidrógeno, alquilo de C_{1-6} (por ejemplo, metilo, etilo, n-propilo o i-propilo), alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} , cicloalquilmetilo- C_{3-6} , $-(CR^xR^y)_n-NR^{11}R^{12}$, arilmetilo- C_{6-10} , heterociclilo- $(CR^xR^y)_n$ - o heteroarilo- $(CR^xR^y)_n$; y en donde

5 cualquiera de dichos alquilo de C_{1-6} , alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} , cicloalquilmetilo- C_{3-6} , arilmetilo- C_{6-10} , heterociclilo- $(CR^xR^y)_n$ - o heteroarilo- $(CR^xR^y)_n$ - se sustituye opcionalmente con 1, 2 o 3 (por ejemplo, 1 o 2) átomos de halógeno (por ejemplo, flúor o cloro) o grupos alquilo de C_{1-6} (por ejemplo, metilo).

10 En una modalidad, se provee un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo:



en donde:

R^1 representa alquilo de C_{1-6} (por ejemplo, metilo o etilo), alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} , cicloalquilmetilo- C_{3-6} , piridinilmetilo- o bencilo, y cualquiera de los cuales se sustituye opcionalmente

20 con 1, 2 o 3 átomos de halógeno (por ejemplo, 1 o 2) (por ejemplo, flúor o cloro); o un fenilo no sustituido;

R^2 representa hidrógeno, alquilo de C_{1-6} (por ejemplo, metilo,

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etilo, n-propilo o i-propilo), alquenilo de C₂₋₆, alquinilo de C₂₋₆, cicloalquilmetilo-C₃₋₆, o arilmetilo de C₆₋₁₀; y en donde cualquiera de dichos alquilo de C₁₋₆, alquenilo de C₂₋₆, alquinilo de C₂₋₆, cicloalquilmetilo-C₃₋₆ o arilmetilo-C₆₋₁₀ se sustituye opcionalmente con 1, 2 o 3 (por ejemplo, 1 o 2) átomos de halógeno (por ejemplo, flúor o cloro);

R³, R⁴ y R⁵ independientemente representan hidrógeno, flúor o metilo; y

R⁶, R⁷, R⁸, R⁹ y R¹⁰ independientemente representan hidrógeno, halógeno, ciano, alquilo de C₁₋₆, alquenilo de C₂₋₆, alquinilo de C₂₋₆, cicloalquilo de C₃₋₆ o fenilo, y en donde cualquiera de dichos alquilo de C₁₋₆, alquenilo de C₂₋₆, alquinilo de C₂₋₆, cicloalquilo de C₃₋₆ o fenilo se sustituye opcionalmente con 1, 2 o 3 átomos de halógeno; o R⁹ y R¹⁰ junto con los átomos de carbono a los cuales se unen forman un anillo de benceno que se sustituye opcionalmente con 1, 2 o 3 átomos de halógeno;

con la condición de que cuando R⁶ y R¹⁰ representan independientemente hidrógeno o flúor, al menos uno de R⁷, R⁸ y R⁹ sea un átomo de halógeno, o solo uno de R⁷, R⁸ y R⁹ sea un grupo CF₃.

Como se usa en la presente, el término "alquilo" (cuando se usa como un grupo o como parte de un grupo) se refiere a una cadena de hidrocarburo recta o ramificada que contiene el número especificado de átomos de carbono. Por ejemplo, alquilo de C₁₋₆ significa una cadena de hidrocarburo recta o ramificada que contiene al menos 1 y a lo más 6 átomos de carbono. Ejemplos de alquilo incluyen, pero no se limitan a, metilo (Me),

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etilo (Et), n-propilo, i-propilo, t-butilo, n-hexilo e i-hexilo.

Como se usa en la presente, el término "alquenilo" se refiere a una cadena de hidrocarburo recta o ramificada que contiene el número especificado de átomos de carbono en donde al menos un enlace carbono-carbono es un enlace doble. Ejemplos de alquenilo incluyen, pero no se limitan a etenilo, propenilo, n-butenilo, i-butenilo, n-pentenilo e i-pentenilo.

Como se usa en la presente, el término "alquinilo" se refiere a una cadena de hidrocarburo recta o ramificada que contiene el número especificado de átomos de carbono en donde al menos un enlace carbono-carbono es un enlace triple. Ejemplos de alquinilo incluyen, pero no se limitan a etinilo, propinilo, butinilo, i-pentinilo, n-pentinilo, i-hexinilo y n-hexinilo.

El término "cicloalquilo" a menos que se especifique lo contrario significa un anillo no aromático de 3 a 6 miembros cerrado, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo.

El término "arilo" como se usa aquí se refiere a un anillo hidrocarburo monocíclico o bicíclico de C₆₋₁₀ en donde al menos un anillo es aromático. Ejemplos de dichos grupos incluyen fenilo y naftilo.

El término "halógeno" se usa aquí para describir, a menos que se indique otra cosa, un grupo seleccionado de flúor, cloro, bromo o yodo.

El término "heteroarilo" como se usa en este documento significa un sistema de anillo aromático monocíclico de 5 a 6 miembros o aromático bicíclico de 8 a 10 miembros fusionado que contiene 1 a 3 heteroátomos seleccionados de oxígeno, nitrógeno y azufre. Ejemplos adecuados de dichos

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anillos aromáticos monocíclicos incluyen tienilo, furanilo, pirrolilo, triazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, isotiazolilo, isoxazolilo, tiadiazolilo, pirazolilo, pirimidilo, piridazinilo, pirazinilo y piridilo. Ejemplos adecuados de dichos sistemas de anillo aromático bicíclico fusionado incluyen quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, cinnolinilo, naftiridinilo, indolilo, indazolilo, pirrolopiridinilo, benzofuranilo, benzodioxinilo, benzotienilo, bencimidazolilo, benzoxazolilo, bencisoxazolilo, benzotiazolilo, benzisotiazolilo, benzoxadiazolilo, benzotiadiazolilo y lo similar. Grupos heteroarilo, como se describió anteriormente, se pueden enlazar al resto de la molécula vía un átomo de carbono o, cuando está presente, vía un átomo de nitrógeno adecuado excepto cuando se indique otra cosa.

El término "heterociclilo" significa un anillo monocíclico de 4 a 7 miembros o un anillo bicíclico de 8 a 12 miembros fusionado que puede ser saturado o parcialmente insaturado que contiene 1 a 4 heteroátomos seleccionados de oxígeno, nitrógeno y azufre. Ejemplos de dichos anillos monocíclicos incluyen pirrolidinilo, azetidino, pirazolidinilo, oxazolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, hidantoinilo, valerolactamilo, oxiranilo, oxetanilo, dioxolanilo, dioxanilo, oxatolanilo, oxatianilo, ditianilo, dihidrofuranilo, tetrahidrofuranilo, dihidropiranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidropirimidinilo, tetrahidrothiofenilo, tetrahidrotiopiranilo, diazepanilo, azepanilo y lo similar. Ejemplos de dichos anillos bicíclicos incluyen indolinilo, isoindolinilo, benzopiranilo, quinuclidinilo, 2,3,4,5-tetrahidro-1*H*-3-benzazepina, tetrahidroisoquinolinilo y lo similar.

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Se debe entender que la presente invención cubre y describe todas las combinaciones posibles de modalidades particulares, adecuadas, u otras modalidades de grupos o aspectos (por ejemplo, de R^1 , R^2 , R^x , R^y , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} y/o n), por ejemplo todas las
5 combinaciones posibles de modalidades de diferentes grupos de aspectos, modalidades las cuales se describen en la presente.

En ciertas modalidades particulares de la invención, R^1 representa alquilo de C_{1-6} (por ejemplo, metilo o etilo), alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} , cicloalquilmetilo- C_{3-6} , piridinilmetilo- o
10 bencilo, cualquiera de los cuales se sustituye opcionalmente con 1, 2 o 3 átomos de halógeno (por ejemplo, 1 o 2) (por ejemplo, flúor o cloro); o un fenilo no sustituido;

En una modalidad de la invención, R^1 representa alquilo de C_{1-6} no sustituido (por ejemplo, metilo o etilo) o cicloalquilo de C_{3-6} ; o un bencilo
15 opcionalmente sustituido con 1, 2 o 3 átomos de halógeno (por ejemplo, flúor o cloro). En una modalidad particular R^1 representa alquilo de C_{1-4} (por ejemplo, metilo o etilo). En una modalidad adicional, R^1 representa hidrógeno o metilo.

En una modalidad particular de la invención, R^1 representa
20 metilo, etilo o etilo sustituido con 1, 2 o 3 átomos de flúor (por ejemplo, metilo, etilo, $-\text{CH}_2\text{-CF}_3$, $-\text{CH}_2\text{-CHF}_2$ o $-\text{CH}_2\text{-CH}_2\text{F}$).

En una modalidad preferida, R^1 representa metilo o etilo, en particular metilo.

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En ciertas modalidades particulares de la invención, R^2 representa hidrógeno, alquilo de C_{1-6} (por ejemplo, metilo, etilo, n-propilo o i-propilo), alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} (por ejemplo, ciclopentilo), cicloalquilmetilo- C_{3-6} (por ejemplo, ciclopropilmetilo- o 5 ciclobutilmetilo-), $-(CR^xR^y)_n-NR^{11}R^{12}$, arilmetilo- C_{6-10} , heterociclilo- $(CR^xR^y)_n-$ o heteroarilo- $(CR^xR^y)_n-$; y en donde dicho alquilo de C_{1-6} se sustituye opcionalmente con 1, 2 o 3 (por ejemplo, 1 o 2) átomos de halógeno (por ejemplo, flúor),

y en donde el heteroarilo- $(CR^xR^y)_n-$ se sustituye opcionalmente 10 (por ejemplo en el anillo heteroarilo) con 1, 2 o 3 (por ejemplo, 1 o 2, por ejemplo 1) átomos de halógeno (por ejemplo, flúor o cloro) o grupos alquilo de C_{1-6} (por ejemplo, metilo, etilo, n-propilo o i-propilo, por ejemplo metilo), o el heteroarilo- $(CR^xR^y)_n-$ se sustituye opcionalmente en el anillo heteroarilo con un alcoxi de C_{1-3} (por ejemplo, metoxi), ciano o grupo trifluorometilo.

15 En ciertas modalidades particulares de la invención, R^2 representa hidrógeno, alquilo de C_{1-6} (por ejemplo, metilo, etilo, n-propilo o i-propilo), alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} (por ejemplo, ciclopentilo), cicloalquilmetilo- C_{3-6} (por ejemplo, ciclopropilmetilo- o 20 ciclobutilmetilo-), $-(CR^xR^y)_n-NR^{11}R^{12}$, arilmetilo- C_{6-10} , heterociclilo- $(CR^xR^y)_n-$ o heteroarilo- $(CR^xR^y)_n-$; y en donde cualquiera de dichos alquilo de C_{1-6} , alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} , cicloalquilmetilo- C_{3-6} , arilmetilo- C_{6-10} , heterociclilo- $(CR^xR^y)_n-$ o heteroarilo- $(CR^xR^y)_n-$ se sustituye opcionalmente con 1, 2 o 3 (por ejemplo, 1 o 2) átomos de halógeno (por

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ejemplo, flúor o cloro) o grupos metilo, o el heteroarilo-(CR^xR^y)_n- se sustituye opcionalmente en el anillo heteroarilo con un alcoxi de C₁₋₃ (por ejemplo, metoxi), ciano o grupo trifluorometilo.

En ciertas modalidades particulares de la invención, R² representa hidrógeno o alquilo de C₁₋₆ no sustituido (por ejemplo, metilo, etilo, n-propilo o i-propilo), bencilo o cicloalquilmetilo-C₃₋₆ (por ejemplo, ciclopropilmetilo- o ciclobutilmetilo-). En otra modalidad R² representa hidrógeno o alquilo de C₁₋₄ (por ejemplo, metilo, etilo, n-propilo o i-propilo).

En una modalidad más particular, R² representa hidrógeno o metilo. En una modalidad preferida, R² representa metilo.

En una modalidad particular, R² representa hidrógeno, alquilo de C₁₋₆ (por ejemplo, metilo o etilo), heterociclilo-(CR^xR^y)_n- o heteroarilo-(CR^xR^y)_n-; y cualquiera de dichos alquilo de C₁₋₆, heterociclilo-(CR^xR^y)_n- o heteroarilo-(CR^xR^y)_n- se sustituye opcionalmente con 1, 2 o 3 átomos de halógeno (por ejemplo, flúor o cloro, en particular flúor) o grupos alquilo de C₁₋₆ (por ejemplo, metilo, etilo, n-propilo o i-propilo, en particular metilo).

En una modalidad particular de la invención, R² representa hidrógeno, metilo, etilo o etilo sustituido con 1, 2 o 3 átomos de flúor (por ejemplo, hidrógeno, metilo, etilo, -CH₂-CF₃, -CH₂-CHF₂ o -CH₂-CH₂F).

En una modalidad particular de la invención, R² representa heteroarilo (por ejemplo, piridinilo, pirimidinilo, imidazolilo o pirazolilo) opcionalmente sustituido con 1, 2 o 3 grupos alquilo de C₁₋₆ (por ejemplo, metilo, etilo, n-propilo o i-propilo, en particular metilo).

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En una modalidad particular de la invención, R^2 representa piridinilo, pirimidinilo, imidazolilo o pirazolilo, en donde cualquiera de dichos grupos se sustituye opcionalmente con 1 o 2 (por ejemplo, uno) átomos de flúor o cloro (por ejemplo, flúor), con 1 o 2 grupos (por ejemplo, uno) metilo, etilo, n-propilo o i-propilo (en particular metilo), o con un grupo alcoxi de C_{1-3} (por ejemplo, metoxi), ciano o trifluorometilo.

En una modalidad particular, R_2 representa heteroarilmetilo- (por ejemplo, piridinilmetilo o imidazolilmetilo) opcionalmente sustituido con 1, 2 o 3 grupos alquilo de C_{1-6} (por ejemplo, metilo).

En una modalidad particular, R_2 representa heterociclilo-
(CR^xR^y)_n- (por ejemplo, piperidinilo, morfolinilo-(CH₂)₂- o morfolinilo-(CH₂)₃-).
En una modalidad, n representa 2 o 3.

En una modalidad particular, R^x y R^y representan ambos hidrógeno.

En una modalidad particular, n representa 0 o 1, más particularmente 0.

En una modalidad particular, R^1 y R^2 ambos no representan hidrógeno.

En una modalidad preferida de la invención, R^1 y R^2 ambos representan metilo.

En una modalidad particular de la invención, R^1 representa metilo y R^2 representa hidrógeno.

En una modalidad particular de la invención, R^3 y R^4 representan

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ambos hidrógeno. En una modalidad particular, R^5 representa hidrógeno. En una modalidad particular, R^3 , R^4 y R^5 todos representan hidrógeno.

En una modalidad particular de la invención, R^6 , R^7 , R^8 , R^9 y R^{10} representan independientemente hidrógeno, halógeno (por ejemplo, cloro o flúor), ciano, trifluorometilo o alquilo de C_{1-6} no sustituido. En una modalidad más particular, R^6 , R^7 , R^8 , R^9 y R^{10} representan independientemente hidrógeno, halógeno (por ejemplo, cloro o flúor), ciano, metilo o trifluorometilo. En una modalidad más particular, R^6 , R^7 , R^8 , R^9 y R^{10} representan independientemente, hidrógeno, halógeno (por ejemplo, cloro o flúor), metilo o trifluorometilo. En una modalidad todavía más particular, R^6 , R^7 , R^8 , R^9 y R^{10} representan independientemente, hidrógeno, cloro, flúor, bromo, metilo o trifluorometilo. En una modalidad aún más particular, R^6 , R^7 , R^8 , R^9 y R^{10} representan independientemente, hidrógeno, cloro, flúor, metilo o trifluorometilo.

En una modalidad particular, R^6 representa hidrógeno. En una modalidad alternativa particular, R^6 representa cloro, flúor o metilo; más particularmente metilo.

Preferiblemente, R^7 representa hidrógeno.

En una modalidad particular, R^6 y R^7 ambos representan hidrógeno. En una modalidad particular alternativa, R^6 representa cloro, flúor o metilo (más particularmente metilo), y R^7 representa hidrógeno.

En una modalidad particular, R^8 representa hidrógeno o halógeno (por ejemplo, cloro o flúor). En una modalidad más particular, R^8

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representa hidrógeno, cloro o flúor.

En una modalidad particular, R^9 representa hidrógeno, halógeno (por ejemplo, cloro o flúor) o trifluorometilo. En una modalidad más particular, R^9 representa hidrógeno, cloro, flúor o trifluorometilo.

5 En una modalidad particular, R^{10} representa halógeno (por ejemplo, cloro o flúor), alquilo de C_{1-6} (por ejemplo, metilo) o trifluorometilo. En una modalidad más particular, R^{10} representa cloro, flúor, metilo o trifluorometilo. En una modalidad más particular todavía, R^{10} representa cloro, flúor o metilo. Preferiblemente, R^{10} representa cloro o metilo.

10 En una modalidad más particular,
 R^6 y R^7 ambos representan hidrógeno,
 R^8 representa hidrógeno, cloro o flúor,
 R^9 representa hidrógeno, cloro, flúor o trifluorometilo, y
 R^{10} representa cloro, flúor, metilo o trifluorometilo.

15 En una modalidad todavía más particular,
 R^6 y R^7 ambos representan hidrógeno,
 R^8 representa hidrógeno, cloro o flúor,
 R^9 representa hidrógeno, cloro, flúor o trifluorometilo, y
 R^{10} representa cloro, flúor o metilo.

20 Preferiblemente,
 R^6 y R^7 ambos representan hidrógeno,
 R^8 representa hidrógeno, cloro o flúor,
 R^9 representa hidrógeno, cloro, flúor o trifluorometilo, y

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R^{10} representa cloro, flúor o metilo (en particular, cloro o metilo), en donde uno o ambos (por ejemplo, uno) de R^8 y R^9 es/son diferente(s) de hidrógeno.

Más preferiblemente,

5 R^6 y R^7 ambos representan hidrógeno,

R^8 representa hidrógeno o flúor,

R^9 representa trifluorometilo, y

R^{10} representa cloro o metilo.

Preferiblemente,

10 R^6 representa hidrógeno, cloro, flúor o metilo,

R^7 representa hidrógeno,

R^8 representa cloro o flúor,

R^9 representa hidrógeno, y

R^{10} representa cloro o metilo.

15 Más preferiblemente,

R^6 representa hidrógeno, cloro, flúor o metilo,

R^7 representa hidrógeno,

R^8 representa cloro,

R^9 representa hidrógeno, y

20 R^{10} representa cloro o metilo.

En una modalidad particularmente preferida, cada uno de R^6 , R^7 y R^8 representa hidrógeno y R^9 representa trifluorometilo, y R^{10} representa cloro.

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En una modalidad particularmente preferida, cada uno de R^6 , R^7 y R^9 representa hidrógeno y R^8 y R^{10} ambos representan cloro.

En una modalidad particularmente preferida, R^6 y R^7 ambos representan hidrógeno, R^8 y R^9 ambos representan flúor, y R^{10} representa
5 cloro.

En una modalidad particularmente preferida, cada uno de R^6 , R^7 y R^8 representa hidrógeno, R^9 representa trifluorometilo, y R^{10} representa metilo.

En una modalidad particularmente preferida, R^6 y R^7 ambos representan hidrógeno, R^8 representa flúor, R^9 representa trifluorometilo, y R^{10}
10 representa cloro.

En una modalidad particularmente preferida, R^6 es metilo, R^7 y R^9 ambos representan hidrógeno, y R^8 y R^{10} ambos representan cloro.

En una modalidad particularmente preferida, cada uno de R^6 , R^8 y R^{10} representa cloro, y R^7 y R^9 ambos representan hidrógeno.
15

En una modalidad preferida, cada uno de R^6 , R^7 y R^8 representa hidrógeno, R^9 representa trifluorometilo, y R^{10} representa flúor.

En una modalidad particularmente preferida, cada uno de R^6 , R^7 y R^9 representa hidrógeno, R^8 representa flúor, y R^{10} representa cloro.

En una modalidad preferida, cada uno de R^6 , R^7 y R^9 representa hidrógeno, R^8 representa cloro, y R^{10} representa metilo.
20

En una modalidad preferida, cada uno de R^6 , R^7 y R^8 representa hidrógeno, R^9 representa cloro, y R^{10} representa metilo.

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En una modalidad preferida, R^6 y R^7 ambos representan hidrógeno, R^8 representa flúor, y R^9 y R^{10} ambos representan cloro.

En una modalidad preferida, cada uno de R^6 , R^7 y R^8 representa hidrógeno y R^9 y R^{10} ambos representan cloro.

- 5 En una modalidad preferida, R^6 es flúor, R^7 y R^9 ambos representan hidrógeno, y R^8 y R^{10} ambos representan cloro.

- En todas las modalidades de la invención descritas aquí, cuando R^6 y R^{10} representan independientemente hidrógeno o flúor, al menos uno de R^7 , R^8 y R^9 es un átomo de halógeno, o solo uno de R^7 , R^8 y R^9 es un grupo
- 10 CF_3 .

- En una modalidad particular de la invención descrita aquí, cuando R^6 y R^{10} representan independientemente hidrógeno o flúor, al menos uno de R^7 , R^8 y R^9 es un átomo de halógeno. En una modalidad más particular de la invención descrita aquí, cuando R^6 y R^{10} representan
- 15 independientemente hidrógeno o flúor, al menos uno de R^7 , R^8 y R^9 es un átomo de halógeno, y solo uno de R^7 , R^8 y R^9 es un grupo CF_3 .

En una modalidad particular de la invención, se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde:

- 20 R^1 representa alquilo de C_{1-6} no sustituido, cicloalquilo de C_{3-6} ; o un bencilo opcionalmente sustituido con 1, 2 o 3 átomos de halógeno;

R^2 representa hidrógeno o metilo;

R^3 , R^4 y R^5 todos representan hidrógeno; y

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R^6 , R^7 , R^8 , R^9 y R^{10} representan independientemente hidrógeno, cloro, flúor, bromo, metilo o trifluorometilo;

con la condición de que cuando R^6 y R^{10} representan independientemente hidrógeno o flúor, al menos uno de R^7 , R^8 y R^9 sea un átomo de halógeno, o solo uno de R^7 , R^8 y R^9 sea un grupo CF_3 .

Un aspecto particular de la invención provee un compuesto o sal seleccionado de un compuesto de los ejemplos E1 a E50, como se muestra y/o nombra posteriormente, o una sal farmacéuticamente aceptable del mismo.

Un aspecto particular de la invención provee un compuesto o sal seleccionado de un compuesto de los ejemplos E51 a E127, como se muestra y/o nombra posteriormente, o una sal farmacéuticamente aceptable del mismo.

Un aspecto particular de la invención provee un compuesto seleccionado de los ejemplos E1 a E5, E7, E8, E10 a E13, E15, E18, E19, E21, E23, E25 a E28, E30, E32 a E35, E39, E41, E42, E45, E51, E52, E54, E55, E57 a E61, E64 a E70, E72 a E79, E81, E82, E85, E86, E88, E89, E91 a E97, E99, E100, E102, E104 a E108, E110 a E113, E115 a E120, y E122 a E127 como un compuesto o una sal farmacéuticamente aceptable del mismo.

Un aspecto preferido de la invención provee un compuesto o una sal farmacéuticamente aceptable del mismo, que es:

N -{[2-cloro-3-(trifluorometil)fenil]metil}-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida (en particular, (4S)- N -{[2-cloro-3-(trifluorometil)fenil]metil}-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida),

N -[(2,4-diclorofenil)metil]-1,3-dimetil-2-oxo-4-

imidazolidinacarboxamida,

N-[(2-cloro-3,4-difluorofenil)metil]-1,3-dimetil-2-oxo-4-

imidazolidinacarboxamida,

N-[[2-fluoro-3-(trifluorometil)fenil]metil]-1,3-dimetil-2-oxo-4-

5 imidazolidinacarboxamida,

1,3-dimetil-2-oxo-*N*-[(2,3,4-trifluorofenil)metil]-4-

imidazolidinacarboxamida,

N-[(2-cloro-4-fluorofenil)metil]-1,3-dimetil-2-oxo-4-

imidazolidinacarboxamida,

10 *N*-[[2-cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-4-

imidazolidinacarboxamida,

N-[[2-Cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-1-(2-

pirimidinil)-4-imidazolidinacarboxamida,

N-[[2-Cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-1-(4-

15 piperidinil)-4-imidazolidinacarboxamida,

N-[[2-Cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-1-(3-

piridinil)-4-imidazolidinacarboxamida,

N-[[2-Cloro-3-(trifluorometil)fenil]metil]-3-metil-1-(6-metil-3-

piridinil)-2-oxo-4-imidazolidinacarboxamida,

20 *N*-[[2-Cloro-3-(trifluorometil)fenil]metil]-3-metil-1-(2-metil-4-

piridinil)-2-oxo-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-metil-1-(2-metil-3-piridinil)-2-oxo-4-

imidazolidinacarboxamida (en particular, (4*S*)-*N*-[(2,4-diclorofenil)metil]-3-

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metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida),

N-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-1-(2-metil-4-piridinil)-2-oxo-4-imidazolidinacarboxamida,

5 *N*-[(2-Cloro-3,4-difluorofenil)metil]-3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida,

N-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-(2-piridinil)-4-imidazolidinacarboxamida,

N-[(2-Cloro-3,4-difluorofenil)metil]-3-metil-1-(3-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxamida,

10 *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-1-(3-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-metil-1-(3-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxamida,

15 *N*-[(2-Cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida,

20 *N*-[(2-Cloro-4-fluorofenil)metil]-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida,

N-[(2-Cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida,

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N-[(3-Cloro-2-metilfenil)metil]-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida,

N-[(2-Cloro-3,4-difluorofenil)metil]-3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida,

5 *N*-[(2-Cloro-3,4-difluorofenil)metil]-3-metil-1-(1-metil-1H-pirazol-5-il)-2-oxo-4-imidazolidinacarboxamida,

N-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-1-[2-(4-morfolinil)etil]-2-oxo-4-imidazolidinacarboxamida, o

10 *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-(5-pirimidinil)-4-imidazolidinacarboxamida;

o una sal farmacéuticamente aceptable del mismo.

Un aspecto preferido de la invención provee un compuesto o una sal farmacéuticamente aceptable del mismo, que es:

15 *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxamida,

N-{[2-Cloro-3-(trifluorometil)fenil]metil}-1-(2,6-dimetil-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida,

20 *N*-[(2,4-Diclorofenil)metil]-1-(2,6-dimetil-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida,

N-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida,

N-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-imidazolidinacarboxamida,

5 *N*-[(2,4-Diclorofenil)metil]-3-metil-1-(1-metil-1H-imidazol-5-il)-2-oxo-4-imidazolidinacarboxamida,

N-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-1-(1-metil-1H-imidazol-5-il)-2-oxo-4-imidazolidinacarboxamida,

10 *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-[6-(trifluorometil)-4-pirimidinil]-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida,

N-{[2-Cloro-3-(trifluorometil)fenil]metil}-1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida,

15 *N*-[(2,4-Diclorofenil)metil]-1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida,

N-{[2-Cloro-3-(trifluorometil)fenil]metil}-1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida,

20 *N*-[(2,4-Diclorofenil)metil]-3-metil-1-[6-(metiloxi)-3-piridinil]-2-oxo-4-imidazolidinacarboxamida,

N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-1-[6-(metiloxi)-3-piridinil]-2-oxo-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-1-metil-2-oxo-3-(2,2,2-trifluoroetil)-4-

imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-etil-1-metil-2-oxo-4-

imidazolidinacarboxamida,

N-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-etil-1-metil-2-oxo-4-

5 imidazolidinacarboxamida,

N-[(2-Cloro-4-fluorofenil)metil]-3-etil-1-metil-2-oxo-4-

imidazolidinacarboxamida,

N-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-(2-

pirazinil)-4-imidazolidinacarboxamida,

10 1-(2-Cloro-3-piridinil)-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-

imidazolidinacarboxamida,

N-[(2-Cloro-3,4-difluorofenil)metil]-1-(2-cloro-3-piridinil)-3-metil-2-

oxo-4-imidazolidinacarboxamida,

1-(2-Cloro-3-piridinil)-*N*-{[2-cloro-3-(trifluorometil)fenil]metil}-3-

15 metil-2-oxo-4-imidazolidinacarboxamida,

3-Metil-*N*-{[2-metil-3-(trifluorometil)fenil]metil}-2-oxo-4-

imidazolidinacarboxamida,

N-[(2,3-Diclorofenil)metil]-3-metil-2-oxo-4-

imidazolidinacarboxamida,

20 *N*-[(3-Cloro-2-metilfenil)metil]-3-metil-2-oxo-4-

imidazolidinacarboxamida,

N-[(2,4-Dicloro-6-metilfenil)metil]-3-metil-2-oxo-4-

imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-1-(5-fluoro-2-pirimidinil)-3-metil-2-oxo-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-etil-2-oxo-4-imidazolidinacarboxamida,

5 *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-etil-2-oxo-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-metil-1-[4-(metiloxi)-2-pirimidinil]-2-oxo-4-imidazolidinacarboxamida,

10 1-(5-Cloro-2-pirimidinil)-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida,

N-[(2-Cloro-3,4-difluorofenil)metil]-3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida,

15 *N*-[(2,4-Diclorofenil)metil]-1-(2-fluoro-4-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida,

N-[(2-Cloro-3,4-difluorofenil)metil]-1-(2-fluoro-4-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida,

20 *N*-[(3-Cloro-2-metilfenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida,

N-[(2,3-Diclorofenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida,

N-[(2,3-Dicloro-4-fluorofenil)metil]-1,3-dimetil-2-oxo-4-

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imidazolidinacarboxamida,

N-{[2-Cloro-4-fluoro-3-(trifluorometil)fenil]metil}-1,3-dimetil-2-oxo-

4-imidazolidinacarboxamida,

N-[(2,4-Dicloro-6-metilfenil)metil]-1,3-dimetil-2-oxo-4-

5 imidazolidinacarboxamida,

1,3-Dimetil-*N*-{[2-metil-3-(trifluorometil)fenil]metil}-2-oxo-4-

imidazolidinacarboxamida,

N-[(4-Cloro-2-metilfenil)metil]-1,3-dimetil-2-oxo-4-

imidazolidinacarboxamida,

10 *N*-[(2-Cloro-4-cianofenil)metil]-1,3-dimetil-2-oxo-4-

imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-(2,2-difluoroetil)-1-metil-2-oxo-4-

imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-1-(3-fluoro-2-piridinil)-3-metil-2-oxo-4-

15 imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-metil-1-(1-metil-1*H*-pirazol-5-il)-2-oxo-

4-imidazolidinacarboxamida,

1-(2-Ciano-3-piridinil)-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-

imidazolidinacarboxamida,

20 *N*-[(2,4-Diclorofenil)metil]-1-(2,2-difluoroetil)-3-metil-2-oxo-4-

imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-metil-2-oxo-1-(2,2,2-trifluoroetil)-4-

imidazolidinacarboxamida,

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N-[(2,4-Diclorofenil)metil]-1-(2-fluoroetil)-3-metil-2-oxo-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-1-etil-3-metil-2-oxo-4-imidazolidinacarboxamida,

5 *N*-[(2,4-Dicloro-6-fluorofenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida,

1,3-Dimetil-2-oxo-*N*-[(2,4,6-triclorofenil)metil]-4-imidazolidinacarboxamida,

N-[(2,4-Dicloro-6-fluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida,

10 3-Metil-2-oxo-*N*-[(2,4,6-triclorofenil)metil]-4-imidazolidinacarboxamida,

N-[(2,4-Diclorofenil)metil]-3-metil-1-(1-metiletil)-2-oxo-4-imidazolidinacarboxamida,

15 1-(Ciclopropilmetil)-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida,

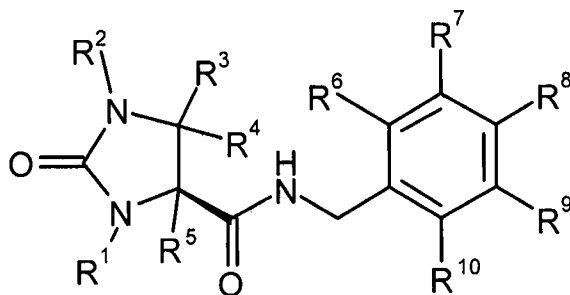
1-(Ciclobutilmetil)-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida, o

1-Ciclopentil-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida;

o una sal farmacéuticamente aceptable del mismo.

Un aspecto adicional de la presente invención provee un compuesto de fórmula (IA) o una sal farmacéuticamente aceptable del mismo:

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(IA)

en donde:

R¹ representa alquilo de C₁₋₄ o cicloalquilo de C₃₋₄, cualquiera de los cuales se sustituye opcionalmente con 1, 2 o 3 átomos de halógeno (por ejemplo, flúor),

y R², R^x, R^y, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² y n son como se definen aquí para el compuesto de fórmula (I) o su sal,

y en donde más del 50% (por ejemplo más del 70%, en particular más del 90%, tal como más del 95%) en molaridad del compuesto de fórmula (IA) o las sal farmacéuticamente aceptable del mismo tiene la estequiometría indicada en el átomo de carbono-anillo unido a R⁵.

En una modalidad particular, el compuesto de fórmula (IA) o la sal farmacéuticamente aceptable del mismo tiene un exceso enantiomérico de más de 70% (por ejemplo, más de 80%, en particular más del 90%) con respecto a la estequiometría indicada en el átomo de carbono-anillo unido a R⁵.

En una modalidad particular, en un compuesto de fórmula (IA) o una sal del mismo, R¹ representa alquilo de C₁₋₄ no sustituido o cicloalquilo de

C₃₋₄; más particularmente metilo, etilo, n-propilo, i-propilo, ciclopropilo, o ciclobutilo; más particularmente todavía metilo, etilo, n-propilo o i-propilo.

En una modalidad más particular, en un compuesto de fórmula (IA) o una sal del mismo, R¹ representa metilo o etilo.

- 5 En una modalidad particular, en un compuesto de fórmula (IA) o una sal del mismo, R³, R⁴ y R⁵ todos representan hidrógeno.

Todas las modalidades, por ejemplo, características o aspectos particulares o preferibles, de la invención (por ejemplo, modalidades del compuesto o sal de la invención y/o de composiciones farmacéuticas y/o sus
10 usos) que se describen en la presente en relación a un compuesto de fórmula (I) o una sal del mismo, también se describen por la presente y se contemplan en relación a un compuesto de fórmula (IA) o una sal del mismo, al grado apropiado o posible, con todos los cambios necesarios que se han realizado a los términos.

- 15 Un aspecto particular alternativo de la invención provee un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, como se describe aquí, en donde el compuesto o sal es sustancialmente racémico (por ejemplo, racémico) en el átomo de anillo-carbono unido a R⁵.

Antagonistas de P2X7 pueden ser útiles en prevenir, tratar o
20 mejorar una variedad de estados de dolor (por ejemplo, dolor neuropático, dolor inflamatorio crónico, y dolor visceral), inflamación y neurodegeneración, en particular enfermedad de Alzheimer. Antagonistas de P2X7 también pueden constituir agentes terapéuticos útiles en el manejo de artritis

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reumatoide y enfermedad inflamatoria del intestino.

Los compuestos de la presente invención que modulan la función del receptor P2X7 y son capaces de antagonizar los efectos de ATP en el receptor P2X7 ("antagonistas del receptor P2X7") puede ser antagonistas competitivos, agonistas inversos, o moduladores alostéricos negativos de la función del receptor P2X7.

Ciertos compuestos de fórmula (I) pueden en algunas circunstancias formar sales de adición de ácido de los mismos. Se apreciará que para el uso en compuestos medicinales de fórmula (I) se pueden usar como sales, en dicho caso las sales pueden ser farmacéuticamente aceptables. Sales farmacéuticamente aceptables incluyen aquellas descritas por Berge, Bighley y Monkhouse, J. Pharm. Sci., 1977, 66, 1-19. Cuando un compuesto de la presente invención es básico, en una modalidad una sal farmacéuticamente aceptable se prepara de un ácido farmacéuticamente aceptable, tal como un ácido inorgánico u orgánico, por ejemplo, por mezcla del compuesto y el ácido. Dichos ácidos incluyen el ácido acético, benecenosulfónico, benzoico, canforsulfónico, cítrico, etanosulfónico, fumárico, glucónico, glutámico, bromhídrico, clorhídrico, isetiónico, láctico, maleico, málico, mandélico, metanosulfónico, mucico, nítrico, pamoico, pantotenico, fosfórico, succínico, sulfúrico, tartárico, p-toluenosulfónico, y lo similar. En una modalidad particular, el ácido farmacéuticamente aceptable es el ácido bencenosulfónico, canforsulfónico, etanosulfónico, bromhídrico, clorhídrico, metanosulfónico, nítrico, fosfórico, sulfúrico, o p-toluenosulfónico.

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Ejemplos de sales farmacéuticamente aceptables incluyen sales formadas de los ácidos maleico, fumárico, benzoico, ascórbico, pamoico, succínico, clorhídrico, sulfúrico, bismetilenoisalicílico, metanosulfónico, etanodisulfónico, propiónico, tartárico, salicílico, cítrico, glucónico, aspártico, 5 esteárico, palmítico, itacónico, glicólico, p-aminobenzoico, glutámico, bencenosulfónico, ciclohexilsulfámico, fosfórico y nítrico.

Los compuestos de fórmula (I) o sales de los mismos se pueden preparar en forma cristalina o no cristalina, y si es cristalina, opcionalmente puede ser solvatada, por ejemplo como el hidrato. Esta invención incluye 10 dentro de su alcance solvatos (por ejemplo, hidratos), tales como solvatos estequiométricos (por ejemplo, hidratos), de los compuestos o sales de los mismos, así como compuestos o sales de los mismos que contienen cantidades variables de solvente (por ejemplo, agua).

Los compuestos de fórmula (I) o sales de los mismos son 15 capaces de existir en formas estereoisoméricas (por ejemplo, diastereómeros y enantiómeros) y la invención se extiende a cada una de estas formas estereoisoméricas y a mezclas de las mismas incluyendo racematos. Las formas estereoisoméricas diferentes se pueden separar una de la otra por medio de métodos usuales, o cualquier isómero dado se puede obtener por 20 síntesis estereoespecífica o asimétrica. En ejemplos donde la composición estereoquímica del producto final se ha determinado por HPLC quiral (más específicamente por métodos (A), (B), (C) o (D) como se expone en los ejemplos), el nombre y estructura estereoespecífica correspondiente

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generalmente se han asignado al producto final donde el exceso enantiomérico (e.e.) de dicho producto es mayor del 70%. La asignación de estereoquímica absoluta se basa en la quiralidad conocida del material de inicio. En ejemplos donde la composición del producto final no se ha

5 caracterizado por HPLC quiral, la estereoquímica del producto final no se ha indicado. Sin embargo, la quiralidad del componente principal de la mezcla de productos del compuesto o sal generalmente se esperará que refleje esta del material de inicio; y/o el exceso enantiomérico generalmente dependerá del método sintético usado y es probable que sea similar a aquel medido para un

10 ejemplo análogo (donde dicho ejemplo existe). De este modo compuestos o sales mostradas en una forma quiral se espera que sean capaces de prepararse en la forma quiral alternativa usando el material de inicio apropiado. Alternativamente, si los materiales de inicio racémicos se usan, se puede esperar que un producto racémico se pueda producir y los enantiómeros

15 sencillos se puedan separar mediante los métodos usuales. La invención también se extiende a cualquier forma tautomérica y sus mezclas.

La invención en cuestión también incluye compuestos isotópicamente marcados, los cuales son idénticos a aquellos recitados en la fórmula (I), o sales de los mismos, pero por el hecho de que uno o más

20 átomos son remplazados por un átomo que tiene una masa atómica o número de masa diferente de la masa atómica o número de masa más comúnmente encontrado en la naturaleza. Ejemplos de isotopos que se pueden incorporar en compuestos o sales de la invención incluyen isotopos de hidrógeno,

carbono, nitrógeno, oxígeno, fósforo, flúor, yodo, y cloro, tal como ^3H , ^{11}C , ^{14}C , ^{18}F , ^{123}I y ^{125}I .

Los compuestos de la presente invención y sales farmacéuticamente aceptables de dichos compuestos que contienen los

5 isotopos antes mencionados y/o otros isotopos de otros átomos se encuentran dentro del alcance de la presente invención. Los compuestos marcados isotópicamente o sales de la presente invención, por ejemplo aquellos en donde los isotopos radioactivos tales como ^3H , ^{14}C se incorporan, son potencialmente útiles en ensayos de distribución de tejido fármaco y/o sustrato.

10 Isotopos tritiados, es decir ^3H , y carbono 14, es decir ^{14}C son, por ejemplo, seleccionados opcionalmente por su fácil preparación y capacidad de detección. Isotopos ^{11}C y ^{18}F generalmente son útiles en PET (tomografía de emisión de positrones), e isotopos ^{125}I generalmente son útiles en SPECT (tomografía computarizada de emisión de fotones sencilla). PET o SPECT son

15 útiles en la formación de imagen del cerebro. Además, la sustitución con isotopos más pesados tales como deuterio, es decir, ^2H , puede producir a veces ciertos efectos que resultan de estabilidad metabólica mucho mayor, por ejemplo, requerimientos incrementados de vida media *in vivo* o de dosificación reducida y, por tanto, se pueden seleccionar en algunas

20 circunstancias. Los compuestos marcados isotópicamente de fórmula (I) o sales de los mismos de esta invención están en una modalidad y en algunos casos preparados al realizar los procedimientos descritos en los esquemas y/o en los ejemplos posteriores, al sustituir un reactivo marcado isotópicamente

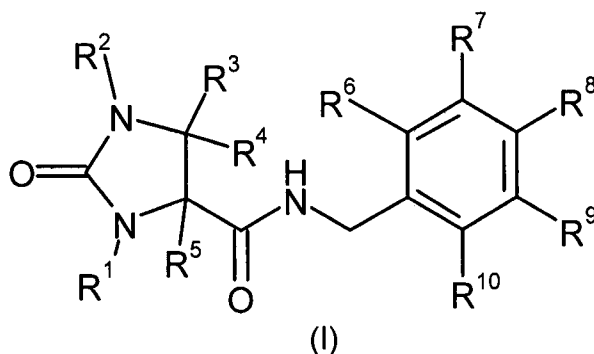
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disponible fácilmente por un reactivo marcado no isotópicamente.

Un aspecto particular adicional de la invención provee un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo que no es un compuesto marcado isotópicamente radioactivo o sal. En una
5 modalidad particular, el compuesto o sal no es un compuesto marcado isotópicamente o sal.

Preparación de compuestos

10



Los compuestos de fórmula (I), en donde las variables son como
15 se definieron anteriormente, y sales y solvatos de los mismos se pueden preparar mediante la metodología descrita en adelante, constituyendo un aspecto adicional de esta invención.

De acuerdo a un aspecto adicional de la invención, se provee un procedimiento para la preparación de un compuesto de fórmula (I) o una sal
20 farmacéuticamente aceptable del mismo que comprende:

(a) Acoplamiento de un ácido carboxílico de fórmula (2) (o un derivado activado del mismo) con una amina de fórmula (3) (ver el esquema 1), en donde R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, y R¹⁰ son como se definieron

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anteriormente. Los compuestos (2) y (3) se protegen opcionalmente.

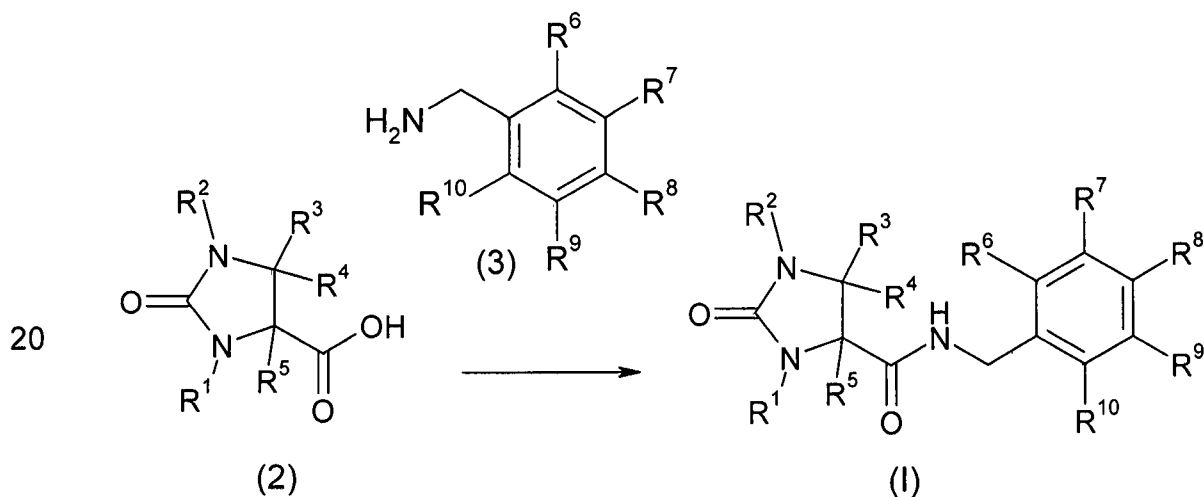
(b) Desprotección de un compuesto de fórmula (I) que se protege.

Ejemplos de grupos protectores y los medios para su remoción se pueden encontrar en T.W. Greene y P.G.M. Wuts 'Protective Groups in Organic
5 Synthesis' (J.Wiley and Sons, 3^a Ed. 1999).

(c) Interconversión de compuestos de fórmula (I) a otros compuestos de fórmula (I). Ejemplos de procedimientos de interconversión convencionales incluyen epimerización, oxidación, reducción, alquilación, sustitución aromática, sustitución nucleofílica, acoplamiento de amida e
10 hidrólisis de éster. Un ejemplo de interconversión es interconversión de un compuesto de fórmula (I) en donde R² representa hidrógeno a un compuesto de fórmula (I) en donde R² representa un grupo diferente de hidrógeno como se define en la presente.

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ESQUEMA 1



El acoplamiento de un ácido de fórmula (2) y una amina de

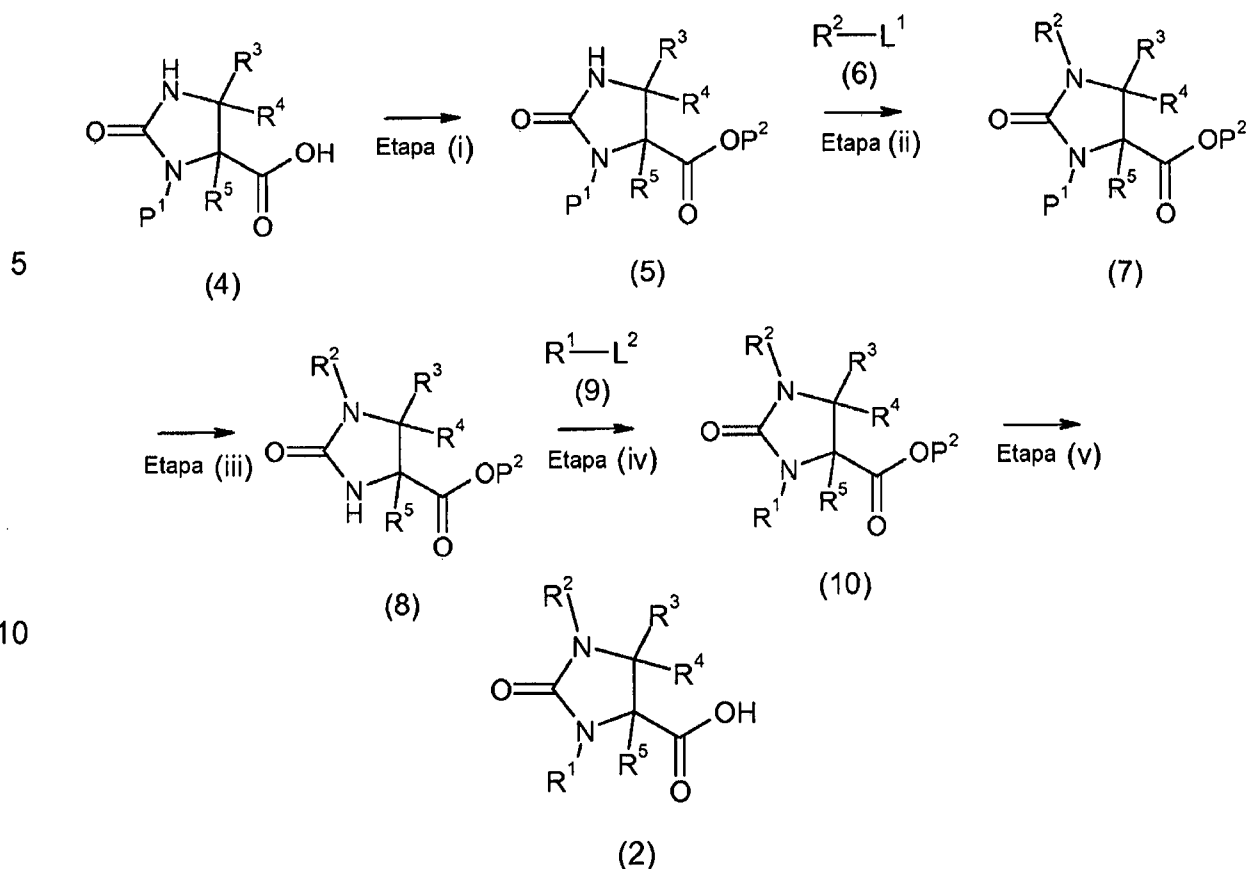
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fórmula (3) normalmente comprende el uso de agentes de activación, tales como clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida o carbodiimida soportada con polímero, 1-hidroxibenzotriazol (HOBT) o 1-hidroxi-7-azabenzotriazol (HOAt), y opcionalmente una base adecuada tal como una alquilamina terciaria (por ejemplo, diisopropiletilamina, N-etil morfolina, trietilamina) o piridina, en un solvente adecuado tal como DMF y/o diclorometano y en una temperatura adecuada, por ejemplo, entre 0°C y temperatura ambiente. Alternativamente el acoplamiento de (2) y (3) se puede llevar a cabo por tratamiento con hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio y una alquilamina terciaria adecuada tal como diisopropiletilamina en un solvente adecuada tal como dimetilformamida a una temperatura adecuada como por ejemplo la temperatura ambiente. Alternativamente, el compuesto de fórmula (2) se puede empelar como un derivado activado (por ejemplo, cloruro ácido, anhídrido mezclado, éster activo (por ejemplo, O-acil-isourea)), y bajo dichas circunstancias el procedimiento (a) típicamente comprende el tratamiento de dicho derivado activado con una amina (Ogliaruso, M.A.; Wolfe, J.F. en *The Chemistry of Functional Groups* (Ed. Patai, S.) *Suppl.B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp442-8; Beckwith, A.L.J. en *The Chemistry of Functional Groups* (Ed. Patai, S.) *Suppl.B: The Chemistry of Amides* (Ed. Zabricky, J.)(John Wiley and Sons, 1970), pp 73 ff).

Métodos representativos para la preparación de compuestos de fórmula (2) se muestran en los esquemas 2 y 3 posteriores:

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ESQUEMA 2



En donde R^1 , R^2 , R^3 , R^4 y R^5 son como se definieron
 15 anteriormente. P^1 representa un grupo protector amino adecuado como por
 ejemplo benciloxi carbonilo y P^2 representa un grupo protector carboxilato
 adecuado tal como alquilo de C_{1-6} , por ejemplo t-butilo o metilo. L^1 y L^2
 representan grupos salientes adecuados tales como halógeno (por ejemplo,
 bromo, yodo).

20 La etapa (i) normalmente comprende protección estándar del
 ácido carboxílico (4) como el éster carboxílico correspondiente por ejemplo
 mediante tratamiento con cloruro de tionilo en un solvente adecuado tal como
 metanol a una temperatura adecuada como por ejemplo entre 0°C y

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temperatura ambiente.

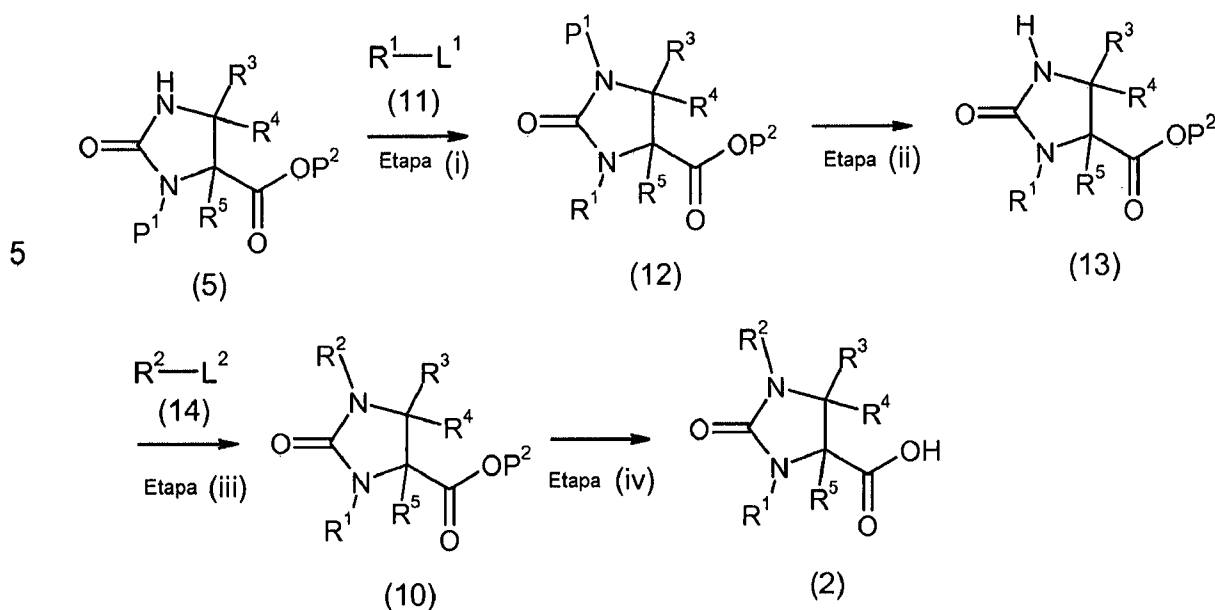
La etapa (ii) típicamente comprende el tratamiento del compuesto (5) con una base adecuada como por ejemplo carbonato de potasio y un agente de alquilación (6) tal como un haluro de alquilo (por ejemplo, yoduro de metilo) a una temperatura adecuada, como por ejemplo entre la temperatura ambiente y 80°C, en un solvente adecuado, tal como dimetoxietano, para producir el compuesto (7).

La etapa (iii) comprende la desprotección de (7) usando procedimientos estándar tales como tratamiento con hidrógeno y 5-10% paladio sobre carbón en un solvente adecuado como por ejemplo acetato de etilo y a una temperatura adecuada tal como temperatura ambiente.

La etapa (iv) típicamente comprende el tratamiento del compuesto (8) con una base adecuada como por ejemplo hidruro de sodio y un agente de alquilación (9) tal como un haluro de alquilo (por ejemplo, yoduro de metilo) a una temperatura adecuada, como por ejemplo entre -10°C y temperatura ambiente, en un solvente adecuado, tal como dimetilformamida o tetrahidrofurano.

La desprotección de la etapa (v) comprende normalmente un procedimiento estándar para la conversión de un éster carboxílico (10) a un ácido (2), tal como el uso de una sal hidróxido apropiada (por ejemplo, hidróxido de litio) en un solvente apropiado tal como una mezcla de tetrahidrofurano y agua a una temperatura adecuada tal como entre 0°C y temperatura ambiente.

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ESQUEMA 3

En donde R^1 , R^2 , R^3 , R^4 y R^5 son como se definieron anteriormente. P^1 representa un grupo protector amino adecuado como por ejemplo benciloxi carbonilo y P^2 representa un grupo protector carboxilato adecuado tal como alquilo de C_{1-6} , por ejemplo t-butilo o metilo. L^1 y L^2 representan grupos salientes adecuados tales como halógeno (por ejemplo, bromo, yodo o cloro).

Métodos análogos a aquellos descritos en el esquema 3 y posteriores se han reportado previamente en S. Saijo et al., Chem. Pharm. Bull., 1980, 28(5), 1459-1467 (por ejemplo, ver pp. 1459-60 y 1463-1464, incorporada en la presente para referencia), para la preparación de ciertos ejemplos de compuestos (12), (13) y (10) del esquema 3 aquí, en donde R^1 y R^2 representan metilo, P^1 representa benciloxicarbonilo y P^2 representa metilo.

La etapa (i) típicamente comprende el tratamiento de (5) con una

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base adecuada como por ejemplo hidruro de sodio y un agente de alquilación adecuado (11) tal como yoduro de metilo en un solvente adecuado tal como dimetilformamida y a una temperatura adecuada, como por ejemplo entre 0°C y temperatura ambiente.

5 La etapa (ii) comprende normalmente la desprotección de (12) usando procedimientos estándar tales como tratamiento con hidrógeno y 10% de paladio sobre carbón (en el caso donde P^1 = benciloxi carbonilo) en un solvente adecuado tal como metanol y a una temperatura adecuada tal como temperatura ambiente.

10 Cuando el grupo saliente L^2 se une a un carbono hibridizado sp^3 , por ejemplo, R^2-L^2 es un haluro de alquilo, la etapa (iii) típicamente comprende el tratamiento de (13) con una base adecuada tal como hidruro de sodio y un agente de alquilación adecuado (14) como por ejemplo yoduro de metilo en un solvente adecuado tal como dimetilformamida y a una temperatura adecuada como por ejemplo entre 0°C y temperatura ambiente. Alternativamente, donde 15 $R^2 = H$ la etapa (iii) se puede omitir.

 Cuando el grupo saliente L^2 se une a un carbono hibridizado sp^2 , por ejemplo, R^2-L^2 es un arilo o haluro de alquilo, la etapa (iii) típicamente comprende el uso de un complejo de paladio (0) tal como 20 tris(dibencilidenoacetona)dipaladio(0) en presencia de una base tal como carbonato de cesio, un ligando tal como XantphosTM, en un solvente apropiado como 1,4-dioxano, a una temperatura apropiada tal como reflujo. Alternativamente, la etapa (iii) típicamente comprende el uso de una sal de

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cobre (I), tal como yoduro de cobre (I), en presencia de una base tal como fosfato de potasio, un ligando tal como trans-N,N-dimetilciclohexano-1,2-diamina, en un solvente apropiado tal como 1,4-dioxano, a una temperatura apropiada tal como reflujo.

5 Cuando el grupo saliente L^2 se une a un carbono hibridizado sp^2 activado, por ejemplo, R^2-L^2 es una 2-bromopirimidina, la etapa (iii) típicamente comprende el uso de una base adecuada, tal como hexametildisilazida de litio, en un solvente apropiado tal como tetrahidrofurano, a una temperatura apropiada.

10 La etapa de desprotección (iv) normalmente comprende un procedimiento estándar para la conversión de un éster carboxílico (10) a un ácido (2), tal como el uso de una sal hidróxido apropiada (por ejemplo, hidróxido de litio) en un solvente apropiado tal como una mezcla de tetrahidrofurano y agua a una temperatura adecuada tal como entre 0°C y
15 temperatura ambiente.

 Cuando P^2 es un grupo butilo terciario, la etapa (iv) de desprotección comprende típicamente la reacción de un compuesto de fórmula (10) con un ácido, por ejemplo ácido trifluoroacético en un solvente apropiado tal como diclorometano a una temperatura apropiada tal como
20 temperatura ambiente.

 Los compuestos de las fórmulas generales (3), (4), (6), (9), (11) y (14) típicamente están disponibles de fuentes comerciales o se pueden preparar por una persona con experiencia en la técnica usando los métodos

Lab

descritos en la literatura química (o usando métodos análogos).

Cuando sea relevante, las sales farmacéuticamente aceptables se pueden preparar, por ejemplo, convencionalmente por reacción con el ácido o derivado de ácido apropiado.

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Indicaciones clínicas

Se cree que, como compuestos o sales farmacéuticamente aceptables de la presente invención modulan la función del receptor P2X7 y son capaces de antagonizar los efectos de ATP en el receptor P2X7 (antagonistas del receptor P2X7), pueden ser útiles en el tratamiento de dolor, incluyendo dolor agudo, dolor crónico, dolor articular crónico, dolor musculoesquelético, dolor neuropático, dolor inflamatorio, dolor visceral, dolor asociado con cáncer, dolor asociado con migraña, dolor de cabeza por tensión y dolores de cabeza acuminados, dolor asociado con trastornos funcionales del intestino, dolor de espalda baja y cuello, dolor asociado con dislocaciones y torceduras, dolor mantenido simpáticamente; miositis, dolor asociado con influenza u otras infecciones virales tales como el resfriado común, dolor asociado con fiebre reumática, dolor asociado con isquemia miocárdial, dolor post-operativo, quimioterapia por cáncer, dolor de cabeza, dolor dental y dismenorrea.

Condiciones de dolor articular crónico incluyen artritis reumatoide, osteoartritis, espondilitis reumatoide, artritis gotosa y artritis juvenil.

Dolor asociado con trastornos funcionales del intestino incluye

VAD

dispepsia no ulcérica, dolor de tórax no cardíaco y síndrome de intestino irritable.

Síndromes de dolor neuropático incluyen: neuropatía diabética, ciática, dolor de espalda baja no específica, neuralgia trigeminal, dolor de

5 esclerosis múltiple, fibromialgia, neuropatía relacionada con VIH, neuralgia post-herpética, neuralgia trigeminal, y dolor que resulta de trauma físico, amputación, síndrome de extremidad fantasma, cirugía espinal, cáncer, toxinas o condiciones inflamatorias crónicas. Además, condiciones de dolor neuropático incluyen dolor asociado con sensaciones no dolorosas

10 normalmente tales como "clavos y agujas" (paraestésias y disestésias), sensibilidad incrementada al tacto (hiperestesia), sensación de dolor después de estimulación inocua (alodinia dinámica, estática, térmica o por frío), sensibilidad incrementada a estímulos nocivos (hiperalgesia térmica, fría, mecánica), sensación de dolor continuo después de la remoción de la

15 estimulación (hiperpatia) o una ausencia o déficit en trayectorias sensoriales selectivas (hipoalgesia).

Otras condiciones que potencialmente se pueden tratar por compuestos o sales farmacéuticamente aceptables de la presente invención incluyen fiebre, inflamación, enfermedades inmunológicas, enfermedades de

20 función de plaqueta anormal (por ejemplo, enfermedades vasculares oclusivas), impotencia o disfunción eréctil; enfermedad ósea caracterizada por metabolismo óseo anormal o resorción; efectos secundarios hemodinámicos de fármacos anti-inflamatorios no esteroideos (NSAID) e inhibidores

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ciclooxigenasa-2 (COX-2), enfermedades cardiovasculares; enfermedades neurodegenerativas y/o neurodegeneración, neurodegeneración después de trauma, tinnitus, dependencia de un agente de inducción de dependencia tales como opioides (por ejemplo, morfina), depresivos del CNS (por ejemplo, etanol), psico-estimulantes (por ejemplo, cocaína) y nicotina; complicaciones de diabetes tipo I, disfunción de riñón, disfunción de hígado (por ejemplo, hepatitis, cirrosis), disfunción gastrointestinal (por ejemplo, diarrea), cáncer de colon, vejiga sobre-reactiva e incontinencia urgente. Depresión y alcoholismo pueden tratarse potencialmente por compuestos o sales farmacéuticamente aceptables de la presente invención.

Condiciones inflamatorias incluyen condiciones de la piel (por ejemplo, quemaduras por el sol, quemaduras, eczema, dermatitis, dermatitis alérgica, soriasis), meningitis, enfermedades oftálmicas tales como glaucoma, retinitis, retinopatías, uveítis y de lesión aguda al tejido ocular (por ejemplo, conjuntivitis), trastornos inflamatorios del pulmón (por ejemplo, asma, bronquitis, enfisema, rinitis alérgica, síndrome de insuficiencia respiratoria, enfermedad del criador de palomas, pulmón de granjero, enfermedad pulmonar obstructiva crónica (COPD), hipersensibilidad de las vías respiratorias); trastornos del tracto gastrointestinal (por ejemplo, úlcera aftosa, enfermedad de Crohn, gastritis atópica, gastritis varialoforme, colitis ulcerativa, enfermedad celíaca, ileitis regional, síndrome del intestino irritable, enfermedad inflamatoria del intestino, enfermedad de reflujo gastrointestinal); trasplante de órganos y otras condiciones con un componente inflamatorio tal

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como enfermedad vascular, migraña, periarteritis nodosa, tiroiditis, anemia aplásica, enfermedad de Hodgkin, esclerodoma, miastenia gravis, esclerosis múltiple, sorcoidosis, síndrome nefrótico, síndrome de Bechet, gingivitis, isquemia al miocardio, pirexia, lupus eritematoso sistémico, polimiositis, 5 tendinitis, bursitis, y síndrome de Sjogren.

Enfermedades inmunológicas incluyen enfermedades autoinmunes, enfermedades de deficiencia inmunológica o trasplante de órgano.

Enfermedades óseas caracterizadas por metabolismo óseo 10 anormal o resorción incluyen osteoporosis (especialmente osteoporosis post-menopáusica), hiper-calcemia, hiperparatiroidismo, enfermedades óseas de Paget, osteolisis, hipercalcemia de malignidad con o sin metástasis ósea, artritis reumatoide, periodontitis, osteoartritis, ostealgia, osteopenia, cáncer, caquexia, calculosis, litiasis (especialmente urolitiasis), carcinoma sólido, gota 15 y espondilitis anquilosante, tendinitis y bursitis.

Enfermedades cardiovasculares incluyen hipertensión o isquemia miocardiaca; aterosclerosis; insuficiencia venosa funcional u orgánica; terapia varicosa; hemorroides, y estados de shock asociados con una caída marcada en la presión arterial (por ejemplo, choque séptico).

20 Enfermedades neurodegenerativas incluyen demencia, particularmente demencia degenerativa (incluyendo demencia senil, demencia con cuerpos de Lewy, enfermedad de Alzheimer, enfermedad de Pick, corea de Huntington, enfermedad de Parkinson y enfermedad de Creutzfeldt-Jakob,

esclerosis lateral amiotrófica (ALS) y enfermedad de neurona motora); demencia vascular (incluyendo demencia multi-infarto); así como demencia asociada con lesiones de ocupación de espacio intracraneal; trauma; infecciones y condicione relacionadas (incluyendo infección de VIH, meningitis y herpes); metabolismo, toxinas, anoxia y deficiencia de vitaminas; y deterioro cognoscitivo medio asociado con envejecimiento, particularmente deterioro de la memoria asociado con la edad.

Los compuestos de fórmula (I) o sales farmacéuticamente aceptables también pueden ser útiles para la neuroprotección y en el tratamiento de neurodegeneración después de trauma tal como apoplejía, interrupción cardíaca, derivación pulmonar, lesión cerebral traumática, lesión de la médula espinal o lo similar.

Los compuestos o sales farmacéuticamente aceptables de la presente invención pueden ser útiles también en el tratamiento de crecimiento maligno celular y/o metástasis, y leucemia mioblástica.

Complicaciones de diabetes tipo I incluyen microangiopatía diabética, retinopatía diabética, nefropatía diabética, degeneración macular, glaucoma, síndrome nefrótico, anemia aplástica, uveitis, enfermedad de Kawasaki y sarcoidosis.

Disfunción de riñón incluye nefritis, glomerulonefritis, particularmente glomerulonefritis proliferante mesangial y síndrome nefrítico.

Se entiende que la referencia al tratamiento incluye el tratamiento de síntomas establecidos y tratamiento profiláctico, a menos que

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se establezca explícitamente lo contrario.

De acuerdo a un aspecto adicional de la invención, por lo tanto proveemos un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para usarse en la terapia y/o para uso en la medicina humana o veterinaria.

De acuerdo a otro aspecto de la invención, proveemos un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para usarse en el tratamiento o prevención (por ejemplo, tratamiento) de una condición que es mediada por los receptores P2X7, por ejemplo una condición o enfermedad descrita en la presente (en particular dolor, inflamación o una enfermedad neurodegenerativa, más particularmente dolor tal como dolor inflamatorio, dolor neuropático o dolor visceral), por ejemplo, en un mamífero tal como un humano o roedor, por ejemplo, humano o rata, por ejemplo, humano.

De acuerdo a un aspecto adicional de la invención, proveemos un método de tratamiento de un sujeto humano o animal (por ejemplo, roedor, por ejemplo, rata), por ejemplo un sujeto humano, que padece de una condición que es mediada por los receptores P2X7, por ejemplo una condición o enfermedad descrita aquí (en particular dolor, inflamación o una enfermedad neurodegenerativa, más particularmente dolor tal como dolor inflamatorio, dolor neuropático o dolor visceral), que comprende la administración a dicho sujeto de una cantidad efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

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De acuerdo a un aspecto adicional de la invención, proveemos un método de tratamiento de un sujeto humano o animal (por ejemplo, roedor, por ejemplo, rata), por ejemplo un sujeto humano, que padece de dolor, inflamación, una enfermedad inmunológica, una enfermedad ósea o una enfermedad neurodegenerativa (en particular dolor, inflamación o una enfermedad neurodegenerativa, más particularmente dolor tal como dolor inflamatorio, dolor neuropático o dolor visceral), dicho método comprende la administración a dicho sujeto de una cantidad efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

10 De acuerdo a un aspecto adicional de la invención proveemos un método de tratamiento de un sujeto humano o animal (por ejemplo, roedor, por ejemplo, rata), por ejemplo un sujeto humano, que padece de dolor inflamatorio, dolor neuropático o dolor visceral, dicho método comprende la administración a dicho sujeto de una cantidad efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

De acuerdo a un aspecto adicional de la invención proveemos un método de tratamiento de un sujeto, por ejemplo un sujeto humano, que padece de enfermedad de Alzheimer dicho método comprende la administración a dicho sujeto de una cantidad efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

20 De acuerdo a otro aspecto de la invención, proveemos el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para la elaboración de un medicamento para el tratamiento o

prevención (por ejemplo, tratamiento) de una condición que es mediada por la acción de los receptores P2X7, por ejemplo una condición o enfermedad descrita en la presente (en particular dolor, inflamación o una enfermedad neurodegenerativa, más particularmente dolor tal como dolor inflamatorio, dolor neuropático o dolor visceral), por ejemplo, en un mamífero tal como un humano o roedor, por ejemplo, humano o rata, por ejemplo, humano.

De acuerdo a otro aspecto de la invención proveemos el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para la elaboración de un medicamento para el tratamiento o prevención (por ejemplo, tratamiento) de dolor, inflamación, una enfermedad inmunológica, una enfermedad ósea o una enfermedad neurodegenerativa (en particular dolor, inflamación o una enfermedad neurodegenerativa, más particularmente dolor tal como dolor inflamatorio, dolor neuropático o dolor visceral), por ejemplo, en un mamífero tal como un humano o roedor, por ejemplo, humano o rata, por ejemplo, humano.

De acuerdo a otro aspecto de la invención proveemos el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para la elaboración de un medicamento para el tratamiento o prevención (por ejemplo, tratamiento) de dolor inflamatorio, dolor neuropático o dolor visceral, por ejemplo, en un mamífero tal como un humano o roedor, por ejemplo, humano o rata, por ejemplo, humano.

En un aspecto de la invención, proveemos el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo

para la elaboración de un medicamento para el tratamiento o prevención (por ejemplo, tratamiento) de enfermedad de Alzheimer, por ejemplo, en un mamífero tal como un humano o roedor, por ejemplo, humano o rata, por ejemplo, humano.

- 5 Con el fin de usar un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para el tratamiento de humanos y otros mamíferos normalmente se formula de acuerdo con la práctica farmacéutica estándar como una composición farmacéutica. Por lo tanto en otro aspecto de la invención se provee una composición farmacéutica que
- 10 comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, adaptado para usarse en medicina humana o veterinaria.

- Con el fin de usar un compuesto de fórmula (I) una sal farmacéuticamente aceptable del mismo en la terapia, normalmente se formulará en una composición farmacéutica de acuerdo con la práctica
- 15 farmacéutica estándar.

- La presente invención también provee una composición farmacéutica, que comprende un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, y opcionalmente un portador o excipiente farmacéuticamente aceptable.

- 20 La composición farmacéutica se puede usar en un método de tratamiento o en un uso o en un tratamiento o prevención, como se describe aquí.

 Una composición farmacéutica de la invención, que se puede

preparar al mezclar, por ejemplo a temperatura ambiente y presión atmosférica, usualmente se adapta para administración oral, parenteral o rectal. Como tal, la composición farmacéutica puede estar en la forma de tabletas, cápsulas, preparaciones orales líquidas, polvos, gránulos, pastillas, 5 polvos reconstituibles, soluciones inyectables o infusionables o suspensiones o supositorios. Composiciones administrables oralmente generalmente se prefieren.

Las tabletas y cápsulas para administración oral pueden estar en forma de dosis unitaria, y pueden contener excipientes, tales como agentes de 10 unión, sustancias de relleno, lubricantes de formación de tabletas, desintegrantes y/o agentes humectantes aceptables. Las tabletas se pueden recubrir, por ejemplo, de acuerdo a métodos conocidos en la práctica farmacéutica normal.

Preparaciones orales líquidas pueden estar en la forma de, por 15 ejemplo, suspensión acuosa o aceitosa, soluciones, emulsiones, jarabes o elíxires, o pueden estar en la forma de un producto seco para reconstitución con agua u otro vehículo adecuado antes de usarse. Dichas preparaciones líquidas pueden contener aditivos convencionales tales como agentes de suspensión, agentes emulsionantes, vehículos no acuosos (que pueden incluir 20 aceites comestibles), conservadores, y si se desea, saborizantes o colorantes convencionales.

Para la administración parenteral, las formas de dosificación unitaria fluidas son, por ejemplo, preparadas utilizando un compuesto de la

invención o sal farmacéuticamente aceptable del mismo y un vehículo estéril. En una modalidad particular, el compuesto o sal, dependiendo del vehículo y concentración usada, es suspendida o disuelta en el vehículo. En la preparación de soluciones, el compuesto o sal se puede, por ejemplo, disolver para inyección y filtrar en forma esterilizada antes del llenado en un frasco adecuado o ampolleta y sellado. En una modalidad, el o los adyuvantes tales como anestésicos locales, un conservador y/o un agente de regulación del pH se disuelven en el vehículo. Para incrementar la estabilidad, la composición puede, por ejemplo, congelarse después del llenado en el frasco y el agua removida bajo vacío. Suspensiones parenterales típicamente se preparan en sustancialmente la misma manera, excepto que el compuesto o sal normalmente se suspenda en el vehículo en lugar de disolverse, y la esterilización no se realiza usualmente fácilmente por medio de filtración. El compuesto o sal se puede esterilizar, por ejemplo, por exposición a óxido de etileno antes de la suspensión en un vehículo estéril. En una modalidad particular, un agente tensoactivo o agente de humectación se incluye en la composición para facilitar la distribución uniforme del compuesto o sal de la invención.

En una modalidad, la composición contiene de 0.1 a 99% en peso, en particular de 10 a 60% en peso, del material activo (el compuesto o sal farmacéuticamente aceptable de la invención), por ejemplo, dependiendo en el método de administración.

La dosis del compuesto o sal farmacéuticamente aceptable del

mismo usado en el tratamiento o prevención (por ejemplo, tratamiento) de los trastornos/enfermedades/condiciones mencionadas anteriormente pueden variar en la manera usual con la seriedad de los trastornos, el peso del paciente que padece, y/o otros factores similares. Sin embargo, como una

5 regla general, en una modalidad una dosis unitaria adecuada de 0.05 a 1000 mg, por ejemplo 0.05 a 200 mg, tal como 20 a 40 mg, del compuesto o sal farmacéuticamente aceptable de la invención (medida como el compuesto), se puede usar. En una modalidad, dicha dosis unitaria para administración una vez al día, por ejemplo, a un mamífero tal como un humano; alternativamente

10 dicha dosis unitaria puede ser para la administración más de una vez al día (por ejemplo, dos veces), por ejemplo a un mamífero tal como un humano. Dicha terapia se puede extender por un número de semanas o meses.

Combinaciones

15 Los compuestos de fórmula (I) o sales de los mismos se pueden usar en combinación con otros agentes terapéuticos, por ejemplo medicamentos reclamados por ser útiles en el tratamiento de los trastornos mencionados anteriormente.

Ejemplos adecuados de otros agentes terapéuticos pueden

20 incluir un agonista de β_2 (también conocido como agonistas de adrenoceptor β_2 ; por ejemplo formoterol) y/o un corticosteroide (por ejemplo, budesonida, fluticasona (por ejemplo, como propionato o ésteres furoato), mometasona (por ejemplo, como furoato), beclometasona (por ejemplo, ésteres 17-

propionato o 17,21-dipropionato), ciclesonida, triamcinolona (por ejemplo, como acetonida), flunisolida, rofleponida y butixocort (por ejemplo, como éster propionato), para el tratamiento de trastornos respiratorios (tales como asma y enfermedad pulmonar obstructiva crónica (COPD)) como se describe en WO

5 2007/008155 y WO 2007/008157.

Un agente terapéutico adicional puede incluir un inhibidor reductasa de coenzima A 3-hidroxi-3-metilglutarilo (HMG CoA) (por ejemplo, atorvastatina, fluvastatina, lovastatina, pravastatina, rosuvastatina, y simvastatina) para el tratamiento de trastornos cardiovasculares (tales como

10 aterosclerosis) como se describe en WO 2006/083214.

Un agente terapéutico adicional puede incluir un fármaco anti-inflamatorio no esteroide (NSAID; por ejemplo, ibuprofeno, naproxeno, aspirina, celecoxib, diclofenac, etodolac, fenoprofeno, indometacina, cetoprofeno, cetoralac, oxaprozin, nabumetona, sulindac, tolmetin, rofecoxib,

15 valdecoxib, lumaricoxib, meloxicam, etoricoxiband y parecoxib) para el tratamiento de una enfermedad o trastorno inflamatorio (tal como artritis reumatoide u osteoartritis) como se describe en WO 2005/025571.

Un agente terapéutico adicional puede incluir un inhibidor del factor de necrosis tumoral α (TNF α) (por ejemplo, Etanercept o un anticuerpo

20 anti-TNF α tal como Infliximab y Adalimumab) para el tratamiento de una enfermedad o trastorno inflamatorio (tal como artritis reumatoide u osteoartritis) como se describe en WO 2004/105798.

Un agente terapéutico adicional puede incluir ácido 2-hidroxi-5-



[[4-[(2-piridinilamino)sulfonil]fenil]azo]benzoico (sulfasalazina) para el tratamiento de una enfermedad o trastorno inflamatorio (tal como artritis reumatoide) como se describe en WO 2004/105797.

Un agente terapéutico adicional puede incluir ácido N-[4-[(2,4-diamino-6-pteridinil)metil]metilamino]benzoil]-L-glutámico (metotrexato) para el tratamiento de una enfermedad o trastorno inflamatorio (tal como artritis reumatoide) como se describe en WO 2004/105796.

Un agente terapéutico adicional puede incluir un inhibidor de enzima convertasa TNF α (TACE) para el tratamiento de una enfermedad o trastorno inflamatorio (tal como artritis reumatoide) como se describe en WO 2004/073704.

Un agente terapéutico adicional puede incluir:

a) sulfasalazina;

b) una estatina, tal como atorvastatina, lovastatina, pravastatina, simvastatina, fluvastatina, cerivastatina, crilvastatina, dalvastatina, rosuvastatina, tenivastatina, fluindostatina, velostatina, dalvastatina, nisvastatina, bervastatina, pitavastatina, rivastatina, glenvastatina, eptastatina, tenivastatina, flurastatina, rosuvastatina o itavastatina;

c) un agente glucocorticoide, tal como dexametasona, metilprednisolona, prednisolona, prednisona e hidroclorisona

d) un inhibidor de p38 cinasa;

e) un anticuerpo anti-IL-6-receptor;

f) anakinra;

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g) un anticuerpo anti-IL-1 monoclonal;

h) un inhibidor de proteína tirosina quinasa JAK3;

i) un anticuerpo monoclonal factor de estimulación de colonia anti-macrófagos (M-CSF), o

5 j) un anticuerpo monoclonal anti-CD20, tales como rituximab, PRO70769, HuMax-CD20 (Genmab AJS), AME-133 (Applied Molecular Evolution) o hA20 (Immunomedics, Inc.),

para el tratamiento de una enfermedad mediada por IL-1 (tal como artritis reumatoide) como se describe en WO 2006/003517.

10 Cuando los compuestos se usan en combinación con otros agentes terapéuticos, los compuestos se pueden administrar consecutivamente o simultáneamente por medio de cualquier ruta conveniente.

La invención provee de este modo, en un aspecto adicional, una combinación que comprende un compuesto de fórmula (I) o una sal
15 farmacéuticamente aceptable del mismo junto con un agente o agentes terapéuticos adicionales.

Las combinaciones referidas anteriormente se pueden presentar convenientemente para usarse en la forma de una formulación farmacéutica y de este modo formulaciones farmacéuticas que comprenden una combinación
20 como se definió anteriormente junto con un portador o excipiente farmacéuticamente aceptable comprende un aspecto adicional de la invención. Los componentes individuales de dichas combinaciones se pueden administrar consecutivamente o simultáneamente en formulaciones

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farmacéuticas separadas o combinadas.

Cuando un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo se usa en combinación con un segundo agente terapéutico activo contra el mismo estado de enfermedad la
5 dosis de cada compuesto puede diferir de aquella cuando el compuesto se usa solo.

Las siguientes descripciones y ejemplos ilustran la preparación de compuestos o sales de la invención pero no se pretende que sean limitantes.

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EJEMPLOS

Los métodos generales (a)-(c), junto con los métodos sintéticos mostrados en los esquemas 1, 2 o 3 anteriores, para la preparación de
15 compuestos o sales de la presente invención se ilustran adicionalmente por medio de los siguientes ejemplos.

Algunas abreviaturas usadas aquí son:

DCM - diclorometano

DMF – N,N-dimetilformamida

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TFA – ácido trifluoroacético

XantphosTM se refiere a 4,5-bis(difenilfosfino)-9,9-dimetilxanteno, que es comercialmente disponible, por ejemplo, de Aldrich, No. CAS 161265-03-8.

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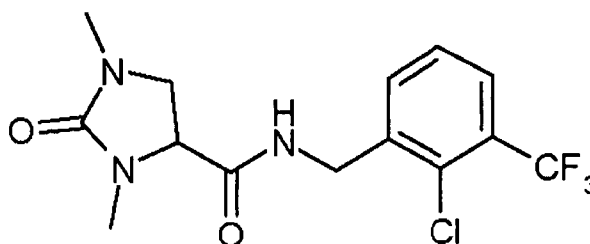
Acido (4S)-2-Oxo-3-[[fenilmetil]oxi]carbonil}-4-imidazolidinacarboxílico, que se usa aquí como el material de inicio original en muchos de los ejemplos, por ejemplo, ejemplos 1 y 13, es disponible comercialmente, por ejemplo, de Sigma-Aldrich, RU o US (No. catálogo 392308); y tiene el número de CAS 59760-01-9. Este compuesto y su preparación también se describe en M.P. Doyle y J.T. Colyer, Tetrahedron: Asymmetry, 2003, 14(22), 3601-3604 (ver, por ejemplo, Experimental 4.2, y la sección de resultados y discusión primer párrafo y ecuación (1)), incorporada aquí para referencia.

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EJEMPLO 1

N-[[2-cloro-3-(trifluorometil)fenil]metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida (E1) (en una forma obtenible o preparada de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil}-4-imidazolidinacarboxílico)

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Acido 1,3-dimetil-2-oxo-4-imidazolidinacarboxílico crudo (0.098 g, ~0.619 mmoles, preparado como se describe posteriormente) se disuelve en dimetilformamida (5 ml) y se trata con 1-hidroxibenzotriazol (0.092 g, 0.681 mmoles), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (0.131 g, 0.681 mmoles), [(2-cloro-3-trifluorometilfenil)metil]amina (0.156 g, 0.743

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mmoles) y N-etilmorfolina (0.166 ml, 1.30 mmoles). La mezcla se agita a temperatura ambiente (22°C) durante 18 horas entonces se reduce *in vacuo* para dar un residuo que se purifica por medio de HPLC automatizada dirigida con masa para proporcionar una goma incolora. La trituración de la goma con dietil éter (1 ml) y secado dan una goma amarillo pálido que se purifica adicionalmente por medio de cromatografía de columna en gel de sílice instantánea (eluyendo con un gradiente de 0-100% acetato de etilo en diclorometano (en 10 etapas)) para dar el producto parcialmente puro (~80%) como un sólido blanco (0.042 g). Una etapa de purificación final, nuevamente usando HPLC automatizada dirigida con masa, dan N-[[2-cloro-3-(trifluorometil)fenil]metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida como un sólido blanco (0.031 g).

LC/EM $[M+H]^+ = 350$, tiempo de retención = 2.29 minutos.

Exceso enantiomérico = 99.1%, como se determina por cromatografía quiral método (C), indicativo de (4S)-N-[[2-cloro-3-(trifluorometil)fenil]metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida, tiempo de retención = 8.30 minutos.

El ácido 1,3-dimetil-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico (10.25 g, 38.8 mmoles) se disuelve en metanol anhidro (100 ml) y se enfría a 0°C bajo argón. Cloruro de tionilo (4.25 ml, 58.2 mmoles) entonces se añade a gotas a la mezcla y después la mezcla se deja

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calentar a temperatura ambiente y se agita durante la noche. La mezcla se reduce *in vacuo* y el residuo se divide entre diclorometano (300 ml) y carbonato ácido de sodio acuoso saturado (100 ml). La capa acuosa se separa y se extrae con diclorometano (300 ml). Las capas orgánicas entonces
5 se combinan, se pasan a través de una frita hidrofóbica y se reducen *in vacuo* para dar 1-(fenilmetil)-2-oxo-1,5-imidazolidinacarboxilato de 5-metilo (10.67 g) como un sólido blanco.

(ii) 1-(Fenilmetil)-2-oxo-1,5-imidazolidinacarboxilato de 5-metilo (10.67 g, 38 mmoles) y carbonato de potasio (10.6 g, 76 mmoles) se
10 suspenden en dimetoxietano (150 ml) y se tratan con yoduro de metilo (9.46 ml, 152 mmoles). La mezcla de reacción se calienta a reflujo y se agita bajo argón durante 18 horas. La mezcla entonces se enfría y se evapora *in vacuo* y el residuo resultante se divide entre acetato de etilo (750 ml) y salmuera (200 ml). La capa orgánica se separa, se pasa a través de una frita hidrofóbica y se
15 reduce *in vacuo*. El residuo resultante se purifica por medio de cromatografía de columna en gel de sílice instantánea automatizada (Biotage SP4), eluyendo con un gradiente de 20-60% de acetato de etilo en hexano, para dar 1-(fenilmetil)-3-metil-2-oxo-1,5-imidazolidinacarboxilato de 5-metilo (5.77 g) como un aceite color naranja.

20 (iii) Una suspensión de 1-(fenilmetil)-3-metil-2-oxo-1,5-imidazolidinacarboxilato de 5-metilo (5.77 g) y 5% paladio sobre carbón (5 g) en acetato de etilo (300 ml) se coloca bajo una atmósfera de hidrógeno y se agita durante 24 horas. La mezcla entonces se filtra y se reduce *in vacuo* para

dar 1-metil-2-oxo-4-imidazolidinacarboxilato de metilo (2.76) como un sólido blanco que se usa sin purificación adicional.

(iv) Una solución de 1-metil-2-oxo-4-imidazolidinacarboxilato de metilo (1.76 g, 11.1 mmoles) en dimetilformamida anhidra (20 ml) se enfría a -
5 10°C bajo argón y se trata con yoduro de metilo (2.76 ml, 44.4 mmoles). Hidruro de sodio (60% en aceite, 0.422 g, 10.5 mmoles) entonces se añade en porciones durante un periodo de 20 minutos. La mezcla se deja calentar a temperatura ambiente (en el baño de enfriamiento) y se agita durante 18 horas. La mezcla de reacción entonces se reduce *in vacuo* y el residuo se
10 divide entre acetato de etilo (150 ml) y salmuera (50 ml). La capa acuosa (que contiene una suspensión fina) se separa y se extrae con más acetato de etilo (100 ml). Los extractos orgánicos entonces se combinan, se pasan a través de una frita hidrofóbica, y se reducen *in vacuo* para producir un aceite color naranja. Este material se purifica por cromatografía de columna en gel de
15 sílice instantánea, eluyendo con 50% de acetato de etilo en hexano y entonces con un gradiente de 50-100% en hexano, para dar 1,3-dimetil-2-oxo-4-imidazolidinacarboxilato de metilo (1.123 g) como un aceite incoloro se usa sin purificación adicional.

(v) 1,3-dimetil-2-oxo-4-imidazolidinacarboxilato de metilo (1.12 g)
20 se disuelve en 10 ml de una mezcla 3:2 de tetrahidrofurano y agua respectivamente, después se enfría a 0°C y se trata con hidróxido de litio (0.156 g). La reacción se agita entre 0-5°C durante 4 horas, después se acidifica con cloruro ácido acuoso 2N (4 ml) y se reduce *in vacuo*. El residuo

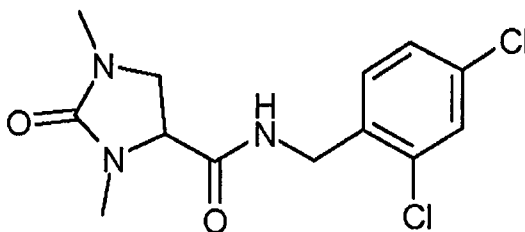
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se disuelve en metanol y se carga sobre cartuchos de extracción de fase sólida 2 x 10 g de NH₂ (SPE) y se eluye con metanol (2 volúmenes de columna) y después con una mezcla 10% de cloruro ácido acuoso 2N en metanol (2 volúmenes columna). Estas últimas fracciones se combinan y se
 5 evaporan para dar ácido 1,3-dimetil-2-oxo-4-imidazolidinacarboxílico crudo (0.098 g) como una goma incolora que se usa sin alguna purificación adicional.

EJEMPLO 2

N-[(2,4-diclorofenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida

10 (E2) (en una forma obtenible o preparada del ácido (4S)-2-oxo-3-
 {[(fenilmetil)oxi]carbonil)-4-imidazolidinacarboxílico)



15

N-[(2,4-diclorofenil)metil]-1,3-dimetil-2-oxo-4-

imidazolidinacarboxamida (E2) se prepara de manera análoga a aquella descrita anteriormente para la síntesis de N-[(2-cloro-3-(trifluorometil)fenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida (E1)
 20 pero usando [(2,4-diclorofenil)metil] amina en lugar de [(2-cloro-3-trifluorometilfenil)metil]amina.

LC/EM [M+H]⁺ = 316, tiempo de retención = 2.19 minutos.

Además, el 1,3-dimetil-2-oxo-4-imidazolidinacarboxilato de metilo

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usado en el procedimiento anterior (ver descripción del método usado para preparar el ácido 1,3-dimetil-2-oxo-4-imidazolidinacarboxílico) se prepara de una manera ligeramente diferente y se describe a continuación:

1-Metil-2-oxo-4-imidazolidinacarboxilato de metilo (1 g, 6.32
5 mmoles) (preparado como se describe en la etapa (iii) del ejemplo 1, iniciando con ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil-4-imidazolidinacarboxílico) se disuelve en tetrahidrofurano anhidro (10 ml), se enfría a -10°C bajo argón y se trata con yoduro de metilo (1.57 ml, 25.3 mmoles). Hidruro de sodio (60% en aceite, 0.24 g, 6.0 mmoles) entonces se añade en porciones durante un
10 periodo de 15 minutos y la mezcla se deja calentar a temperatura ambiente y se agita durante 18 horas. La mezcla de reacción entonces se reduce *in vacuo* y el residuo se divide entre acetato de etilo (40 ml) y salmuera (20 ml). La capa orgánica se separa, se pasa a través de una frita hidrofóbica, y se reduce *in vacuo* para producir un aceite color amarillo. Este material se
15 purifica por cromatografía de columna en gel de sílice instantánea automatizada (Biotage SP4), eluyendo con 50% de acetato de etilo en hexano (5 volúmenes columna) y entonces con un gradiente de 50-80% en hexano (15 volúmenes columna), para dar 1,3-dimetil-2-oxo-4-imidazolidinacarboxilato de metilo (0.479 g) como un aceite amarillo que se usa sin purificación
20 adicional.

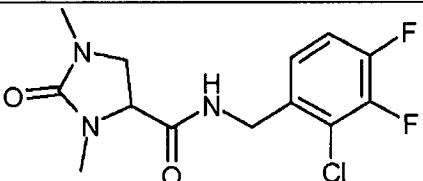
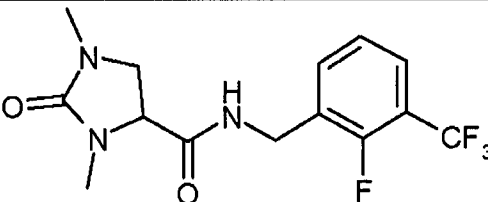
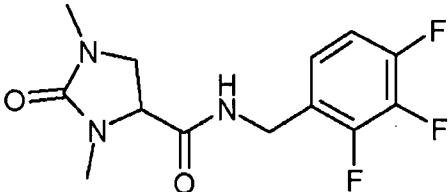
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EJEMPLOS 3-7

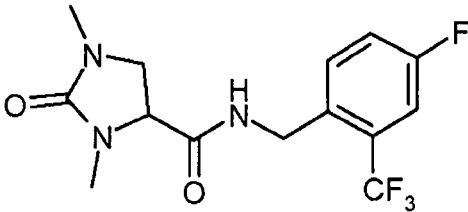
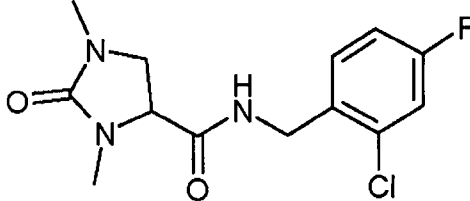
**(En formas obtenibles o preparadas del ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)**

- 5 De una manera análoga a la descrita para el ejemplo 2 anterior los compuestos tabulados posteriormente (cuadro 1) se preparan al sustituir la amina apropiada (o su sal) por la [(2,4-diclorofenil)metil]amina usada en el procedimiento anterior. Todas las aminas usadas para elaborar las aminas mostradas en el cuadro 1 están disponibles de fuentes comerciales o se
- 10 pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

CUADRO 1

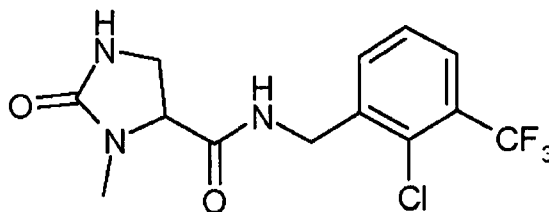
No. ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (mins)
E3	 N-[(2-cloro-3,4-difluorofenil)metil]- 1,3-dimetil-2-oxo-4- imidazolidinacarboxamida	318	2.06
E4	 N-[[2-fluoro-3- (trifluorometil)fenil]metil]-1,3-dimetil- 2-oxo-4-imidazolidinacarboxamida	334	2.18
E5	 1,3-dimetil-2-oxo-N-[(2,3,4- trifluorofenil)metil]-4- imidazolidinacarboxamida	302	1.93

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No. ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (mins)
E6	 <i>N</i> -[[4-fluoro-2-(trifluorometil)fenil]metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida	334	2.16
E7	 <i>N</i> -[(2-cloro-4-fluorofenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida	300	1.97

EJEMPLO 8

N-[[2-cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (E8) (por ejemplo, en una forma obtenible o preparada del ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico)



Acido 3-metil-2-oxo-4-imidazolidinacarboxílico crudo (~0.63

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mmoles, preparado como se describe posteriormente) se disuelve en dimetilformamida (3 ml) y se trata con 1-hidroxibenzotriazol (0.094 g, 0.69 mmoles), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (0.132 g, 0.69 mmoles), [(2-cloro-3-trifluorometilfenil)metil]amina (0.145 g, 0.69 mmoles) y N-etilmorfolina (0.169 ml, 1.32 mmoles). La mezcla se agita a 22°C durante 20 horas entonces se reduce *in vacuo* para dar un residuo que se purifica por medio de HPLC automatizada dirigida con masa para proporcionar N-[[2-cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-4-imidazolidinacarboxamida como un sólido blanco (0.105 g).

10 LC/EM $[M+H]^+ = 336$, tiempo de retención = 2.18 minutos.

El ácido 3-metil-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) Una solución de 1-(fenilmetil)-2-oxo-1,5-imidazolidinacarboxilato de 5-metilo (5 g, 18 mmoles) (preparada como se describe en la etapa (i) del ejemplo 1, iniciando con ácido (4S)-2-oxo-3-[[{(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico) en dimetilformamida (27 ml) se añade a gotas a una suspensión de hidruro de sodio (60% en aceite, 0.72 g, 18 mmoles) en dimetilformamida (45 ml) a 0°C bajo una atmósfera de argón. El baño de enfriamiento se remueve y la mezcla se agita bajo argón durante 1 hora y después de trata con yoduro de metilo (5.6 ml). La mezcla se agita a 22°C durante 18 horas adicionales y entonces se reduce *in vacuo* para dar un residuo que se divide entre acetato de etilo (250 ml) y salmuera (75 ml). La capa orgánica se separa, usando una frita hidrofóbica, y entonces se

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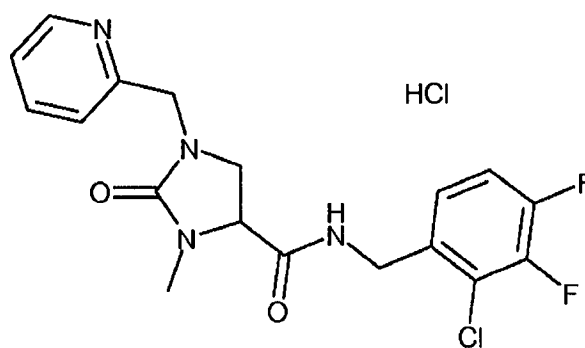
reduce *in vacuo* para producir un aceite color naranja. El aceite se purifica por cromatografía de columna en gel de sílice instantánea, eluyendo con 30% de acetato de etilo en hexanos (3 volúmenes columna) y entonces con un gradiente de 30-70% de acetato de etilo en hexanos (10 volúmenes columna),
5 para dar 1-(fenilmetil) 3-metil-2-oxo-1,4-imidazolidinadicarboxilato de 4-metilo (3.65 g) como un aceite incoloro.

(ii) 1-(Fenilmetil) 3-metil-2-oxo-1,4-imidazolidinadicarboxilato de 4-metilo (3.65 g, 12.5 mmoles) se disuelve en metanol (300 ml) y se hidrogena en presencia de 10% paladio sobre carbón (0.5 g). La mezcla se agita durante
10 18 horas a 22°C, entonces se filtra y se reduce *in vacuo* para dar 3-metil-2-oxo-4-imidazolidinadicarboxilato de metilo (1.90 g) como un sólido blanco que se usa en la siguiente etapa sin purificación adicional.

(iii) 3-Metil-2-oxo-4-imidazolidinadicarboxilato de metilo (0.150 g, 0.948 mmoles) se disuelve en una mezcla 3:2 de tetrahidrofurano y agua
15 respectivamente (2.5 ml) y se enfría a 0°C. La mezcla entonces se trata con hidróxido de litio (0.068 g, 2.84 mmoles) y se agita con enfriamiento con hielo/agua durante 5 horas adicionales. La mezcla se acidifica a pH 1 mediante la adición de ácido clorhídrico 2N (3 ml) y la mezcla resultante entonces se reduce *in vacuo* para dar ácido 3-metil-2-oxo-4-
20 imidazolidinacaroxílico como un sólido blanco (0.260 g) que se usa sin alguna purificación adicional.

EJEMPLO 9**Clorhidrato de N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-1-(2-piridinilmetil)-4-imidazolidinacarboxamida (E9)**

5



Una mezcla de ácido 3-metil-2-oxo-1-(2-piridinilmetil)-4-imidazolidinacarboxílico crudo (~0.7 mmoles), hidrato de 1-hidroxibenzotriazol (113 mg, 0.84 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (161 mg, 0.84 mmoles), y N-etil morfolina (0.27 ml, 2.1 mmoles) en diclorometano (20 ml)/N,N-dimetilformamida (2 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de [(2-cloro-3,4-difluorofenil)metil]amina (150 mg, 0.84 mmoles) en diclorometano (5 ml) se añade y la reacción se agita a temperatura ambiente durante 18 horas. La mezcla se diluye con diclorometano y la solución se lava con solución saturada de carbonato ácido de sodio, agua y salmuera, se seca y se evapora. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo con 0-10% metanol en diclorometano. El residuo se tritura con éter/hexanos y el sólido se seca. El residuo se disuelve en diclorometano (2 ml), cloruro de hidrógeno (1M en éter, 0.1 ml) se añade y el solvente se evapora. El sólido se co-evapora con acetato de etilo y éter y después se tritura con éter. El sólido

se colecta y se seca para dar clorhidrato de N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-1-(2-piridinilmetil)-4-imidazolidinacarboxamida (40 mg).

LC/EM $[M+H]^+ = 395$, tiempo de retención = 1.85 minutos.

El ácido 3-metil-2-oxo-1-(2-piridinilmetil)-4-

5 imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) Una suspensión de hidruro de sodio (240 mg, 6 mmoles, 60% dispersión en aceite) en N-metil-2-pirrolidinona (6 ml) se agita a 0°C bajo argón. Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de metilo (474
10 mg, 3 mmoles) (preparada como se describe en la etapa (ii) del ejemplo 8) en N-metil-2-pirrolidinona (3 ml) se añade a gotas durante 10 minutos. La reacción se agita a 0°C durante 15 minutos y bromhidrato de 2-(bromometil)piridina (835 mg, 3.3 mmoles) se añade a gotas durante 5 minutos. La mezcla se agita a 0°C durante 30 minutos y después a
15 temperatura ambiente durante 20 horas. La reacción se trata con agua helada y se extrae con diclorometano. La mezcla se aplica a un cartucho de iones SCX y se lava con metanol y entonces amoníaco 2M en metanol. Las fracciones básicas se combinan y se evaporan. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo con metanol 0-10% en
20 diclorometano para dar 3-metil-2-oxo-1-(2-piridinilmetil)-4-imidazolidinacarboxilato de metilo (190 mg),

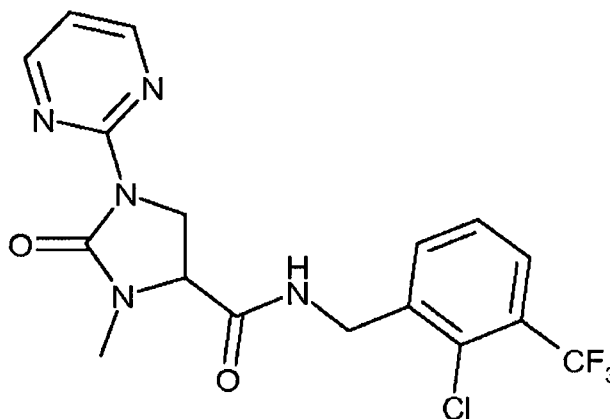
LC/EM $[M+H]^+ = 250$.

(ii) Una solución agitada de 3-metil-2-oxo-1-(2-piridinilmetil)-4-

imidazolidinacarboxilato de metilo (190 mg, 0.76 mmoles) en tetrahidrofurano (1.5 ml)/agua (1 ml) a 0°C se trata con hidróxido de litio (55 mg, 2.28 mmoles) y la mezcla de reacción se agita a 0-5°C durante 3 horas. La reacción se acidifica a pH 2 con ácido clorhídrico 2N y el solvente se evapora. El residuo se seca para dar ácido 3-metil-2-oxo-1-(2-piridinilmetil)-4-imidazolidinacarboxílico que se usa crudo en la siguiente etapa.

EJEMPLO 10

N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida (E10)



Una suspensión de ácido 3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxílico (0.6 mmoles) en diclorometano (10 ml) se trata con hidrato de 1-hidroxibenzotriazol (98 mg, 0.72 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (138 mg, 0.72 mmoles) y N-etil morfolina (0.3 ml, 2.4 mmoles) se agita a temperatura ambiente durante 10 minutos. Se añade {[2-cloro-3-(trifluorometil)fenil]metil}amina (126 mg, 0.6 mmoles). La reacción se diluye con diclorometano (10 ml) y N,N-dimetilformamida (1 ml) y

se agita a temperatura ambiente durante 18 horas. Clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida adicional (138 mg, 0.72 mmoles) se añade y la suspensión se agita a temperatura ambiente durante 5 días. La mezcla se diluye con diclorometano y la solución se lava con solución saturada de carbonato ácido de sodio, agua, solución de ácido cítrico, agua y salmuera, se
5 seca y se evapora. El residuo se purifica por medio de HPLC automatizada dirigida por masa. El sólido se tritura con éter/hexanos, se colecta y se seca para dar N-[[2-cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida (42 mg).

10 LC/EM $[M+H]^+ = 414$, tiempo de retención = 2.30 minutos.

El ácido 3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) Una suspensión de 3-metil-2-oxo-4-imidazolidinacarboxilato de metilo (316 mg, 2 mmoles) (preparada como se describe en la etapa (ii) del
15 ejemplo 8) en THF (10 ml) se agita a -40°C . Se añade hexametildisilazida de litio (2 ml, solución 1M en THF) a gotas y la mezcla se agita a -40°C durante 15 minutos y después a -70°C durante 1 hora. Una solución de 2-bromopirimidina (318 mg, 2 mmoles) en THF (1 ml) se añade a gotas y la reacción se agita a -70°C durante 1 horas y después se calienta a 0°C durante
20 1 hora y después se agita a temperatura ambiente durante la noche. La mezcla de reacción se diluye con solución de ácido cítrico y diclorometano. La capa orgánica se separa, se lava con agua y salmuera, se seca y se evapora. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo

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con metanol 0-10% en diclorometano para dar 3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxilato de metilo crudo (144 mg), que se usa en la siguiente etapa,

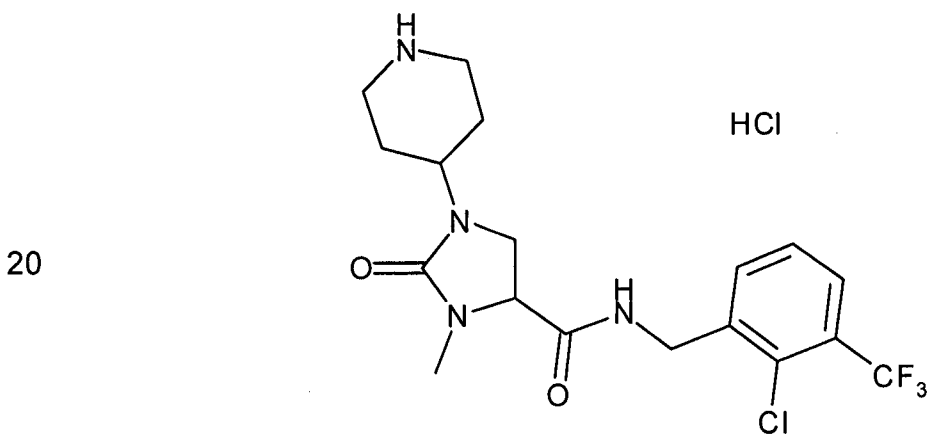
$$\text{LC/EM } [M+H]^+ = 237.$$

- 5 (ii) Una solución agitada de 3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxilato de metilo (144 mg, 0.6 mmoles) en tetrahidrofurano (1.5 ml) a 0°C se trata con hidróxido de litio (72 mg, 3 mmoles) en agua (1 ml) y la mezcla de reacción se agita a 0-5°C durante 1 hora. La reacción se acidifica a pH 2 con ácido clorhídrico 2N y el solvente se evapora. El residuo
- 10 se seca para dar ácido 3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxílico que se usa crudo en la siguiente etapa,

$$\text{LC/EM } [M+H]^+ = 223.$$

EJEMPLO 11

- 15 Clorhidrato de N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-(4-piperidinil)-4-imidazolidinacarboxamida (E11)



Una solución de 4-{4-[[[2-cloro-3-

(trifluorometil)fenil]metil]amino)carbonil]-3-metil-2-oxo-1-imidazolidinil}-1-

piperidinacarboxilato de 1,1-dimetiletilo (218 mg, 0.42 mmoles) en 1,4-dioxano (3 ml) se trata con cloruro de hidrógeno 4M en 1,4-dioxano (1 ml) y la reacción

se agita a temperatura ambiente durante 4 horas. El solvente se evapora y la

5 goma se disuelve en metanol y el solvente se evapora. El residuo se tritura

con éter y el sólido se colecta y se seca para dar clorhidrato de N-[[2-cloro-3-

(trifluorometil)fenil]metil]-3-metil-2-oxo-1-(4-piperidinil)-4-

imidazolidinacarboxamida (153 mg, 80%),

LC/EM $[M+H]^+ = 419$, tiempo de retención = 1.75 minutos.

10 El 4-{4-[[2-cloro-3-(trifluorometil)fenil]metil]amino)carbonil]-3-metil-2-oxo-1-imidazolidinil}-1-piperidinacarboxilato de 1,1-dimetiletilo usado en el método descrito anteriormente se prepara como sigue:

(i) Una solución de 4-oxo-1-piperidinacarboxilato de 1,1-dimetiletilo (3.0 g, 15 mmoles) en THF (45 ml) se agita a -78°C bajo argón. Se
15 añade hexametildisilazida de litio (15 ml, 15 mmoles, solución 1M en THF) a gotas y la reacción se agita a -78°C durante 1 hora. Una solución de 1,1,1-trifluoro-N-fenil-N-[(trifluorometil)sulfonyl]metanosulfonamida (6.43 g, 18 mmoles) en THF (12 ml) se añade a gotas. La reacción se calienta a temperatura ambiente durante 2 horas. La reacción se temple por medio de la
20 adición de agua y el THF se evapora. El residuo se extrae con éter. La capa de éter se separa y se lava con agua, solución de hidróxido de sodio 2N, agua y salmuera, se seca y se evapora. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo con 5-25% acetato de etilo en

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hexanos para dar 4-[[trifluorometil]sulfonil]oxi}-3,6-dihidro-1(2H)-piridinacarboxilato de 1,1-dimetiletilo (2.91 g, 59%).

(ii) Una solución de 4-[[trifluorometil]sulfonil]oxi}-3,6-dihidro-1(2H)-piridinacarboxilato de 1,1-dimetiletilo (2.65 g, 8 mmoles), 3-metil-2-oxo-4-imidazolidinacarboxilato de metilo (1.26 g, 8 mmoles) (preparado como se describe en la etapa (ii) del ejemplo 8) en 1,4-dioxano (50 ml) se trata con carbonato de cesio (3.91 g, 12 mmoles), XantphosTM (348 mg, 0.6 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (183 mg, 0.2 mmoles). La mezcla se purga con argón y la reacción se calienta a reflujo durante 1 hora. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con agua y se extrae con acetato de etilo. Las capas orgánicas se lavan con agua y salmuera, se seca y se evapora. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo con 0-100% acetato de etilo en hexanos para dar 4-{3-metil-4-[(metiloxi)carbonil]-2-oxo-1-imidazolidinil}-3,6-dihidro-1(2H)-piridinacarboxilato de 1,1-dimetiletilo (1.7 g, 63%),

LC/EM $[M+H]^+ = 340$.

(iii) Una solución de 4-{3-metil-4-[(metiloxi)carbonil]-2-oxo-1-imidazolinil}-3,6-dihidro-1(2H)-piridinacarboxilato de 1,1-dimetiletilo (1.36 g, 4 mmoles) en acetato de etilo (30 ml) que contiene paladio sobre carbón (100 mg, 10% pasta) se hidrogena a temperatura ambiente y presión durante 24 horas. La mezcla se filtra a través de Celite y el filtrado se evapora. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo con 50-100% acetato de etilo en hexanos para dar 4-{3-metil-4-[(metiloxi)carbonil]-2-oxo-1-

imidazolidinil)-1-piperidinacarboxilato de 1,1-dimetiletilo (205 mg, 15%),

LC/EM $[M+H]^+ = 342$.

(iv) Una solución de 4-{3-metil-4-[(metiloxi)carbonil]-2-oxo-1-imidazolidinil)-1-piperidinacarboxilato de 1,1-dimetiletilo (200 mg, 0.58 mmoles)
5 en THF (3 ml) se agita a 0°C. Una solución de hidróxido de litio (15 mg, 0.64 mmoles) en agua (2 ml) se añade y la reacción se agita a 0°C bajo argón durante 90 minutos. La solución se acidifica a pH 4 con ácido clorhídrico 2N y el solvente se evapora. El residuo se co-evapora con tolueno y el residuo se seca sobre pentóxido fosforoso bajo alto vacío para dar ácido 1-(1-{[(1,1-
10 dimetiletil)oxi]carbonil}-4-piperidinil)-3-metil-2-oxo-4-imidazolidinacarboxílico crudo que se usa en la siguiente etapa,

LC/EM $[M+H]^+ = 328$.

(v) A una suspensión agitada de ácido 1-(1-{[(1,1-dimetiletil)oxi]carbonil}-4-piperidinil)-3-metil-2-oxo-4-imidazolidinacarboxílico
15 (0.55 mmoles) en diclorometano (10 ml) se añade hidrato de 1-hidroxibenzotriazol (89 mg, 0.66 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (127 mg, 0.66 mmoles) y N-etil morfolina (0.21 ml, 1.6 mmoles) y la mezcla se agita a temperatura ambiente durante 15 minutos. Se añade una solución de {[2-cloro-3-(trifluorometil)fenil]metil}amina
20 (115 mg, 0.55 mmoles) y la reacción se agita a temperatura ambiente durante 3 horas. La reacción se diluye con diclorometano y la solución se lava con solución saturada de carbonato ácido de sodio, agua, solución de ácido cítrico, agua y salmuera, se seca y se evapora. El residuo se purifica por medio de

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cromatografía en gel de sílice eluyendo con 5-10% metanol en diclorometano para a dar 4-{4-[[{2-cloro-3-(trifluorometil)fenil]metil}amino]carbonil]-3-metil-2-oxo-1-imidazolidinil}-1-piperidinacarboxilato de 1,1-dimetiletilo (243 mg, 85%).

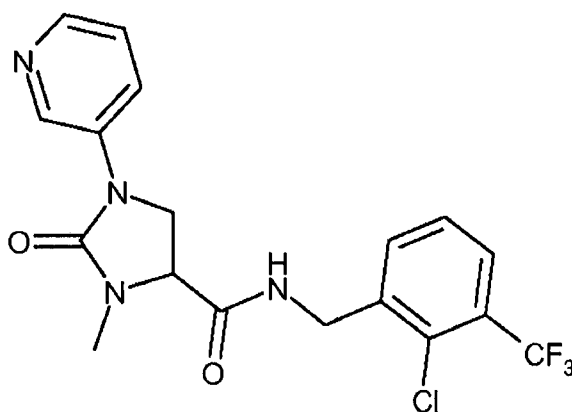
LC/EM $[M+H]^+ = 519$, tiempo de retención = 2.89 minutos.

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EJEMPLO 12

N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-(3-piridinil)-4-imidazolidinacarboxamida (E12)

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Una mezcla de ácido 3-metil-2-oxo-1-(2-piridinil)-4-imidazolidinacarboxílico crudo (0.8 mmoles), hidrato de 1-hidroxibenzotriazol (147 mg, 0.96 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (184 mg, 0.96 mmoles), y N-etil morfolina (0.307 ml, 2.4 mmoles) en diclorometano (15 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de {[2-cloro-3-(trifluorometil)fenil]metil}amina (168 mg, 0.8 mmoles) en diclorometano (1 ml) se añade y la reacción se agita a temperatura ambiente durante 4 horas. La mezcla se divide entre diclorometano y solución de carbonato ácido de sodio

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saturada. La fase orgánica se separa, se lava con agua y salmuera, se seca y se evapora. El residuo se purifica por HPLC automatizada dirigida por masa. El sólido se disuelve en metanol (5 ml) y HCl anhidro en éter (1M, 0.5 ml) se añade y la solución se evapora. El sólido resultante se colecta, lava con éter y se seca para dar un sólido amarillo pálido. El sólido se disuelve en metanol y se aplica a un cartucho iónico SCX y se lava con metanol y entonces amoníaco 2M en metanol. Las fracciones básicas se combinan y se evaporan y el residuo resultante se tritura con éter, se colecta y se seca para dar N-[[2-cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-1-(3-piridinil)-4-imidazolidinacarboxamida (27 mg, 8%).

LC/EM $[M+H]^+ = 413$ tiempo de retención = 1.96 minutos.

El ácido 3-metil-2-oxo-1-(3-piridinil)-4-imidazolidinacarboxílico usado en el método descrito anteriormente se preparó como sigue:

(i) Una solución de 3-bromopiridina (316 mg, 2.0 mmoles) y 3-metil-2-oxo-4-imidazolidinacarboxilato de metilo (316 mg, 2 mmoles) (preparada como se describe en la etapa (ii) del ejemplo 8) en 1,4-dioxano (10 ml) se trata con carbonato de cesio (977 mg, 3 mmoles), XantphosTM (87 mg, 0.15 mmoles) (4,5-bis(difenilfosfino)-9,9-dimetilxanteno, por ejemplo disponible de Aldrich, No. CAS 161265-03-8) y tris(dibencilidenoacetona)dipaladio (0) (45.8 mg, 0.05 mmoles) y la mezcla se calienta bajo reflujo y bajo argón durante 22 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con agua y se extrae con acetato de etilo (x3). Las capas orgánicas se combinan, se lavan con

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agua y salmuera y se evaporan *in vacuo*. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo con 0-10% metanol en diclorometano para dar 3-metil-2-oxo-1-(3-piridinil)-4-imidazolidinacarboxilato de metilo (273 mg, 58%).

5 LC/EM $[M+H]^+ = 236$.

(ii) Una solución de 3-metil-2-oxo-1-(3-piridinil)-4-imidazolidinacarboxilato de metilo (0.27 g, 1.15 mmoles) en tetrahidrofurano (3 ml) a 0°C se trata con una solución de hidróxido de litio (0.030 g, 1.26 mmoles) en agua (2 ml) y la mezcla se agita a 0°C durante 90 minutos. Se añade ácido clorhídrico (2M) para ajustar el pH de la mezcla de reacción a pH 2 y el
10 solvente se evapora. El residuo se seca sobre pentóxido fosforoso para dar ácido 3-metil-2-oxo-1-(3-piridinil)-4-imidazolidinacarboxílico crudo que se usa en la siguiente etapa.

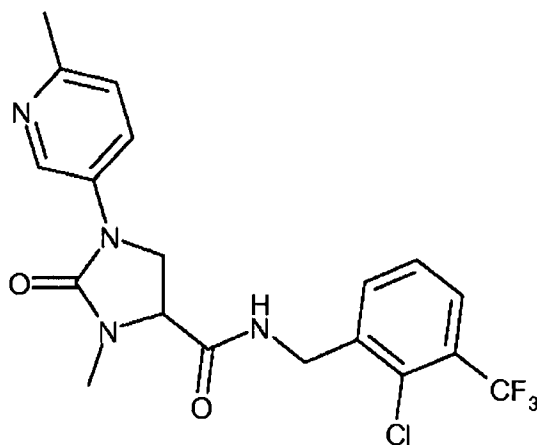
LC/EM $[M+H]^+ = 222$.

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EJEMPLO 13

N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida (E13) (en una forma obtenible o preparada de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil}-4-imidazolidinacarboxílico)



Una mezcla de sal TFA de ácido 3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxílico (175 mg, 0.5 mmoles), hidrato de 1-hidroxibenzotriazol (115 mg, 0.75 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (144 mg, 0.75 mmoles), y N-etil morfolina (0.319 ml, 2.5 mmoles) en diclorometano (8 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de {[2-cloro-3-(trifluorometil)fenil]metil}amina (105 mg, 0.5 mmoles) en diclorometano (2 ml) se añade y la reacción se agita a temperatura ambiente durante 4 horas. La mezcla se divide entre diclorometano y solución saturada de carbonato ácido de sodio. La fase orgánica se separa, se lava con agua y salmuera, se seca y se evapora. El residuo se purifica por cromatografía en gel de sílice eluyendo con 0-10% metanol en diclorometano para dar N-{[2-cloro-3-

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(trifluorometil)fenil]metil}-3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida (95 mg, 44%).

LC/EM $[M+H]^+ = 427$, tiempo de retención = 1.98 minutos.

La sal de TFA de ácido 3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se preparó como sigue:

Etapa (i) se añade oxicloruro fosforoso (2.2 ml, 24 mmoles) a gotas a una solución agitada de ácido (4S)-2-oxo-3-[[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico (5.28 g, 20 mmoles) en piridina (10 ml), terc-butanol (15 ml) y cloroformo (25 ml) a -10°C . La mezcla se agita a -5°C a 0°C durante 30 minutos y después a temperatura ambiente durante 4 horas. La solución se añade a gotas a agua helada agitada (200 ml) que contiene acetato de sodio (~40 g). La mezcla se diluye con cloroformo (100 ml) y la mezcla se agita durante 30 minutos. La capa orgánica se separa, se lava con ácido clorhídrico 0.1M frío, agua, solución saturada de carbonato ácido de sodio, agua y salmuera, se seca (MgSO_4) y se evapora. El residuo se seca para proporcionar 5-(1,1-dimetiletil) 1-(fenilmetil) 2-oxo-1,5-imidazolidinacarboxilato (5.65 g, 88%) como un sólido incoloro.

LC/EM $[M+H]^+ = 321$.

[Para un método similar a esta etapa (i), ver: K. Hayashi et al., J. Med. Chem., 1989, 32(2), 289-297; por ejemplo, ver el esquema 1 y los compuestos (5) y (6a) en la página 289 en esa y síntesis del compuesto (6a) en p. 293 sección experimental en esa, incorporada aquí para referencia].

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Etapa (ii) A una solución agitada de 5-(1,1-dimetiletil) 1-(fenilmetil) 2-oxo-1,5-imidazolidinacarboxilato (4.16 g, 13 mmoles) en DMF (60 ml) a 0°C se añade hidruro de sodio (60% de dispersión en aceite) (0.546 g, 13.65 mmoles). Después de 40 minutos a 0°C se añade yodometano (4.06 ml, 65.0 mmoles) y la reacción se deja calentar a temperatura ambiente. Después de 6 horas el solvente se evapora y el residuo se divide entre acetato de etilo y agua. La fase orgánica se separa, se lava con agua y salmuera, se seca (MgSO₄) y se evapora. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo con 30-100% acetato de etilo en hexanos para proveer 4-(1,1-dimetiletil) 1-(fenilmetil) 3-(metil-2-oxo-1,4-imidazolidinacarboxilato (3.12 g, 9.33 mmoles, 72%) (LC/EM [M+H]⁺ = 335) y 5-(1,1-dimetiletil) 1-(fenilmetil) 3-metil-2-oxo-1,5-imidazolidinacarboxilato (560 mg, 1.675 mmoles, 12%) (LC/EM [M+H]⁺ = 335).

Etapa (iii) Una solución de 4-(1,1-dimetiletil) 1-(fenilmetil) 3-metil-2-oxo-1,4-imidazolidinacarboxilato (3.12 g, 9.33 mmoles) en metanol (40 ml) que contiene Pd/C (400 mg, 10% pasta) se hidrogena a temperatura ambiente y presión durante 18 horas. La mezcla se filtra a través de una almohadilla de filtro y la almohadilla se lava con metanol. Los filtrados se combinan, se evaporan y se secan para proveer 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (1.76 g, 94%).

LC/EM [M+H]⁺ = 201.

(iv) Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (300 mg, 1.5 mmoles) y 5-bromo-2-metilpiridina (258 mg, 1.5

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mmoles) en 1,4-dioxano (10 ml) se trata con carbonato de cesio (733 mg, 2.25 mmoles), XantphosTM (65.1 mg, 0.113 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (34.3 mg, 0.038 mmoles) y la mezcla se calienta bajo reflujo bajo argón durante 18 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con agua y se extrae con acetato de etilo. Las capas orgánicas se combinan, se lavan con agua y salmuera y se evapora *in vacuo*. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo con 0-10% metanol en diclorometano para dar 3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (352 mg, 81%),

LC/EM $[M+H]^+ = 292$.

Etapa (v) Una solución de 3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (352 mg, 1.2 mmoles) en TFA/DCM (1:2, 6 ml) se agita a temperatura ambiente durante 6 horas. La solución se evapora y el residuo se seca para dar ácido crudo (se asume ~ 1.2 mmoles, sal TFA) que se usa en la siguiente etapa.

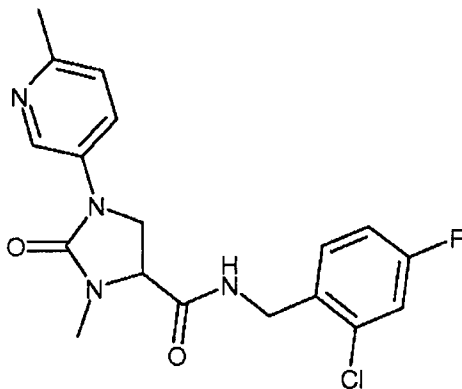
LC/EM $[M+H]^+ = 236$.

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EJEMPLO 14

N-[(2-cloro-4-fluorofenil)metil]-3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida (E14) (en una forma obtenible o preparada de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil}-4-imidazolidinacarboxílico)

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De una manera análoga a aquella descrita en el ejemplo 13 anterior N-[(2-cloro-4-fluorofenil)metil]-3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida se prepara al sustituir [(2-cloro-4-fluorofenil)metil]amina por {[2-cloro-3-(trifluorometil)fenil]metil}amina usada en el procedimiento anterior.

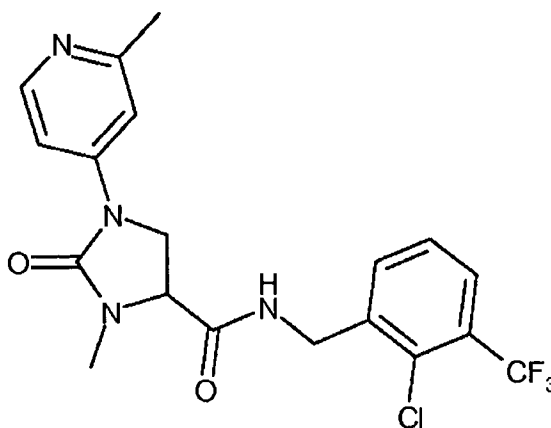
15

LC/EM $[M+H]^+ = 377$, tiempo de retención = 1.71 minutos.

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EJEMPLO 15

N-([2-cloro-3-(trifluorometil)fenil]metil)-3-metil-1-(2-metil-4-piridinil)-2-oxo-4-imidazolidinacarboxamida (E15) (en una forma obtenible o preparada de ácido (4S)-2-oxo-3-{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

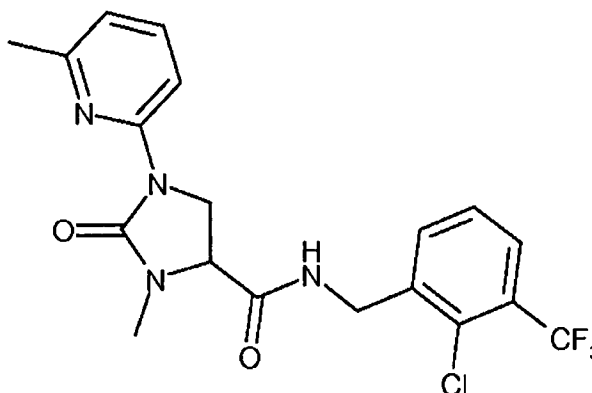


De una manera análoga a aquella descrita en el ejemplo 13 anterior N-([2-cloro-3-(trifluorometil)fenil]metil)-3-metil-1-(2-metil-4-piridinil)-2-oxo-4-imidazolidinacarboxamida se prepara al sustituir 4-bromo-2-metilpiridina por 5-bromo-2-metilpiridina usada en la etapa (iv) del procedimiento anterior.

LC/EM $[M+H]^+ = 427$, tiempo de retención = 1.91 minutos.

EJEMPLO 16

N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-1-(6-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxamida (E16) (en una forma obtenible o preparada de ácido (4S)-2-oxo-3-[[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico)



Una mezcla de sal TFA de ácido 3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxílico (147 mg, 0.42 mmoles), hidrato de 1-hidroxibenzotriazol (96 mg, 0.63 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (121 mg, 0.63 mmoles) y N-etil morfolina (0.27 ml, 2.1 mmoles) en diclorometano (8 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de {[2-cloro-3-(trifluorometil)fenil]metil}amina (88 mg, 0.42 mmoles) en diclorometano (2 ml) se añade y la reacción se agita a temperatura ambiente durante 4 horas. La mezcla se divide entre diclorometano y solución saturada de carbonato ácido de sodio. La fase orgánica se separa, se lava con agua y salmuera, se seca y se evapora. El residuo se purifica por cromatografía en gel de sílice eluyendo con 0-10% metanol en diclorometano para dar N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-1-(6-metil-2-piridinil)-2-oxo-4-

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imidazolidinacarboxamida (110 mg, 61%).

LC/EM $[M+H]^+ = 427$, tiempo de retención = 2.66 minutos.

La sal de TFA de ácido 3-metil-1-(6-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se preparó

5 como sigue:

(i) Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (300 mg, 1.5 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando con ácido (4S)-2-oxo-3-
10 {[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico) y 2-bromo-6-metilpiridina (258 mg, 1.5 mmoles) en 1,4-dioxano (10 ml) se trata con carbonato de cesio (733 g, 2.25 mmoles), XantphosTM (65.1 mg, 0.113 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (34.3 mg, 0.038 mmoles) y la mezcla se calienta a reflujo bajo argón durante 18 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con agua y se extrae
15 con acetato de etilo. Las capas orgánicas se combinan, lavan con agua y salmuera y se evapora *in vacuo*. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo con 0-100% acetato de etilo en isohexano para dar 3-metil-1-(6-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (246 mg, 56%).

20 LC/EM $[M+H]^+ = 292$.

(ii) Una solución de 3-metil-1-(6-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (246 mg, 0.84 mmoles) en TFA/DCM (1:2, 6 ml) se agita a temperatura ambiente durante 6 horas. La

solución se evapora y el residuo se seca para dar la sal TFA del ácido 3-metil-1-(6-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxílico (se asume ~ 0.84 mmoles) que se usa en la siguiente etapa.

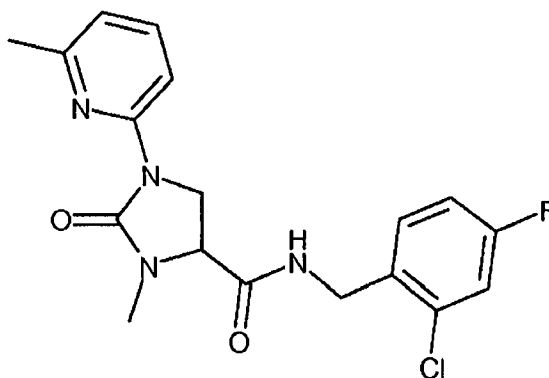
$$\text{LC/EM } [M+H]^+ = 236.$$

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EJEMPLO 17

N-[(2-cloro-4-fluorofenil)metil]-3-metil-1-(6-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxamida (E17) (en una forma obtenible o preparada de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil)-4-imidazolidinacarboxílico)

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De una manera análoga a aquella descrita en el ejemplo 16 anterior N-[(2-cloro-4-fluorofenil)metil]-3-metil-1-(6-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxamida se prepara al sustituir [(2-cloro-4-fluorofenil)metil]amina por {[2-cloro-3-(trifluorometil)fenil]metil}amina usada en el procedimiento anterior.

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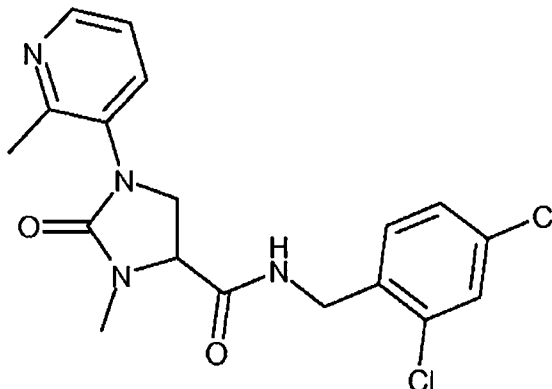
$$\text{LC/EM } [M+H]^+ = 377, \text{ tiempo de retención} = 2.33 \text{ minutos.}$$

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EJEMPLO 18

N-[(2,4-diclorofenil)metil]-3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida (E18) (en una forma obtenible o preparada de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico)

5



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Una mezcla de sal TFA de ácido 3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxílico (279 mg, 0.8 mmoles), hidrato de 1-hidroxibenzotriazol (147 mg, 0.96 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (184 mg, 0.96 mmoles) y N-etil morfolina (0.613 ml, 4.8 mmoles) en diclorometano (18 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de [1-(2,4-diclorofenil)metil]amina (141 mg, 0.8 mmoles) en diclorometano (2 ml) se añade y la reacción se agita a temperatura ambiente durante 4 horas. La mezcla se divide entre diclorometano y solución saturada de carbonato ácido de sodio. La fase orgánica se separa, se lava con agua y salmuera, se seca y se evapora. El residuo se purifica por cromatografía en gel de sílice eluyendo con 0-10% metanol en diclorometano para dar N-[(2,4-diclorofenil)metil]-3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida (147 mg, 47%).

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LC/EM $[M+H]^+ = 393$, tiempo de retención = 1.76 minutos.

Exceso enantiomérico = 95.7%, como se determina por cromatografía quiral método (C), indicativo de (4S)-N-[(2,4-diclorofenil)metil]-3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida, tiempo de retención = 8.06 minutos.

5 La sal de TFA de ácido 3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se preparó como sigue:

(i) Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (600 mg, 3.00 mmoles) (preparada como se describe en la
10 etapa (iii) del ejemplo 13) y 3-bromo-2-metilpiridina (515 mg, 3.00 mmoles) en 1,4-dioxano (20 ml) se trata con carbonato de cesio (1464 mg, 4.49 mmoles), XantphosTM (130 mg, 0.225 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (68.6 mg, 0.075 mmoles) y la mezcla se calienta a reflujo bajo argón durante
18 horas. Después del enfriamiento a temperatura ambiente, la mezcla de
15 reacción se diluye con agua y se extrae con acetato de etilo. Las capas orgánicas se combinan, lavan con agua y salmuera y se evaporan *in vacuo*. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo con 0-10% metanol en diclorometano para dar 3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (738 mg, 85%).

20 LC/EM $[M+H]^+ = 292$.

(ii) Una solución de 3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (738 mg, 2.53 mmoles) en TFA/DCM (1:2, 12 ml) se agita a temperatura ambiente durante 6 horas. La

solución se evapora y el residuo se co-evapora con tolueno y se seca para dar la sal TFA del ácido 3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxílico (se asume ~ 2.5 mmoles) que se usa en la siguiente etapa.

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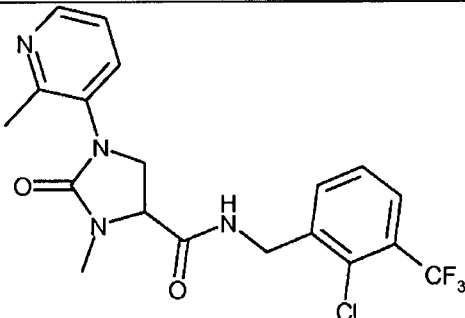
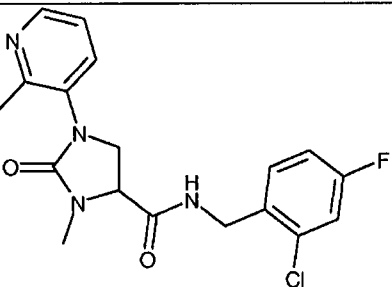
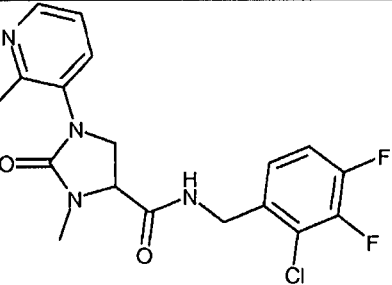
EJEMPLOS 19-22

**(En formas obtenibles o preparadas del ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)**

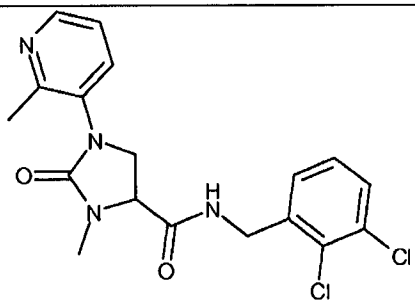
- 10 De una manera análoga a la descrita para el ejemplo 18 anterior los compuestos tabulados posteriormente (cuadro 2) se preparan al sustituir la amina apropiada (o su sal) para la [(2,4-diclorofenil)metil]amina usada en el procedimiento anterior. Todas las aminas usadas para elaborar las aminas mostradas en el cuadro 2 están disponibles de fuentes comerciales o se
- 15 pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

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CUADRO 2

No. ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (mins)
E19	 <i>N</i> -[(2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-1-(2-metil-4-piridinil)-2-oxo-4-imidazolidinacarboxamida	427	1.97
E20	 <i>N</i> -[(2-Cloro-4-fluorofenil)metil]-3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida	377	1.69
E21	 <i>N</i> -[(2-Cloro-3,4-difluorofenil)metil]-3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida	395	1.65

5

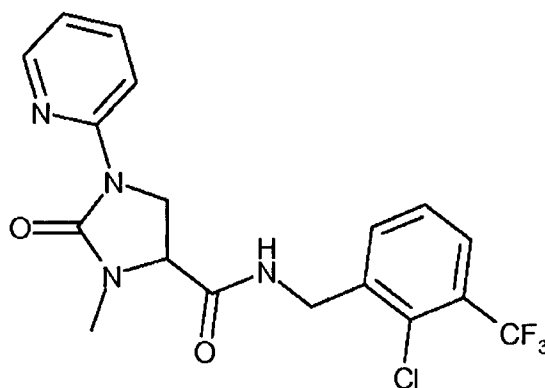
No. ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (mins)
E22	 <i>N</i> -[(2,3-Diclorofenil)metil]-3-metil-1-(2-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida	393	1.73

10

EJEMPLO 23

N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-(2-piridinil)-4-imidazolidinacarboxamida (E23) (en una forma obtenible o preparada de ácido (4*S*)-2-oxo-3-[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

15



20

Una mezcla de sal TFA de ácido 3-metil-2-oxo-1-(2-piridinil)-4-imidazolidinacarboxílico (117 mg, 0.35 mmoles), hidrato de 1-hidroxibenzotriazol (80 mg, 0.525 mmoles), clorhidrato de 1-etil-3-(3-

dimetilaminopropil)carbodiimida (101 mg, 0.525 mmoles) y N-etil morfolina (0.224 ml, 1.75 mmoles) en diclorometano (8 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de {[2-cloro-3-(trifluorometil)fenil]metil}amina (73.4 mg, 0.35 mmoles) en diclorometano (2 ml) se añade y la reacción se agita a temperatura ambiente durante 18 horas. La mezcla se divide entre diclorometano y solución saturada de carbonato ácido de sodio. La fase orgánica se separa, se lava con agua y salmuera, se seca y se evapora. El residuo se purifica por cromatografía en gel de sílice eluyendo con 0-10% metanol en diclorometano para dar N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-(2-piridinil)-4-imidazolidinacarboxamida (90 mg, 62%).

LC/EM $[M+H]^+ = 413$, tiempo de retención = 2.55 minutos.

La sal de TFA de ácido 3-metil-2-oxo-1-(2-piridinil)-4-imidazolidinacarboxílico usada en el método descrito anteriormente se preparó como sigue:

(i) Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (400 mg, 2 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13) y 2-bromopiridina (316 mg, 2 mmoles) en 1,4-dioxano (10 ml) se trata con carbonato de cesio (977 g, 3 mmoles), XantphosTM (87 mg, 0.15 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (45.8 mg, 0.05 mmoles) y la mezcla se calienta a reflujo bajo argón durante 18 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con agua y se extrae con acetato de etilo. Las capas orgánicas se combinan,

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lavan con agua y salmuera y se evapora *in vacuo*. El residuo se purifica por medio de cromatografía en gel de sílice eluyendo con 0-100% acetato de etilo en isohexano (se requieren 2 columnas) para dar 3-metil-2-oxo-1-(2-piridinil)-4-imidazolidinacarboxilato de 1,1-dimetiletilo (198 mg, 36%).

5 LC/EM $[M+H]^+ = 278$.

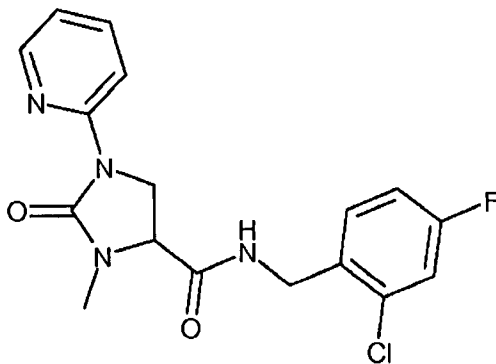
(ii) Una solución de 3-metil-2-oxo-1-(2-piridinil)-4-imidazolidinacarboxilato de 1,1-dimetiletilo (198 mg, 0.71 mmoles) en TFA/DCM (1:2, 4.5 ml) se agita a temperatura ambiente durante 8 horas. La solución se evapora y el residuo se seca para dar la sal TFA del ácido 3-metil-
10 2-oxo-1-(2-piridinil)-4-imidazolidinacarboxílico (se asume ~ 0.71 mmoles) que se usa en la siguiente etapa.

LC/EM $[M+H]^+ = 222$.

EJEMPLO 24

15 N-[(2-cloro-4-fluorofenil)metil]-3-metil-2-oxo-1-(2-piridinil)-4-imidazolidinacarboxamida (E24) (en una forma obtenible o preparada de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico)

20



De una manera análoga a aquella descrita en el ejemplo 23

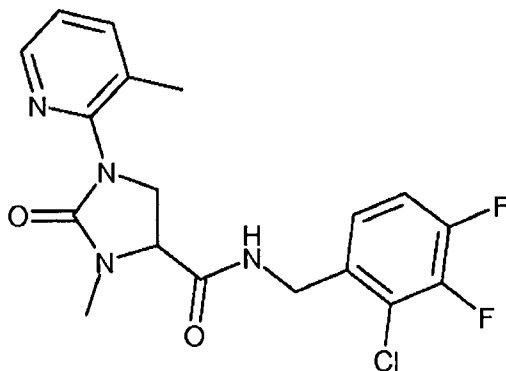
250

anterior N-[(2-cloro-4-fluorofenil)metil]-3-metil-2-oxo-1-(2-piridinil)-4-imidazolidinacarboxamida se prepara al sustituir [(2-cloro-4-fluorofenil)metil]amina por {[2-cloro-3-(trifluorometil)fenil]metil}amina usada en el procedimiento anterior.

5 LC/EM $[M+H]^+ = 363$, tiempo de retención = 2.21 minutos.

EJEMPLO 25

N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-(3-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxamida (E25) (en una forma obtenible o preparada de
 10 ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico)



15

Una mezcla de sal TFA de ácido 3-metil-1-(3-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxílico (279 mg, 0.8 mmoles), hidrato de 1-hidroxibenzotriazol (147 mg, 0.96 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (184 mg, 0.96 mmoles) y N-etil morfolina (0.613 ml, 4.8 mmoles) en diclorometano (20 ml) se agita a temperatura ambiente durante 10 minutos. Clorhidrato de [(2-cloro-3,4-difluorofenil)metil]amina (171 mg, 0.8 mmoles) se añade y la reacción se agita a temperatura ambiente durante 18 horas. La mezcla se diluye con

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diclorometano y se lava con solución de ácido cítrico 3N. La fase orgánica se separa, se lava con salmuera, se seca y se evapora. El residuo se purifica por HPLC automatizada dirigida por masa para dar N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-(3-metil-2-piridinil)-2-oxo-4-

5 imidazolidinacarboxamida (145 mg, 46%).

LC/EM $[M+H]^+ = 395$, tiempo de retención = 2.36 minutos.

La sal de TFA de ácido 3-metil-1-(3-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se preparó como sigue:

10 (i) Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (600 mg, 3 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando con ácido (4S)-2-oxo-3-[[{(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico) y 2-bromo-3-metilpiridina (515 mg, 3 mmoles) en 1,4-dioxano (20 ml) se trata con carbonato de cesio (1464 mg, 4.5 mmoles),
15 XantphosTM (130 mg, 0.225 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (68.6 mg, 0.075 mmoles) y la mezcla se calienta a reflujo bajo argón durante 18 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con agua y se extrae con acetato de etilo. Las capas orgánicas se combinan, lavan con agua y salmuera y se evaporan *in vacuo*. El
20 residuo se purifica por medio de cromatografía en gel de sílice eluyendo con 0-100% acetato de etilo en isohexano para dar 3-metil-1-(3-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (700 mg, 80%).

LC/EM $[M+H]^+ = 292$.

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(ii) Una solución de 3-metil-1-(3-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (700 mg, 2.4 mmoles) en TFA/DCM (1:2, 12 ml) se agita a temperatura ambiente durante 6 horas. La solución se evapora y el residuo se co-evapora con tolueno y se seca para dar la sal TFA del ácido 3-metil-1-(3-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxílico (se
5 asume ~ 2.4 mmoles) que se usa en la siguiente etapa.

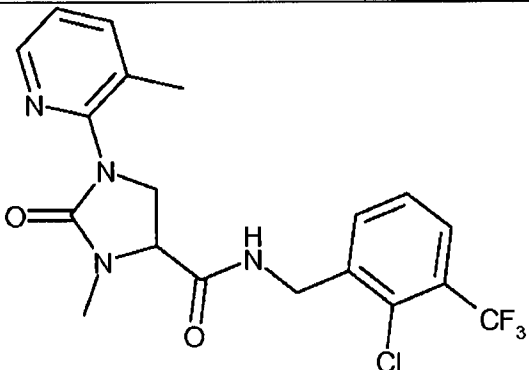
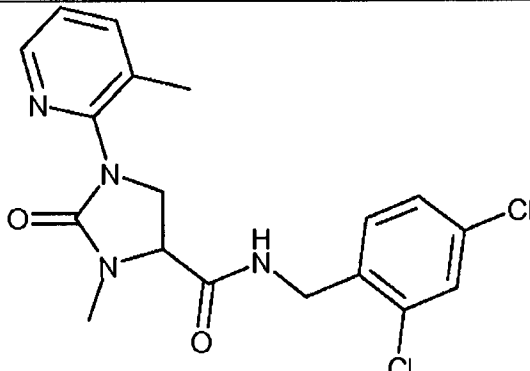
LC/EM $[M+H]^+ = 236$.

EJEMPLOS 26-27

10 (En formas obtenibles o preparadas del ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

De una manera análoga a la descrita para el ejemplo 25 anterior los compuestos tabulados posteriormente (cuadro 3) se preparan al sustituir la
15 amina apropiada (o su sal) para el clorhidrato de [(2-cloro-3,4-difluorofenil)metil]amina usado en el procedimiento anterior. Todas las aminas usadas para elaborar las aminas mostradas en el cuadro 3 están disponibles de fuentes comerciales o se pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

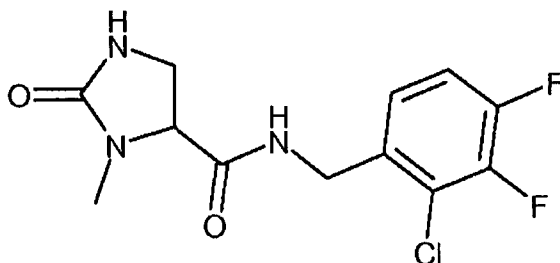
CUADRO 3

No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E26	 N-[(2-cloro-3-(trifluorometil)fenil)metil]-3-metil-1-(3-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxamida	427	2.54
E27	 N-[(2,4-diclorofenil)metil]-3-metil-1-(3-metil-2-piridinil)-2-oxo-4-imidazolidinacarboxamida	393	2.47

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EJEMPLO 28

N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-4-
imidazolidinacarboxamida (E28) (en una forma obtenible o preparada a
partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil}-4-
imidazolidinacarboxílico)



Una mezcla de ácido 3-metil-2-oxo-4-imidazolidinacarboxílico (115 mg, 0.8 mmoles), hidrato de 1-hidroxibenzotriazol (147 mg, 0.96 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (184 mg, 0.96 mmoles) y N-etilmorfolina (0.613 ml, 4.8 mmoles) en diclorometano (18 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de [(2-cloro-3,4-difluorofenil)metil]amina (142 mg, 0.8 mmoles) en diclorometano (2 ml) se añade y la reacción se agita a temperatura ambiente durante 18 horas. La mezcla se diluye con diclorometano (60 ml) y la mezcla se lava con solución de ácido cítrico 3N (30 ml). La fase orgánica se separa, se lava con salmuera, se seca y se evapora. El residuo se purifica mediante HPLC automatizada dirigida de masa para proporcionar N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (95 mg, 39%).

LC/EM $[M+H]^+ = 304$, tiempo de retención = 1.99 minutos.

El ácido 2-metil-2-oxo-4-imidazolidina usado en el método

25

descrito anteriormente se prepara como sigue:

Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (801 mg, 4 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-
5 {[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico) en TFA/DCM (ácido trifluoroacético/diclorometano) (1:2, 9 ml) se agita a temperatura ambiente durante 6 horas. La solución se evapora, el residuo se co-evapora con tolueno y se seca para proporcionar ácido 3-metil-2-oxo-4-imidazolidinacarboxílico crudo (asume ~4 mmoles) que se usa en la siguiente etapa.

10 LC/EM $[M+H]^+ = 145$.

EJEMPLO 29-30

(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-

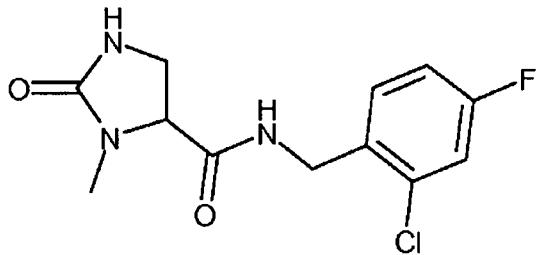
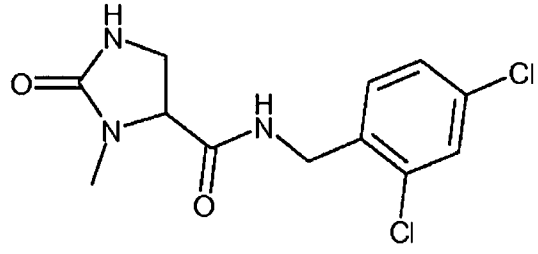
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

15

En una manera análoga a la que se describe para el ejemplo 28 anterior los compuestos tabulados posteriormente (cuadro 4) se preparan mediante la sustitución de la amina apropiada (o su sal) por la [(2-cloro-3,4-difluorofenil)metil]amina usada en el procedimiento anterior. Todas las aminas
20 usadas para producir las aminas mostradas en el cuadro 4 son disponibles de fuentes comerciales o se pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

256

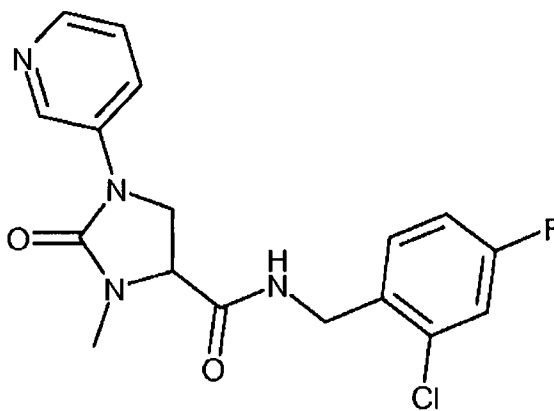
CUADRO 4

No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E29	 N-[(2-cloro-4-fluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida	286	1.89
E30	 N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida	302	2.10

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EJEMPLO 31

N-[(2-cloro-4-fluorofenil)metil]-3-metil-2-oxo-1-(3-piridinil)-4-
imidazolidinacarboxamida (E31) (en una forma obtenible o preparada a
partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil}-4-
imidazolidinacarboxílico)



Una solución de N-[(2-cloro-4-fluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (28.6 mg, 0.1 mmoles) (preparada como se describe en el ejemplo 29) y 3-bromopiridina (15.8 mg, 0.1 mmoles) en 1,4-dioxano (3 ml) se trata con carbonato de cesio (81 mg, 0.25 mmoles), Xantphos™ (4.3 mg, 0.075 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (2.3 mg, 0.025 mmoles) y la mezcla se calienta a reflujo bajo argón durante 18 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con solución saturada de carbonato ácido de sodio y se extrae con diclorometano. Las capas orgánicas se combinan, se lavan con agua y salmuera y se evaporan *in vacuo*. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 0-10% de metanol en diclorometano. El residuo resultante se tritura con éter, el sólido se colecta y

256

se seca para proporcionar N-[(2-cloro-4-fluorofenil)metil]-3-metil-2-oxo-1-(3-piridinil)-4-imidazolidinacarboxamida (18 mg, 50%).

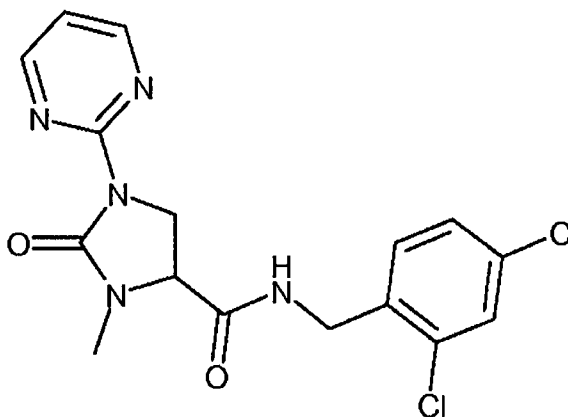
LC/EM $[M+H]^+ = 363$, tiempo de retención 1.68 minutos.

5

EJEMPLO 32

N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida (E32) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico)

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Una mezcla de sal TFA del ácido 3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida (168 mg, 0.5 mmoles), hidrato de 1-hidroxibenzotriazol (101 mg, 0.75 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (144 mg, 0.75 mmoles) y N-etil morfolina (0.316 ml, 2.5 mmoles) en diclorometano (8 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de [1-(2,4-diclorofenil)metil]amina (0.067 ml, 0.5 mmoles) en diclorometano (2 ml) se añade y la reacción se agita a temperatura ambiente durante 4 horas. La mezcla se divide entre

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diclorometano y carbonato ácido de sodio saturado, la fase orgánica se separa, se lava con agua y salmuera, se seca y se evapora. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 0-10% de metanol en diclorometano para proporcionar N-[(2,4-diclorofenil)metil]-3-metil-
5 2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida (20 mg, 10.5% de rendimiento).

LC/EM $[M+H]^+ = 380$, tiempo de retención = 2.22 minutos.

La sal TFA del ácido 3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxílico usada en el método descrito anteriormente se prepara
10 como sigue:

(i) Una solución de 3-metil-2-oxo-4-imidazoldinacarboxilato de 1,1-dimetiletilo (801 mg, 4 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-
15 {[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico) y 2-bromopiridina (636 mg, 4 mmoles) en 1,4-dioxano (20 ml) se trata con carbonato de cesio (1955 mg, 6 mmoles), Xantphos™ (174 mg, 0.3 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (92 mg, 0.1 mmoles) y la mezcla se calienta a reflujo bajo argón durante 1 hora. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con agua y se extrae
20 con acetato de etilo. Las capas orgánicas combinadas, se lavan con agua y salmuera y se evaporan *in vacuo*. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 0-20% de metanol en acetato de etilo para 3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxilato de 1,1-

260

dimetiletilo (360 mg, 32%).

LC/EM $[M+H]^+ = 279$.

(ii) Una solución de 3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxilato de 1,1-dimetiletilo (0.557 g, 2 mmoles) en TFA/DCM
5 (1:2, 7.5 ml) se agita a temperatura ambiente durante 6 horas. La solución se evapora y el residuo se seca para proporcionar sal TFA del ácido (4S)-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxílico (asume ~ 2 mmoles) que se usa en la siguiente etapa.

LC/EM $[M+H]^+ = 223$.

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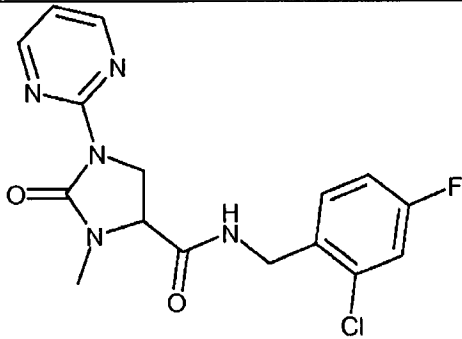
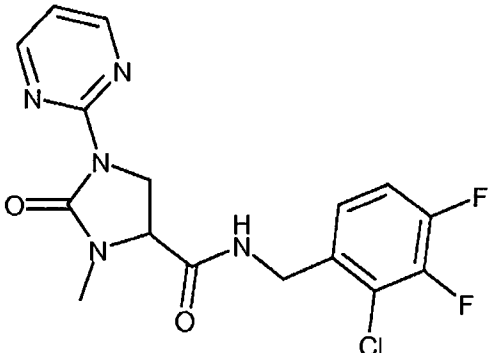
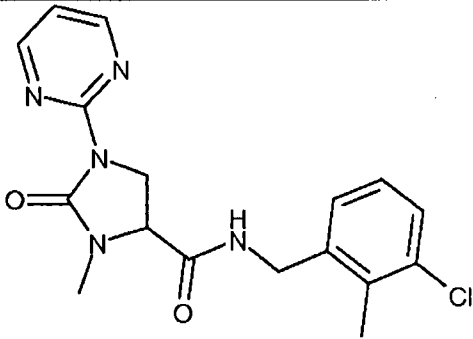
EJEMPLOS 33-35

(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
11 {[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

15 En una manera análoga a la que se describe para el ejemplo 32 anterior los compuestos tabulados posteriormente (cuadro 5) se preparan mediante la sustitución de la amina apropiada (o su sal) por la [1-(2,4-diclorofenil)metil]amina usada en el procedimiento anterior. Todas las aminas
usadas para producir las aminas mostradas en el cuadro 5 son disponibles de
20 fuentes comerciales o se pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

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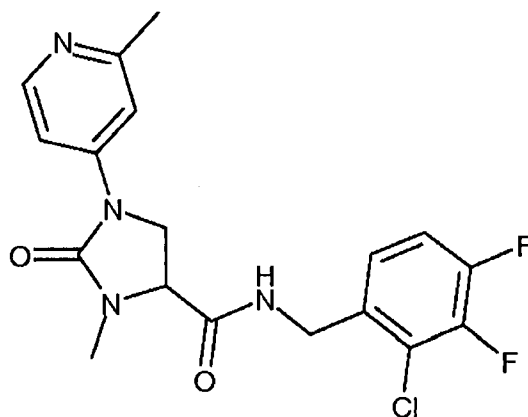
CUADRO 5

No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E33	 N-[(2-cloro-4-fluorofenil)metil]-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida	366	2.03
E34	 N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida	382	2.11
E35	 N-[(3-cloro-2-metilfenil)metil]-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida	360	2.18

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EJEMPLO 36

N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-(2-metil-4-piridinil)-2-oxo-4-imidazolidinacarboxamida (E36) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico)



Una solución de N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (152 mg, 0.5 mmoles) (preparada como se describe en el ejemplo 28) y 4-bromo-2-metilpiridina (86 mg, 0.5 mmoles) en 1,4-dioxano (3 ml) se trata con carbonato de cesio (244 mg, 0.75 mmoles), Xantphos™ (21.7 mg, 0.038 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (11.5 mg, 0.013 mmoles) y la mezcla se calienta a reflujo bajo argón durante 3 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con solución saturada de carbonato ácido de sodio y se extrae con diclorometano. Las capas orgánicas se combinan, se lavan con agua y salmuera y se evaporan *in vacuo*. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 0-10% de metanol en diclorometano. El residuo resultante se tritura con éter, el sólido se colecta y

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se seca para proporcionar N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-(2-metil-4-piridinil)-2-oxo-4-imidazolidinacarboxamida (123 mg, 62%).

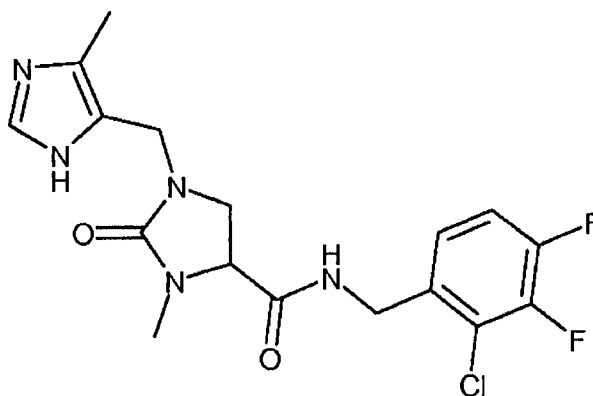
LC/EM $[M+H]^+ = 395$, tiempo de retención = 1.68 minutos.

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EJEMPLO 37

N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-[(4-metil-1H-imidazol-5-il)metil]-2-oxo-4-imidazolidinacarboxamida (E37) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico)

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Una solución de N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (152 mg, 0.5 mmoles) (preparada como se describe en el ejemplo 28), clorhidrato de (4-metil-1H-imidazol-5-il)metanol (93 mg, 0.625 mmoles) y ácido p-tolueno sulfónico monohidratado (19 mg, 0.100 mmoles) en N-metil-2-pirrolidona (1 ml) se calienta a 130°C bajo argón durante 3 horas. La mezcla de reacción se enfría a temperatura ambiente y se diluye con diclorometano. La solución se lava con solución saturada de carbonato ácido de sodio y salmuera, se seca y se evapora. El residuo se

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purifica mediante HPLC automática dirigida de masa, seguido por la trituración con éter para proporcionar N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-[(4-metil-1H-imidazol-5-il)metil]-2-oxo-4-imidazolidinacarboxamida (147 mg, 74%).

LC/EM $[M+H]^+ = 398$, tiempo de retención = 1.57 minutos.

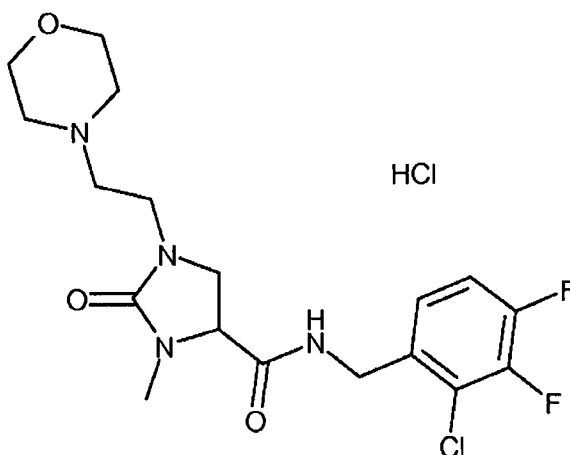
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EJEMPLO 38

Clorhidrato de N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-[2-(4-morfolinil)etil]-2-oxo-4-imidazolidinacarboxamida (E38)

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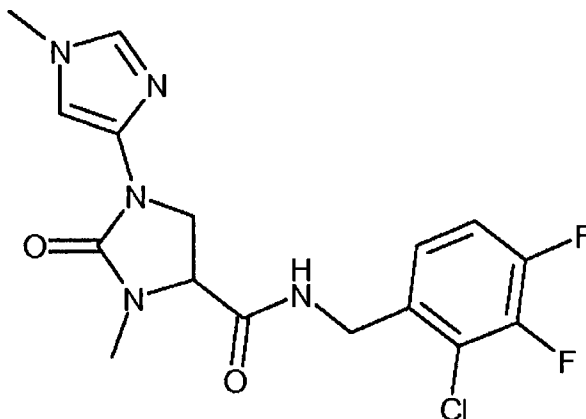
Una mezcla de N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (100 mg, 0.33 mmoles) (preparada como se describe en el ejemplo 28) y carbonato de potasio (91 mg, 0.66 mmoles) en DMF (1 ml) se agita a temperatura ambiente durante 10 minutos y clorhidrato de 4-(2-cloroetil)morfolina (61 mg, 0.33 mmoles) se añade. La mezcla se agita durante 30 minutos y después se calienta a 60°C durante 3 horas y 80°C durante 2 horas. La mezcla se enfría a temperatura ambiente e hidruro de sodio (40 mg, 60% de dispersión en aceite, 1 mmoles) se añade y la mezcla

se calienta a 50°C durante 16 horas. La mezcla de reacción se enfría a temperatura ambiente y se diluye con diclorometano. La solución se lava con solución saturada de carbonato ácido de sodio y salmuera, se seca y se evapora. El residuo se purifica mediante HPLC automática dirigida de masa para proporcionar dos componentes con el mismo ion molecular. Cada componente se convierte a la sal de HCl correspondiente al disolver el producto de HPLC automatizada dirigida de masa en metanol/diclorometano, la adición de un exceso de HCl 1M en éter, la evaporación del solvente, la co-evaporación del residuo con metanol y éter. El residuo se tritura con éter/heptano y el sólido se colecta y se seca para proporcionar clorhidrato de N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-[2-(4-morfolinil)etil]-2-oxo-4-imidazolidinacarboxamida (22 mg, 15%) (LC/EM $[M+H]^+$ = 417, tiempo de retención = 1.40 minutos) y clorhidrato de N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-[2-(4-morfolinil)etil]-2-oxo-4-imidazolidinacarboxamida (6 mg, 4%) (LC/EM $[M+H]^+$ = 417, tiempo de retención = 1.55 minutos).

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EJEMPLO 39

N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida (E39) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil}-4-imidazolidinacarboxílico)



A una mezcla agitada de N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (100 mg, 0.33 mmoles) (preparada como se describe en el ejemplo 28), 4-bromo-1-metil-1H-imidazol (63.8 mg, 0.396 mmoles) en 1,4-dioxano (6 ml) se añade fosfato de potasio (350 mg, 1.65 mmoles), yoduro de cobre (I) (62.8 mg, 0.33 mmoles) y trans-N,N-dimetilciclohexano-1,2-diamina (0.052 ml, 0.33 mmoles) y la mezcla se calienta a reflujo bajo argón durante 1 hora. La mezcla se enfría a temperatura ambiente y se divide entre solución saturada de carbonato ácido de sodio y diclorometano. Los extractos orgánicos se separan, se lavan con agua y salmuera, se secan y se evaporan. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 0-20% de metanol en diclorometano, seguido por HPLC automatizada dirigida de masa para

proporcionar N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida (15 mg, 12%).

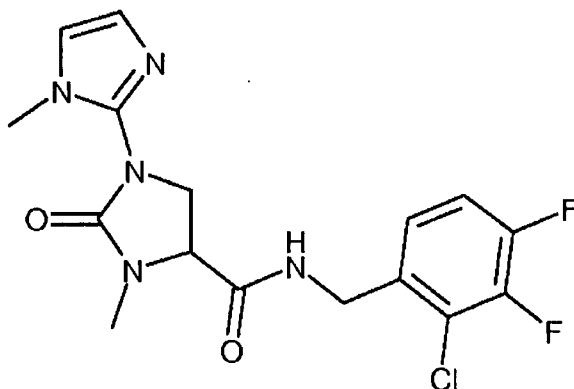
LC/EM $[M+H]^+ = 384$, tiempo de retención = 1.71 minutos.

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EJEMPLO 40

N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-imidazolidinacarboxamida (E40) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

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A una mezcla agitada de N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (91 mg, 0.3 mmoles) (preparada como se describe en el ejemplo 28) y 2-bromo-1-metil-1H-imidazol (48.3 mg, 0.3 mmoles) en 1,4-dioxano (6 ml) se añade fosfato de potasio (318 mg, 1.5 mmoles), yoduro de cobre (I) (57.1 mg, 0.3 mmoles) y trans-N,N-dimetilciclohexano-1,2-diamina (0.047 ml, 0.3 mmoles) y la mezcla se calienta a reflujo bajo argón durante 3 horas. La mezcla se enfría a temperatura ambiente y se divide entre solución saturada de carbonato ácido de sodio y

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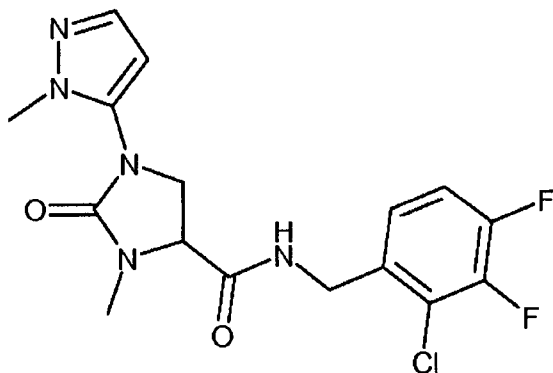
diclorometano. Los extractos orgánicos se separan, se lavan con agua y salmuera, se secan y se evaporan. El residuo se purifica por HPLC automatizada dirigida de masa para proporcionar N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-

5 imidazolidinacarboxamida (22 mg, 19%).

LC/EM $[M+H]^+ = 384$, tiempo de retención = 1.69 minutos.

EJEMPLO 41

10 N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-(1-metil-1H-pirazol-5-il)-2-oxo-4-imidazolidinacarboxamida (E41) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil)-4-imidazolidinacarboxílico)



20 A una solución agitada de N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (60.7 mg, 0.2 mmoles) (preparada como se describe en el ejemplo 28), 5-yodo-1-metil-1H-pirazol (41.6 mg, 0.2 mmoles) en 1,4-dioxano (4 ml) se añade fosfato de potasio (212 mg, 1 mmoles), yoduro de cobre (I) (38.1 mg, 0.2 mmoles) y trans-N,N-

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dimetilciclohexano-1,2-diamina (0.032 ml, 0.2 mmoles) y la mezcla se calienta a reflujo bajo argón durante 1h. La mezcla se enfría a temperatura ambiente y se divide entre solución saturada de carbonato ácido de sodio y diclorometano. Los extractos orgánicos se separan, se lavan con agua y salmuera, se secan y se evaporan. El residuo se purifica por HPLC automatizada dirigida de masa para proporcionar N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-(1-metil-1H-pirazol-5-il)-2-oxo-4-imidazolidinacarboxamida (18 mg, 23%).

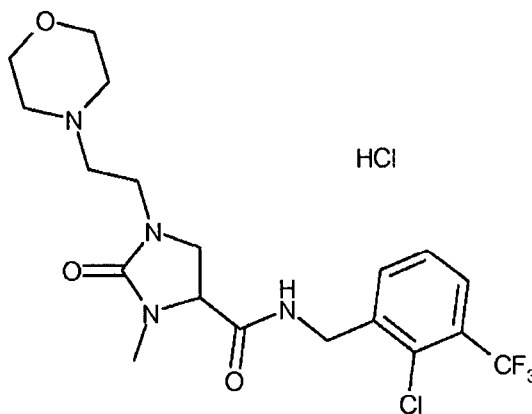
LC/EM $[M+H]^+ = 384$, tiempo de retención = 2.22 minutos.

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EJEMPLO 42

Clorhidrato de N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-1-[2-(4-morfolinil)etil]-2-oxo-4-imidazolidinacarboxamida (E42)

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Una mezcla de sal TFA del ácido 3-metil-1-[2-(4-morfolin)etil]-2-oxo-4-imidazolidinacarboxílico (186 mg, 0.5 mmoles), N-etil morfolina (0.383 ml, 3 mmoles), hidrato de 1-hidroxibenzotriazol (92 mg, 0.6 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (115 mg, 0.6 mmoles) en diclorometano (9 ml) se agita a temperatura ambiente durante 10 minutos.

Una solución de {[2-cloro-3-(trifluorometil)fenil]metil}amina (105 mg, 0.5 mmoles) en diclorometano (1 ml) se añade y la reacción se agita a temperatura ambiente durante 18 horas. La mezcla se diluye con diclorometano y se lava con solución saturada de carbonato ácido de sodio.

- 5 La fase orgánica se separa, se lava con salmuera, se seca y se evapora. El residuo se purifica mediante HPLC automatizada dirigida de masa. El producto de HPLC automatizada dirigida de masa se disuelve en metanol (2 ml) y un exceso de cloruro de hidrógeno 1M en éter (0.5 ml) se añade. El solvente se evapora, el residuo se tritura con éter y el sólido se colecta y se
- 10 seca para proporcionar clorhidrato de N-[[2-cloro-3-(trifluorometil)fenil]metil]-3-metil-1-[2-(4-morfolinil)etil]-2-oxo-4-imidazolidinacarboxamida (73 mg, 30%).

LC/EM $[M+H]^+ = 449$, tiempo de retención = 1.80 minutos.

- La sal de TFA de ácido 3-metil-1-[2-(4-morfolinil)etil]-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara
- 15 como sigue:

- (i) A una solución agitada de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (1.0 g, 5 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13) en N,N-dimetilformamida (20 ml) a 0°C se añade hidruro de sodio (60% de dispersión en aceite) (220 mg, 5.5
- 20 mmoles). Después de 10 minutos una solución de 4-(2-cloroetil)morfolina (898 mg, 6 mmoles) en N,N-dimetilformamida (2 ml) y yoduro de potasio (166 mg, 1 mmoles) se añade y la mezcla se calienta a 70°C durante 2 horas. Después del enfriamiento a temperatura ambiente se añade agua y la mezcla se divide

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entre solución saturada de carbonato ácido de sodio y diclorometano. Los extractos orgánicos se separan, se lava con agua y salmuera, se secan y se evaporan. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 5-10% de amoniaco 2M en metanol y diclorometano para proporcionar 1,1-dimetiletil-3-metil-1-[2-(4-morfolinil)etil]-2-oxo-4-imidazolidinacarboxilato (740 mg, 47%) como un aceite.

$$\text{LC/EM } [M+H]^+ = 314.$$

(ii) Una solución de 1,1-dimetiletil-3-metil-1-[2-(4-morfolin)etil]-2-oxo-4-imidazolidinacarboxilato (740 mg, 2.361 mmoles) en TFA/DCM (1:2, 6 ml) se agita a temperatura ambiente durante 5 horas. La solución se evapora y el residuo se co-evapora con DCM y se seca para proporcionar sal de TFA del ácido 3-metil-1-[2-(4-morfolinil)etil]-2-oxo-4-imidazolidinacarboxílico (asume ~ 2.3 mmoles) que se usa en la siguiente etapa.

$$\text{LC/EM } [M+H]^+ = 258.$$

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EJEMPLOS 43-44

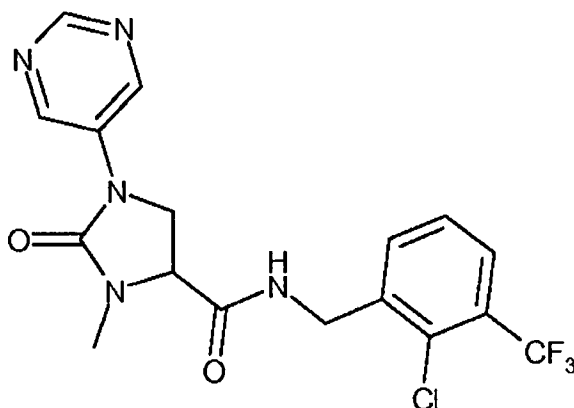
En una manera análoga a la que se describe para el ejemplo 42 anterior los compuestos tabulados posteriormente (cuadro 6) se preparan mediante la sustitución de la amina apropiada (o su sal) por la {[2-cloro-3-(trifluorometil)fenil]metil}amina usada en el procedimiento anterior. Todas las aminas usadas para producir las aminas mostradas en el cuadro 6 son disponibles de fuentes comerciales o se pueden preparar usando rutas

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EJEMPLO 45

N-([2-cloro-3-(trifluorometil)fenil]metil)-3-metil-2-oxo-1-(5-pirimidinil)-4-imidazolidinacarboxamida (E45) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-([(fenilmetil)oxi]carbonil)-4-imidazolidinacarboxílico)



Una solución de ácido 3-metil-2-oxo-1-(5-pirimidinil)-4-imidazolidinacarboxílico (0.6 mmoles) en diclorometano (6 ml) se trata con N-etil morfolina (0.460 ml, 3.60 mmoles), hidrato de 1-hidroxibenzotriazol (110 mg, 0.720 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (138 mg, 0.720 mmoles) y la mezcla se agita a temperatura ambiente durante 10 minutos. Una solución de {[2-cloro-3-(trifluorometil)fenil]metil}amina (126 mg, 0.600 mmoles) en diclorometano (1 ml) se añade y la reacción agitada a temperatura ambiente durante 3 horas. La mezcla se diluye con diclorometano y la solución se lava con ácido cítrico 3N, agua, solución saturada de bicarbonato de sodio y salmuera, se seca y se evapora. El residuo se purifica por HPLC automatizada dirigida de masa para proporcionar N-([2-cloro-3-(trifluorometil)fenil]metil)-3-metil-2-oxo-1-(5-pirimidinil)-4-

imidazolidinacarboxamida (54 mg, 22%).

LC/EM $[M+H]^+ = 414$, tiempo de retención 2.37 minutos.

El ácido 3-metil-2-oxo-1-(5-pirimidinil)-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

- 5 (i) Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (601 mg, 3 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-
10 {[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico y 5-bromopirimidina (477 mg, 3.00 mmoles) en 1,4-dioxano (20 ml) se trata con carbonato de cesio (1466 mg, 4.50 mmoles), Xantphos™ (130 mg, 0.225 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (68.7 mg, 0.075 mmoles) y la mezcla se calienta a reflujo bajo argón durante 3 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con agua y se extrae con acetato de etilo. Las capas orgánicas se combinan, se lavan con agua y
15 salmuera y se evaporan *in vacuo*. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 0-100% de acetato de etilo en isohexano para proporcionar 3-metil-2-oxo-1-(5-pirimidinil)-4-imidazolidinacarboxilato de 1,1-dimetiletilo (349 mg, 42%).

LC/EM $[M+H]^+ = 279$.

- 20 (ii) Una solución de 3-metil-2-oxo-1-(5-pirimidinil)-4-imidazolidinacarboxilato de 1,1-dimetiletilo (630 mg, 2.264 mmoles) en TFA/DCM (1:2, 9 ml) se agita a temperatura ambiente durante 8 horas. La solución se evapora y el residuo se co-evapora con tolueno y se seca para

proporcionar ácido 3-metil-2-oxo-1-(5-pirimidinil)-4-imidazolidinacarboxílico (asume ~ 2.2 mmoles) que se usa en la siguiente etapa.

LC/EM $[M+H]^+ = 223$.

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EJEMPLOS 46-47

**(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
{{{(fenilmetil)oxi}carbonil}-4-imidazolidinacarboxílico)**

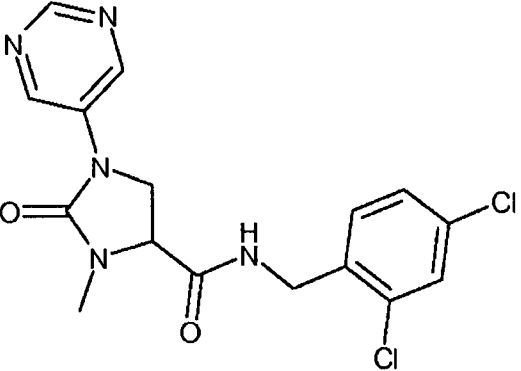
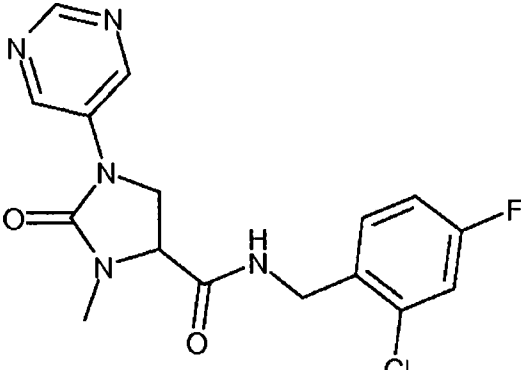
En una manera análoga a la que se describe para el ejemplo 45

10 anterior los compuestos tabulados abajo (cuadro 7) se preparan mediante la sustitución de la amina apropiada (o su sal) por la {[2-cloro-3-(trifluorometil)fenil]metil}amina usada en el procedimiento anterior. Todas las aminas usadas para producir las aminas mostradas en el cuadro 7 son

15 descritas previamente en la literatura química o métodos análogos.

p. 16

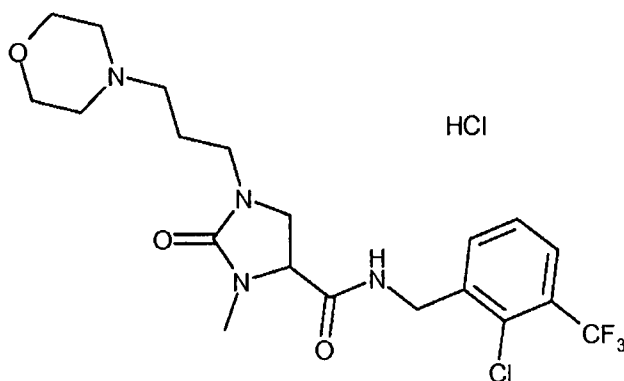
CUADRO 7

No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E46	 N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-1-(5-pirimidinil)-4-imidazolidinacarboxamida	380	2.28
E47	 N-[(2-cloro-4-fluorofenil)metil]-3-metil-2-oxo-1-(5-pirimidinil)-4-imidazolidinacarboxamida	364	2.08

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EJEMPLO 48**Clorhidrato de N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-1-[3-(4-morfolin)propil]-2-oxo-4-imidazolidinacarboxamida (E48)**

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En una manera análoga a la que se describe en el ejemplo 42 anterior clorhidrato de N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-1-[3-(4-morfolinil)propil]-2-oxo-4-imidazolidinacarboxamida se prepara mediante la sustitución de 4-(3-cloropropil)morfolina por 4-(2-cloroetil)morfolina usada en la etapa (i) del ejemplo 42 del procedimiento.

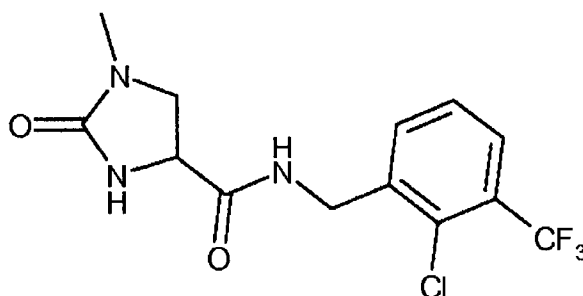
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LC/EM $[M+H]^+ = 463$, tiempo de retención = 1.82 minutos.

778

EJEMPLO 49

N-[[2-cloro-3-(trifluorometil)fenil]metil]-1-metil-2-oxo-4-
imidazolidinacarboxamida (E49) (en una forma obtenible o preparada a
partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-
imidazolidinacarboxílico)



Una mezcla de ácido 1-metil-2-oxo-4-imidazolidinacarboxílico (144 mg, 1 mmoles), N-etil morfolina (0.767 ml, 6.00 mmoles), hidrato de 1-hidroxibenzotriazol (184 mg, 1.200 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (230 mg, 1.200 mmoles) en diclorometano (18 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de [[2-cloro-3-(trifluorometil)fenil]metil]amina (210 mg, 1.000 mmoles) en diclorometano (2 ml) se añade y la reacción se agita a temperatura ambiente durante horas. La mezcla se diluye con diclorometano y la mezcla se lava con solución de ácido cítrico 3N. La fase orgánica se separa, se lava con salmuera, se seca y se evapora. El residuo se purifica mediante HPLC automatizada dirigida de masa para proporcionar la N-[[2-cloro-3-(trifluorometil)fenil]metil]-1-metil-2-oxo-4-imidazolidinacarboxamida (150 mg, 55%).

LC/EM $[M+H]^+ = 336$, tiempo de retención = 2.22 minutos.

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El ácido 1-metil-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) Una solución de 3-metil-2-oxo-1,5-imidazolidinadicarboxilato de 5-(1,1-dimetiletil) 1-(fenilmetilo) (3.8 g, 11.36 mmoles) (preparada como se describe en la etapa (ii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil] 4-imidazolidinacarboxílico) en metanol (50 ml) que contiene Pd/C (10% de pasta, 400 mg) se hidrogena a temperatura y presión ambiente durante 18 horas. La mezcla se filtra a través de una almohadilla de filtro y la almohadilla se lava con metanol. Los filtrados se combinan, se evaporan y se secan para proporcionar 1-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (1.001 g, 5 mmoles) (2.17 g, 95%).

LC/EM $[M+H]^+ = 201$.

(ii) Una solución de 1-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (1.001 g, 5 mmoles) en TFA/DCM (1:2, 7.5 ml) se agita a temperatura ambiente durante 6 horas. La solución se evapora y el residuo se seca para proporcionar ácido 1-metil-2-oxo-4-imidazolidinacarboxílico crudo (asume 5 mmoles), que se usa en la siguiente etapa.

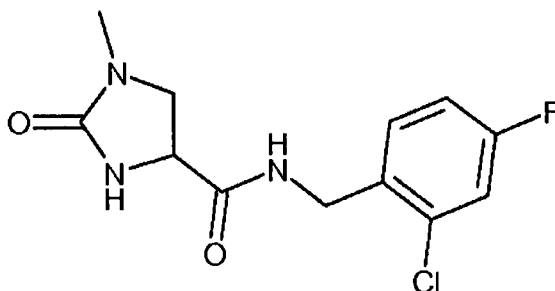
LC/EM $[M+H]^+ = 145$.

280

EJEMPLO 50

N-[(2-cloro-4-fluorofenil)metil]-1-metil-2-oxo-4-imidazolidinacarboxamida
**(E50) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)**

5



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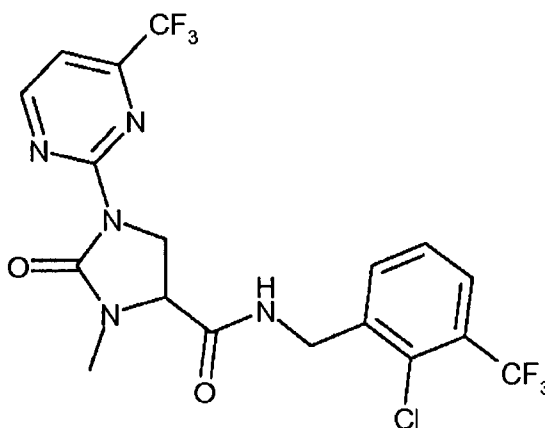
En una manera análoga a la que se describe en el ejemplo 49 anterior N-[(2-cloro-4-fluorofenil)metil]-1-metil-2-oxo-4-imidazolidinacarboxamida se prepara sustituyendo [(2-cloro-4-fluorofenil)metil]amina por la {[2-cloro-3-(trifluorometil)fenil]metil}amina usada en el procedimiento anterior.

15

LC/EM $[M+H]^+ = 286$, tiempo de retención = 1.90 minutos.

EJEMPLO 51

N-[[2-cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxamida (E51) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico)



Una mezcla de ácido 3-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxílico crudo (10 ml de solución 0.05 M en DCM, 0.5 mmoles), N-etilmorfolina (0.383 ml, 3.00 mmoles), hidrato de 1-hidroxibenzotriazol (92 mg, 0.600 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (115 mg, 0.600 mmoles) se agita a temperatura ambiente durante 10 minutos. Una solución de [[2-cloro-3-(trifluorometil)fenil]metil]amina (105 mg, 0.5 mmoles) en diclorometano (1 ml) se añade y la reacción se agita a temperatura ambiente durante 18 horas. La mezcla de reacción se diluye con diclorometano y la solución se lava con solución saturada de carbonato ácido de sodio, agua, ácido cítrico acuoso, agua y salmuera, se seca y se evapora. El residuo se purifica mediante

cromatografía en gel de sílice eluyendo con 0-10% de metanol en diclorometano. El residuo se tritura con éter y el sólido resultante se colecta y se seca para proporcionar N-[[2-cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxamida (150 mg, 5 62%).

LC/EM $[M+H]^+ = 482$, tiempo de retención 2.81 minutos.

El ácido 3-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

10 (i) Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (600 mg, 3 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-
15 {[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico y 2-cloro-4-(trifluorometil)pirimidina (547 mg, 3.00 mmoles) en 1,4-dioxano (20 ml) se trata con carbonato de cesio (1464 mg, 4.49 mmoles), Xantphos™ (130 mg, 0.225 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (68.6 mg, 0.075 mmoles) y la mezcla se calienta a reflujo bajo argón durante 6 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con agua y se extrae con acetato de etilo. Las capas orgánicas se combinan, se
20 lavan con agua y salmuera y se evaporan. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 0-100% de acetato de etilo en isohexano para proporcionar 3-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxilato de 1,1-dimetiletilo (506 mg, 49%).

LC/EM $[M+H]^+ = 347$.

(ii) Una solución de 3-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxilato de 1,1-dimetiletilo (506 mg, 1.46 mmoles) en TFA/DCM (1:2, 9 ml) se agita a temperatura ambiente durante 16 horas. La solución se evapora y el residuo se co-evapora con tolueno y se seca para proporcionar ácido 3-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxílico crudo (asume ~1.5 mmoles) que se usa en la siguiente etapa.

LC/EM $[M+H]^+ = 291$.

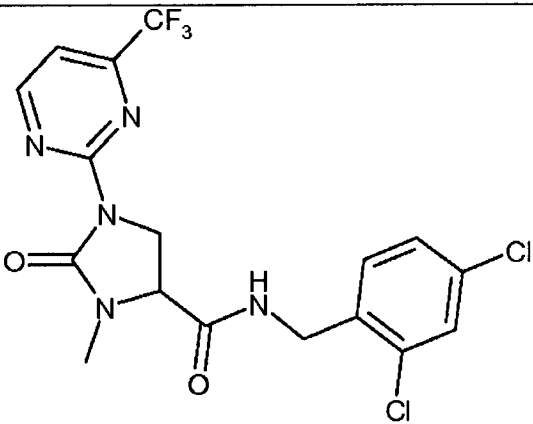
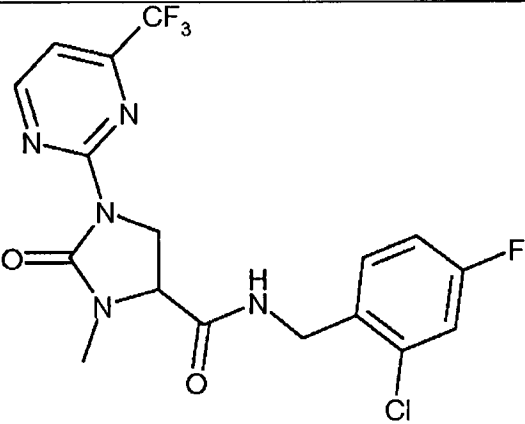
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EJEMPLOS 52-53

(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

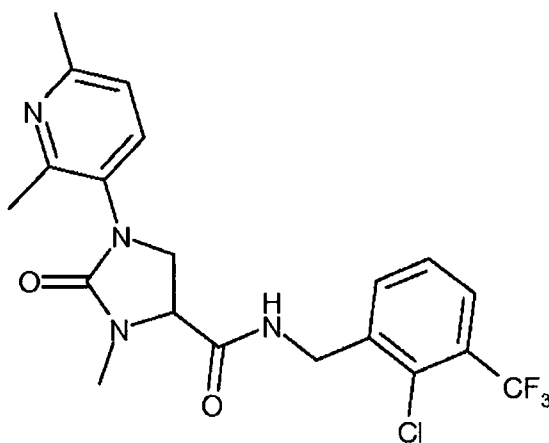
15 En una manera análoga a la que se describe para el ejemplo 51 anterior los compuestos tabulados posteriormente (cuadro 8) se preparan mediante la sustitución de la amina apropiada (o su sal) por la {[2-cloro-3-(trifluorometil)fenil]metil}amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 8 son disponibles de fuentes comerciales o se
20 pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

CUADRO 8

No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E52	 N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxamida	448	2.77
E53	 N-[(2-cloro-4-fluorofenil)metil]-3-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxamida	432	2.60

EJEMPLO 54

N-[[2-cloro-3-(trifluorometil)fenil]metil]-1-(2,6-dimetil-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida (E54) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico)



Una mezcla de sal TFA del ácido 1-(2,6-dimetil-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxílico (10 ml de solución 0.05M en DCM, 0.5 mmoles), N-etilmorfolina (0.383 ml, 3.00 mmoles), hidrato de 1-hidroxibenzotriazol (92 mg, 0.600 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (115 mg, 0.600 mmoles) se agita a temperatura ambiente durante 10 minutos. Una solución de [[2-cloro-3-(trifluorometil)fenil]metil]amina (105 mg, 0.5 mmoles) en diclorometano (1 ml) se añade y la reacción se agita a temperatura ambiente durante 18 horas. La mezcla de reacción se diluye con diclorometano y la solución se lava con solución saturada de carbonato ácido de sodio, agua y salmuera, se seca y se evapora. El residuo se purifica mediante cromatografía en gel de sílice

eluyendo con 0-10% de metanol en diclorometano. El residuo se tritura con éter y el sólido resultante se colecta y se seca para proporcionar N-[[2-cloro-3-(trifluorometil)fenil]metil]-1-(2,6-dimetil-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida (104 mg, 74%).

5 LC/EM $[M+H]^+ = 441$, tiempo de retención = 1.86 minutos.

La sal TFA del ácido 1-(2,6-dimetil-3-piridinil)-3-metil-2-oxo-4-imidazolidacarboxílico usada en el método descrito anteriormente se prepara como sigue:

(i) Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 10 1,1-dimetiletilo (600 mg, 3.00 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico] y 3-bromo-2,6-dimetilpiridina (557 mg, 3.00 mmoles) en 1,4-dioxano (20 ml) se trata con carbonato de cesio (1464 mg, 4.49 mmoles), Xantphos™ (130 mg, 0.225 15 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (68.6 mg, 0.075 mmoles) y la mezcla se calienta a reflujo bajo argón durante 3 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con agua y se extrae con acetato de etilo. Las capas orgánicas se combinan, se lavan con agua y salmuera y se evaporan *in vacuo*. El residuo se purifica 20 mediante cromatografía en gel de sílice eluyendo con 0-10% de metanol en diclorometano. El residuo se disuelve en metanol y se aplica a un cartucho de intercambio iónico SCX y se lava con metanol y después 2M de amoniaco en metanol. Las fracciones básicas se combinan y se evaporan para proporcionar

1-(2,6-dimetil-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (493 mg, 54%).

LC/EM $[M+H]^+ = 306$.

(ii) Una solución de 1-(2,6-dimetil-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (0.489 g, 1.6 mmoles) en TFA/DCM (1:2, 9 ml) se agita a temperatura ambiente durante 16 horas. La solución se evapora y el residuo se co-evapora con tolueno y se seca para proporcionar sal TFA del ácido 1-(2,6-dimetil-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxílico, (asumen ~ 1.6 mmoles) que se usa en la siguiente etapa.

LC/EM $[M+H]^+ = 250$.

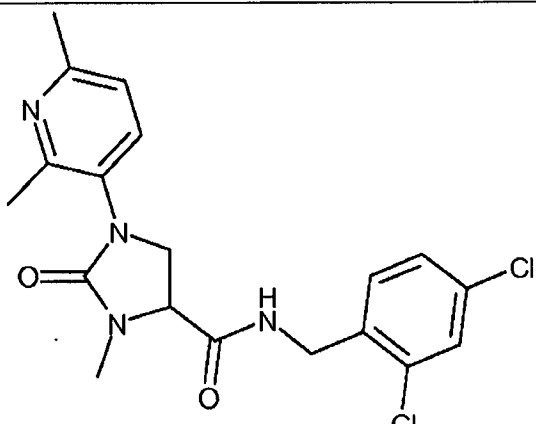
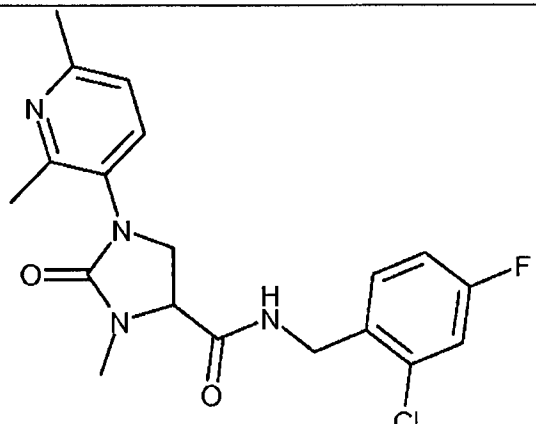
EJEMPLOS 55-56

**(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico**

En una manera análoga a la que se describe para el ejemplo 54 anterior los compuestos tabulados posteriormente (cuadro 9) se preparan mediante la sustitución de la amina apropiada (o su sal) por la {[2-cloro-3-(trifluorometil)fenil]metil}amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 9 son disponibles de fuentes comerciales o se pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

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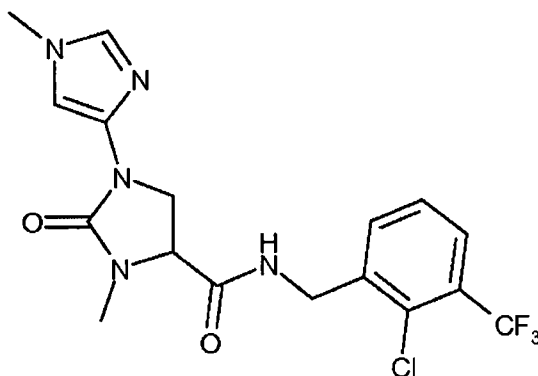
CUADRO 9

No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E55	 N-[(2,4-diclorofenil)metil]-1-(2,6-dimetil-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida	407	1.77
56	 N-[(2-cloro-4-fluorofenil)metil]-1-(2,6-dimetil-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida	391	1.61

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EJEMPLO 57

N-([2-cloro-3-(trifluorometil)fenil]metil)-3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida (E57) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-([(fenilmetil)oxi]carbonil)-4-imidazolidinacarboxílico



Una solución de sal trifluoroacetato del ácido 3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxílico (145 mg, 0.647 mmoles) en diclorometano (4 ml) se trata con hidrato de 1-hidroxiortobenzotriazol (119 mg, 0.776 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (149 mg, 0.776 mmoles) & N-etilmorfolina (0.491 ml, 3.88 mmoles) y la mezcla se agita a temperatura ambiente durante 10 minutos. Después se añade 1-([2-cloro-3-(trifluorometil)fenil]metil)amina (136 mg, 0.647 mmoles) y la reacción se agita a temperatura ambiente alrededor de la semana. La reacción se diluye con diclorometano y se lava con ácido cítrico 3N, solución saturada de carbonato ácido de sodio, agua y salmuera, se separa a través de una frita hidrófoba y la capa orgánica se reduce bajo vacío. El residuo se purifica mediante HPLC automatizada dirigida de masa y se seca por congelamiento

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para proporcionar N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida (30 mg, 10.6% de rendimiento).

LC/EM $[M+H]^+ = 416$, tiempo de retención = 1.92 minutos.

5 La sal trifluoroacetato del ácido 3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxílico usada en el método descrito anteriormente se prepara como sigue:

(i) A una mezcla agitada de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1,-dimetiletilo (200 mg, 0.999 mmoles)

10 (preparada como se describe en la etapa (iii) del ejemplo 13, iniciado a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil}-4-imidazolidinacarboxílico) y 4-bromo-1-metil-1H-imidazol (193 mg, 1.199 mmoles) en 1,4-dioxano (8 ml) se añade fosfato de potasio (1060 mg, 4.99 mmoles), yoduro de cobre (I) (190 mg, 0.999 mmoles) y trans-N,N-dimetilciclohexano-1,2-diamina (0.158 ml,

15 0.999 mmoles) y la mezcla de reacción se agita a reflujo bajo argón por 3 horas. La mezcla se enfría a temperatura ambiente y se diluye con diclorometano (20 ml) y se filtra y se lava a través de diclorometano. El filtrado se concentra bajo vacío y se toma en diclorometano. La solución se lava con 0.880 de amoniaco (x3), agua después salmuera y se separa por frita

20 hidrófoba y la capa orgánica se reduce bajo vacío. El residuo se purifica mediante cromatografía en gel de sílice automatizada Flashmaster eluyendo con 0-20% de metanol en diclorometano para dejar un aceite que cristaliza en reposo. El residuo se seca bajo vacío toda la noche para proporcionar 3-

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metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (285 mg, 87% de rendimiento).

LC/EM $[M+H]^+ = 281$.

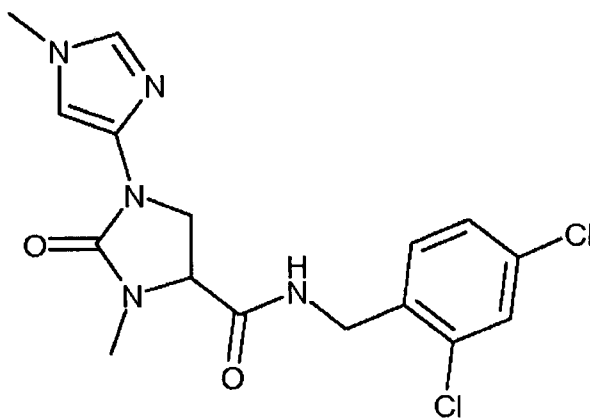
- (ii) Se añade ácido trifluoroacético (1.0 ml, 12.98 mmoles) a una
- 5 solución de 3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (220 mg, 0.785 mmoles) en DCM (2 ml) y la mezcla de reacción se agita a temperatura ambiente durante 5 horas. El solvente se evapora bajo vacío, se forma azeótropo con tolueno y el residuo se seca bajo vacío alrededor de una semana para proporcionar sal
- 10 trifluoroacetato del ácido 3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxílico crudo que se toma a través de la siguiente etapa sin purificación adicional.

LC/EM $[M+H]^+ = 225$.

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EJEMPLO 58

N-[(2,4-diclorofenil)metil]-3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida (E58) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-4-[(fenilmetil)oxi]carbonil)-4-imidazolidinacarboxílico)



Una solución de sal trifluoroacetato del ácido 3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxílico (0.105 g, 0.47 mmoles) (preparada como se describe en la etapa (ii) del ejemplo 57) y N-etil morfolina (0.361 ml, 2.82 mmoles) en diclorometano (5 ml) se trata con hidrato de 1-hidroxibenzotriazol (0.086 g, 0.564 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0.090 g, 0.470 mmoles) y se agita a temperatura ambiente durante 10 minutos. Se añade 1-(2,4-diclorofenil)metanamina (0.063 ml, 0.470 mmoles) y la mezcla de reacción se agita alrededor de la semana. La mezcla de reacción se diluye con diclorometano y se lava con solución saturada de carbonato ácido de sodio, agua y salmuera y se separa usando una frita hidrófoba. El filtrado se concentra bajo vacío y se purifica por HPLC automatizada dirigida de masa

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para proporcionar N-[(2,4-diclorofenil)metil]-3-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida (26 mg, 13.75% de rendimiento).

LC/EM $[M+H]^+ = 382$, tiempo de retención = 1.83 minutos.

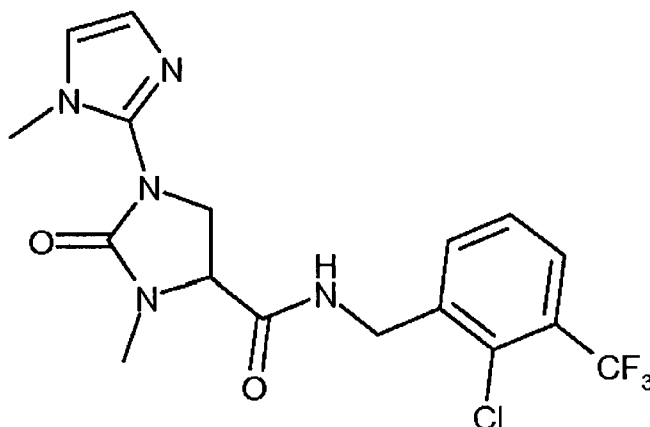
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EJEMPLO 59

N-[(2-cloro-3-(trifluorometil)fenil)metil]-3-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-imidazolidinacarboxamida (E59) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil)-4-imidazolidinacarboxílico)

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Una solución de ácido 3-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-imidazolidinacarboxílico (166 mg, 0.517 mmoles) y N-etil morfolina (0.397 ml, 3.10 mmoles) en diclorometano (5 ml) se trata con hidrato de 1-hidroxibenzotriazol (95 mg, 0.620 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (99 mg, 0.517 mmoles) y se agita a temperatura ambiente durante 10 minutos. Después se añade 1-[2-cloro-3-(trifluorometil)fenil]metanamina (108 mg, 0.517 mmoles) y la reacción se agita

toda la noche a temperatura ambiente. La mezcla de reacción se diluye con diclorometano y se lava con solución saturada de carbonato ácido de sodio, agua y salmuera, se separa a través de una frita hidrófoba y la capa orgánica se reduce bajo vacío. El residuo se purifica mediante HPLC automatizada dirigida de masa para proporcionar N-[[2-cloro-3-(trifluorometil)fenil]metil]-3-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-imidazolidinacarboxamida (67 mg, 29.6% de rendimiento).

LC/EM $[M+H]^+ = 416$, tiempo de retención = 1.89 minutos.

El ácido 3-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) A una solución agitada de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (0.200 g, 1.00 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-[[{(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico) y 2-bromo-1-metil-1H-imidazol (0.146 ml, 1.500 mmoles) en 1,4-dioxano (8 ml) se añade fosfato de potasio (1.062 g, 5.00 mmoles), yoduro de cobre (I) (0.190 g, 1.000 mmoles) y trans-N,N-dimetilciclohexano-1,2-diamina (0.155 ml, 1.000 mmoles) y la mezcla se calienta a reflujo bajo argón toda la noche. La mezcla se enfría a temperatura ambiente y se diluye con diclorometano. El sólido se filtra, se lava con diclorometano y el filtrado se reduce bajo vacío. El residuo se re-disuelve en diclorometano y se lava con 0.880 de solución de amoniac (x2), agua después salmuera y se pasa a través de una frita hidrófoba y la capa

orgánica se reduce bajo vacío. El residuo se purifica mediante cromatografía en gel de sílice Flashmaster eluyendo con 0-10% de metanol en diclorometano para proporcionar 3-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (145 mg, 37.8% de rendimiento).

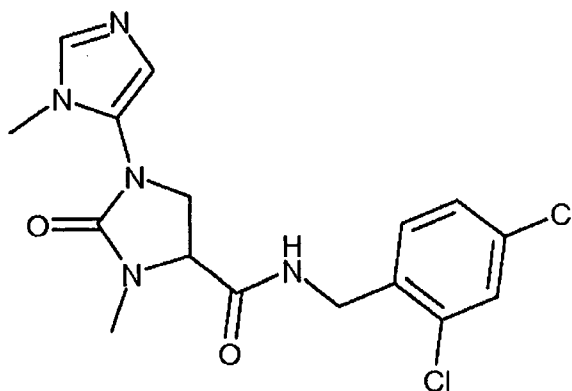
5 LC/EM $[M+H]^+ = 281$.

(ii) Se añade ácido trifluoroacético (0.059 ml, 0.517 mmoles) a una solución de 3-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (145 mg, 0.517 mmoles) en DCM (2 ml) y la reacción se agita a temperatura ambiente toda la noche. La mezcla
10 de reacción se co-evapora con tolueno y se seca para proporcionar ácido 3-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-imidazolidinacarboxílico (asume = 0.517 mmoles) que se usa en la siguiente etapa.

LC/EM $[M+H]^+ = 225$.

EJEMPLO 60

N-[(2,4-diclorofenil)metil]-3-metil-1-(1-metil-1H-imidazol-5-il)-2-oxo-4-imidazolidinacarboxamida (E60) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico)



Una solución de ácido 3-metil-1-(1-metil-1H-imidazol-5-il)-2-oxo-4-imidazolidinacarboxílico (155 mg, 0.458 mmoles) y N-etilmorfolina (0.348 ml, 2.75 mmoles) en diclorometano (5 ml) se trata con hidrato de 1-hidroxibenzotriazol (84 mg, 0.550 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (88 mg, 0.458 mmoles) y se agita a temperatura ambiente durante 10 minutos. Después se añade 1-(2,4-diclorofenil)metanamina (81 mg, 0.458 mmoles) y la mezcla de reacción se agita a temperatura ambiente durante 6 horas. La mezcla de reacción se diluye con diclorometano y se lava con solución saturada de carbonato ácido de sodio, agua y salmuera, se separa a través de una frita hidrófoba y la capa orgánica se reduce bajo vacío. El residuo se purifica por HPLC automatizada dirigida de masa para proporcionar N-[(2,4-diclorofenil)metil]-3-metil-1-(1-metil-

1H-imidazol-5-il)-2-oxo-4-imidazolidinacarboxamida (63 mg, 34.2% de rendimiento).

LC/EM $[M+H]^+ = 382$, tiempo de retención = 1.71 minutos.

El ácido 3-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-

5 imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) A una solución agitada de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (801 mg, 4.00 mmoles) preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido

10 (4S)-2-oxo-3-[[([fenilmetil]oxi)carbonil]-4-imidazolidinacarboxílico) y 5-bromo-1-metilimidazol (644 mg, 4.00 mmoles) en 1,4-dioxano (30 ml) se añade fosfato de potasio (4246 mg, 20.00 mmoles), trans-N,N-dimetilciclohexano-1,2-diamina (0.631 ml, 4.00 mmoles) y yoduro de cobre (I) (762 mg, 4.00 mmoles) y la mezcla se agita a reflujo toda la noche. La mezcla de reacción se diluye

15 con diclorometano y se filtra a través de celite. La almohadilla de filtro se lava con diclorometano y el filtrado se reduce bajo vacío. El residuo se re-disuelve en diclorometano, se lava con 0.880 amoniaco (x2), agua después salmuera y se pasa a través de una frita hidrófoba y la solución se concentra bajo vacío. El residuo se purifica mediante cromatografía en gel de sílice automatizada

20 Flashmaster eluyendo con 0-10% de metanol en diclorometano para proporcionar 3-metil-1-(1-metil-1H-imidazol-5-il)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (393 mg, 32.6% de rendimiento).

LC/EM $[M+H]^+ = 281$.

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(ii) Se añade ácido trifluoroacético (2 ml) a una solución de (4S)-3-metil-1-(1-metil-1H-imidazol-5-il)-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (390 mg, 1.391 mmoles) en diclorometano (4 ml) y se agita a temperatura ambiente durante 2 horas, después se deja reposar toda la noche.

- 5 El solvente se evapora y el residuo se co-evapora con tolueno y se seca bajo vacío calentado (40°C) toda la noche para proporcionar sal TFA del ácido 3-metil-1-(1-metil-1H-imidazol-5-il)-2-oxo-4-imidazolidinacarboxílico (asume ~ 1.4 mmoles) que se usa en la siguiente etapa.

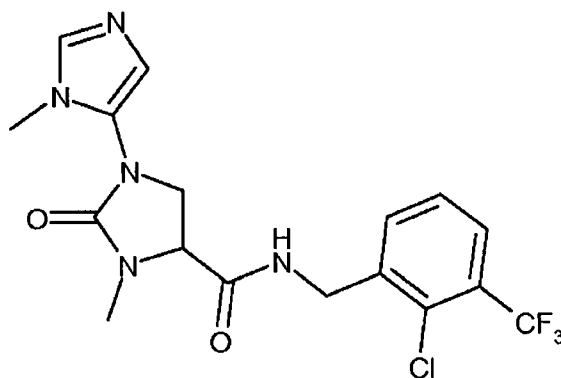
$$\text{LC/EM } [M+H]^+ = 225.$$

10

EJEMPLO 61

N-{{2-cloro-3-(trifluorometil)fenil}metil}-3-metil-1-(1-metil-1H-imidazol-5-il)-2-oxo-4-imidazolidinacarboxamida (E61) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-{{(fenilmetil)oxi}carbonil}-4-imidazolidinacarboxílico)

15



20

En una manera análoga a la que se describe en el ejemplo 60 anterior N-{{2-cloro-3-(trifluorometil)fenil}metil}-3-metil-1-(1-metil-1H-imidazol-

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5-il)-2-oxo-4-imidazolidinacarboxamida se prepara sustituyendo 1-(2,4-diclorofenil)metanamina por la {[2-cloro-3-(trifluorometil)fenil]metil}amina usada en el procedimiento anterior.

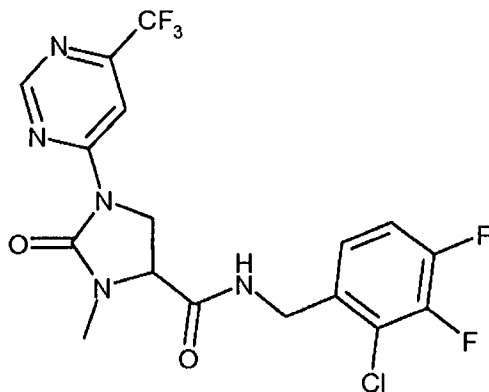
LC/EM $[M+H]^+ = 416$, tiempo de retención = 1.75 minutos.

5

EJEMPLO 62

N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-1-[6-(trifluorometil)-4-pirimidinil]-4-imidazolidinacarboxamida (E62) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil)-4-imidazolidinacarboxílico)

10



15

A una suspensión de ácido 3-metil-2-oxo-1-[6-(trifluorometil)-4-pirimidinil]-4-imidazolidinacarboxílico (200 mg, 0.612 mmoles) y N-etilmorfolina (0.465 ml, 3.67 mmoles) en diclorometano (10 ml)/DMF (1 ml) se añade hidrato de 1-hidroxibenzotriazol (113 mg, 0.735 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (117 mg, 0.612 mmoles) y la mezcla de reacción se agita durante 1 hora a temperatura ambiente. Después se añade 1-(2-cloro-3,4-difluorofenil)metanamina (131 mg, 0.612 mmoles) y la

20

reacción se agita toda la noche. Clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida adicional (117 mg, 0.612 mmoles) se añade y la mezcla de reacción se agita durante 3 horas. La mezcla de reacción se diluye con diclorometano y se lava con solución saturada de carbonato ácido de sodio, agua, solución de ácido cítrico 3N, agua, después salmuera y se separa a través de una frita hidrófoba y la capa orgánica se concentra bajo vacío. El residuo se purifica por cromatografía en gel de sílice automatizada SP4 eluyendo con 10-100% de acetato de etilo en isohexano para proporcionar N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-2-oxo-1-[6-(trifluorometil)-4-pirimidinil]-4-imidazolidinacarboxamida (95 mg, 33.8% de rendimiento).

LC/EM $[M+H]^+ = 450$, tiempo de retención = 2.93 minutos.

El ácido 3-metil-2-oxo-1-[6-(trifluorometil)-4-pirimidinil]-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (800 mg, 4.00 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 3, iniciando a partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico] y 4-cloro-6-(trifluorometil)pirimidina (729 mg, 4.00 mmoles) en 1,4-dioxano (40 ml) se trata con carbonato de cesio (1953 mg, 5.99 mmoles), Xantphos™ (173 mg, 0.300 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (91 mg, 0.100 mmoles) y la mezcla de reacción se calienta a reflujo bajo argón toda la noche. Después del

enfriamiento la reacción se diluye con agua y se extrae con acetato de etilo (x2). Las capas orgánicas se combinan y se lavan con agua y salmuera, se secan sobre sulfato de sodio anhidro y se reducen bajo vacío. El residuo se purifica mediante cromatografía en gel de sílice automatizada Flashmaster eluyendo con 0-30% de acetato de etilo en isohexano para proporcionar 3-metil-2-oxo-1-[6-(trifluorometil)-4-pirimidinil]-4-imidazolidinacarboxilato de 1,1-dimetiletilo (983 mg, 67.5 % de rendimiento).

LC/EM $[M+H]^+ = 347$.

(ii) Se añade ácido trifluoroacético (4 ml, 51.9 mmoles) a una solución de 3-metil-2-oxo-1-[6-(trifluorometil)-4-pirimidinil]-4-imidazolidinacarboxilato de 1,1-dimetiletilo (980 mg, 2.83 mmoles) en diclorometano (8 ml) y la solución se agita a temperatura ambiente durante 6 horas. El solvente se evapora y el residuo se co-evapora con tolueno. El residuo se disuelve en solución saturada de carbonato ácido de sodio y la solución se carga en una columna de amino eluyendo con 10% de ácido clorhídrico 2N en metanol. Las fracciones que contienen el producto se combinan y se reducen bajo vacío y el residuo se tritura con metanol y el sólido se filtra. El filtrado se reduce bajo vacío para proporcionar sal clorhidrato del ácido 3-metil-2-oxo-1-[6-(trifluorometil)-4-pirimidinil]-4-imidazolidinacarboxílico (893 mg, asume ~2.8 mmoles) que se usa en la siguiente etapa.

LC/EM $[M+H]^+ = 291$.

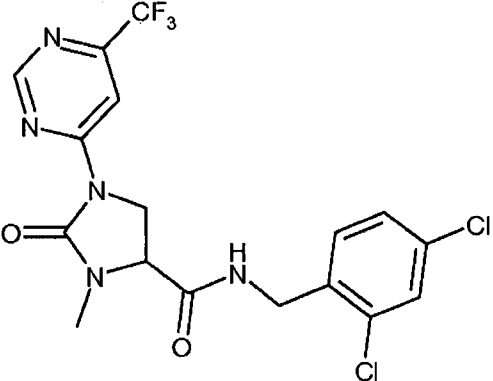
202

EJEMPLOS 63-64

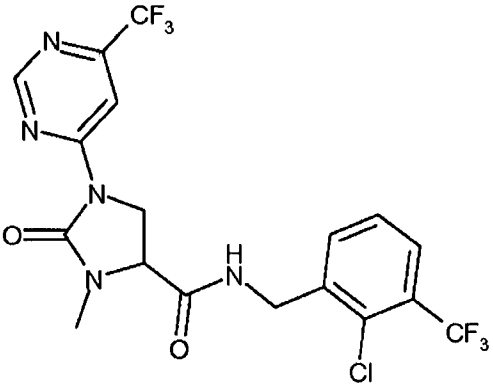
**(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)**

- 5 En una manera análoga a la que se describe para el ejemplo 62 anterior los compuestos tabulados posteriormente (cuadro 10) se preparan mediante la sustitución de la amina apropiada (o su sal) por la 1-(2-cloro-3,4-difluorofenil)metanamina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 10 son disponibles de fuentes comerciales o se
- 10 pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

CUADRO 10

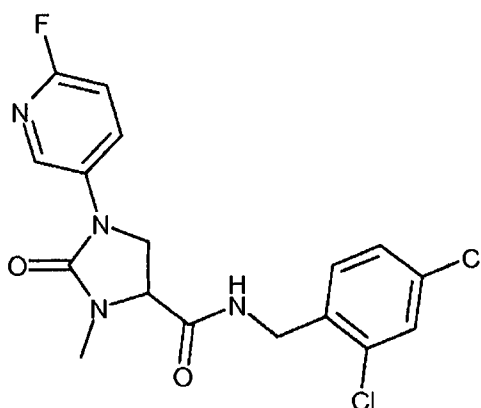
15	No. de ejemplo	Nombre químico	$[M+H]^+$	Tiempo de retención (minutos)
20	E63	 N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-1-[6-(trifluorometil)-4-pirimidinil]-4-imidazolidinacarboxamida	448	3.04

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No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E64	 N-([2-cloro-3-(trifluorometil)fenil]metil)-3-metil-2-oxo-1-[6-(trifluorometil)-4-pirimidinil]-4-imidazolidinacarboxamida	482	3.08

EJEMPLO 65

N-[(2,4-diclorofenil)metil]-1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida (E65) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)



A una solución de sal TFA del ácido 1-(6-fluoro-3-piridinil)-3-

metil-2-oxo-4-imidazolidinacarboxílico (200 mg, 0.836 mmoles) y N-etilmorfolina (0.635 ml, 5.02 mmoles) en diclorometano (10 ml) se añade hidrato de 1-hidroxibenzotriazol (128 mg, 0.836 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (160 mg, 0.836 mmoles) y la mezcla
5 se agita durante 10 minutos. Se añade 1-(2,4-diclorofenil)metanamina (147 mg, 0.836 mmoles) y la reacción se agita a temperatura ambiente durante toda la noche. La mezcla de reacción se diluye con diclorometano y se lava con solución saturada de carbonato ácido de sodio, agua y salmuera, se separa a través de una frita hidrófoba y la capa orgánica se reduce bajo vacío.
10 El residuo se purifica mediante cromatografía en gel de sílice automatizada Flashmaster eluyendo con 10-100% de acetato de etilo en isohexano para proporcionar N-[(2,4-diclorofenil)metil]-1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida (60 mg, 18% de rendimiento).

LC/EM $[M+H]^+ = 397$, tiempo de retención = 2.63 minutos.

15 La sal TFA del ácido 1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) A una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (400 mg, 1.998 mmoles) (preparada como se describe en la
20 etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico) y 5-bromo-2-fluoropiridina (352 mg, 1.998 mmoles) en 1,4-dioxano (20 ml) se añade trans-N,N-dimetilciclohexano-1,2-diamina (0.062 ml, 0.400 mmoles), fosfato de potasio

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(1272 mg, 5.99 mmoles) y yoduro de cobre (I) (38.0 mg, 0.200 mmoles) y la mezcla de reacción se calienta a reflujo bajo argón toda la noche. La mezcla de reacción se deja enfriar y el solvente se evapora. El residuo se divide entre diclorometano y agua. La capa orgánica se separa y se lava con agua (~50 ml) que contiene 0.880 de solución de amoníaco (~5 ml), después salmuera y se pasa a través de una frita hidrófoba y la capa orgánica se reduce bajo vacío. El residuo se purifica mediante cromatografía en gel de sílice automatizada SP4 eluyendo con 10-80% de acetato de etilo en isohexano para proporcionar 1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (422 mg, 68.7% de rendimiento).

LC/EM $[M+H]^+ = 296$.

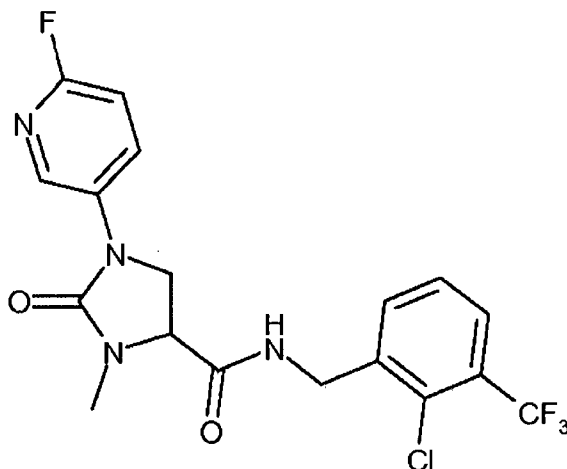
(ii) Se añade ácido trifluoroacético (2 ml) a una solución de 1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (420 mg, 1.422 mmoles) en diclorometano (5 ml) y la mezcla se agita a temperatura ambiente durante 36 horas. La mezcla de reacción se reduce bajo vacío y el residuo se forma en azeótropo con tolueno y se seca bajo vacío caliente para proporcionar sal de TFA del ácido 1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxílico (asume ~ 1.4 mmoles) que se usa en la siguiente etapa.

20 LC/EM $[M+H]^+ = 240$.

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EJEMPLO 66

N-{{2-cloro-3-(trifluorometil)fenil}metil}-1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida (E66) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-{{(fenilmetil)oxi}carbonil}-4-imidazolidinacarboxílico)



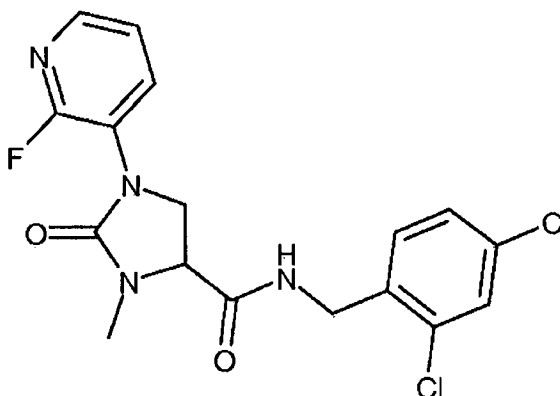
En una manera análoga a la que se describe en el ejemplo 65 anterior N-{{2-cloro-3-(trifluorometil)fenil}metil}-1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida se prepara sustituyendo {{2-cloro-3-(trifluorometil)fenil}metil}amina por la 1-(2,4-diclorofenil)metanamina usada en el procedimiento anterior.

LC/EM $[M+H]^+ = 431$, tiempo de retención = 2.69 minutos.

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EJEMPLO 67

N-[(2,4-diclorofenil)metil]-1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-
imidazolidinacarboxamida (E67) (en una forma obtenible o preparada a
partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil}-4-
imidazolidinacarboxílico)



A una solución de sal TFA del ácido 1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxílico (182 mg, 0.761 mmoles) y N-etilmorfolina (0.578 ml, 4.57 mmoles) en diclorometano (5 ml) se añade hidrato de 1-hidroxibenzotriazol (117 mg, 0.761 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (146 mg, 0.761 mmoles) y la mezcla de reacción se agita durante 10 minutos a temperatura ambiente. Se añade 1-(2,4-diclorofenil)metanamina (134 mg, 0.761 mmoles) y la reacción se agita a temperatura ambiente toda la noche. La mezcla de reacción se diluye con diclorometano y la solución se lava con solución saturada de carbonato ácido de sodio, agua y salmuera, se separa a través de una frita hidrófoba y la capa orgánica se reduce bajo vacío. El residuo se purifica mediante cromatografía en gel de sílice automatizada SP4 eluyendo con 10-100% de acetato de etilo

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en isohexano para proporcionar N-[(2,4-diclorofenil)metil]-1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida (125 mg, 40.5% de rendimiento).

LC/EM $[M+H]^+ = 397$, tiempo de retención = 2.51 minutos.

5 La sal TFA del ácido 1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxílico usada en el método descrito anteriormente se prepara como sigue:

(i) A una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (400 mg, 1.998 mmoles) (preparada como se describe en la

10 etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico) y 2-fluoro-3-yodopiridina (352 mg, 1.998 mmoles) en 1,4-dioxano (20 ml) se añade trans-N,N-dimetilciclohexano-1,2-diamina (0.062 ml, 0.400 mmoles), fosfato de potasio (1272 mg, 5.99 mmoles) y yoduro de cobre (I) (38.0 mg, 0.200 mmoles) y la

15 mezcla de reacción se calienta a reflujo bajo argón toda la noche. La mezcla de reacción se deja enfriar y el solvente se evapora. El residuo se divide entre diclorometano y agua. La capa orgánica se separa y se lava con agua (~50 ml) que contiene 0.880 de solución de amoníaco (~ 5 ml), después salmuera y se pasa a través de una frita hidrófoba y la capa orgánica se reduce bajo vacío.

20 El residuo se purifica mediante cromatografía en gel de sílice automatizada SP4 eluyendo con 10-80% de acetato de etilo en isohexano para proporcionar 1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (405 mg, 67.3 % de rendimiento).

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LC/EM $[M+H]^+ = 296$.

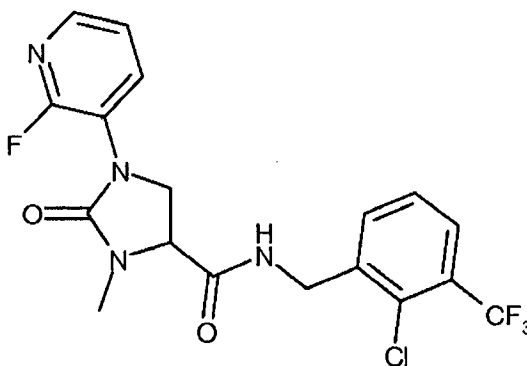
(ii) Se añade ácido trifluoroacético (2 ml) a una solución de (4S)-1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (400 mg, 1.355 mmoles) en diclorometano (5 ml) y la solución se agita a temperatura ambiente durante 36 horas. La mezcla de reacción se reduce bajo vacío y el residuo se forma en azeótropo con tolueno y se seca bajo vacío caliente para proporcionar sal de TFA del ácido 1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxílico (asume ~ 1.35 mmoles) que se usa en la siguiente etapa.

10 LC/EM $[M+H]^+ = 240$.

EJEMPLO 68

N-{[2-cloro-3-(trifluorometil)fenil]metil}-1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida (E68) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil}-4-imidazolidinacarboxílico)

20



En una manera análoga a la que se describe en el ejemplo 65

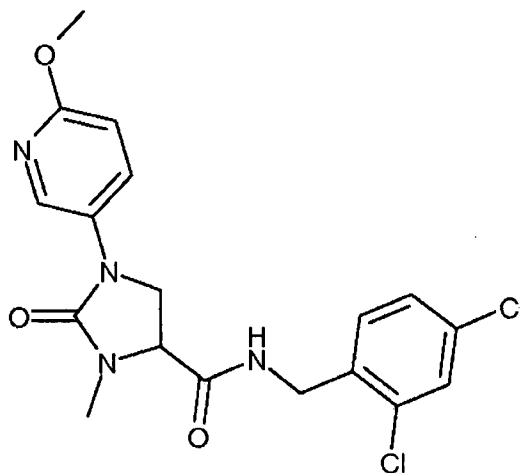
340

anterior N-[[2-cloro-3-(trifluorometil)fenil]metil]-1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida se prepara sustituyendo {[2-cloro-3-(trifluorometil)fenil]metil}amina por la 1-(2,4-diclorofenil)metanamina usada en el procedimiento anterior.

5 LC/EM $[M+H]^+ = 431$, tiempo de retención = 2.56 minutos.

EJEMPLO 69

N-[(2,4-diclorofenil)metil]-3-metil-1-[6-(metiloxi)-3-piridinil]-2-oxo-4-imidazolidinacarboxamida (E69) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico)



15 A una solución de sal TFA del ácido 3-metil-1-[6-(metiloxi)-3-piridinil]-2-oxo-4-imidazolidinacarboxílico (145 mg, 0.404 mmoles) y N-etilmorfolina (0.307 ml, 2.424 mmoles) en diclorometano (5 ml) se añade
20 hidrato de 1-hidroxibenzotriazol (61.9 mg, 0.404 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (77 mg, 0.404 mmoles) y la mezcla

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de reacción se agita durante 10 minutos a temperatura ambiente. Se añade 1-(2,4-diclorofenil)metanamina (71.1 mg, 0.404 mmoles) y la reacción se agita a temperatura ambiente toda la noche. La mezcla de reacción se diluye con diclorometano y la solución se lava con solución saturada de carbonato ácido de sodio, agua y salmuera, se separa a través de una frita hidrófoba y la capa orgánica se reduce bajo vacío. El residuo se purifica mediante cromatografía en gel de sílice automatizada SP4 eluyendo con 10-100% de acetato de etilo en isohexano para proporcionar N-[(2,4-diclorofenil)metil]-3-metil-1-[6-(metiloxi)-3-piridinil]-2-oxo-4-imidazolidinacarboxamida (101 mg, 59.9 % de rendimiento).

LC/EM $[M+H]^+ = 409$, tiempo de retención = 2.34 minutos.

La sal TFA del ácido 1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxílico usada en el método descrito anteriormente se prepara como sigue:

(i) A una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (400 mg, 1.998 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico] y 5-bromo-2-(metiloxi)piridina (0.259 mg, 1.998 mmoles) en 1,4-dioxano (20 ml) se añade carbonato de cesio (2604 mg, 7.99 mmoles), Xantphos™ (87 mg, 0.150 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (91 mg, 0.100 mmoles) y la reacción se calienta a reflujo toda la noche. Después del enfriamiento el solvente se remueve bajo vacío y el residuo se divide entre diclorometano y

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agua. La capa orgánica se separa, se lava con solución saturada de carbonato ácido de sodio, agua y después salmuera y se pasa a través de una frita hidrófoba. La capa orgánica se reduce bajo vacío y el residuo se purifica mediante cromatografía en gel de sílice automatizada Flashmaster eluyendo con 0-30% de acetato de etilo en isohexano para proporcionar 3-metil-1-[6-(metiloxi)-3-piridin]-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (272 mg, 43.4 % de rendimiento).

LC/EM $[M+H]^+ = 308$.

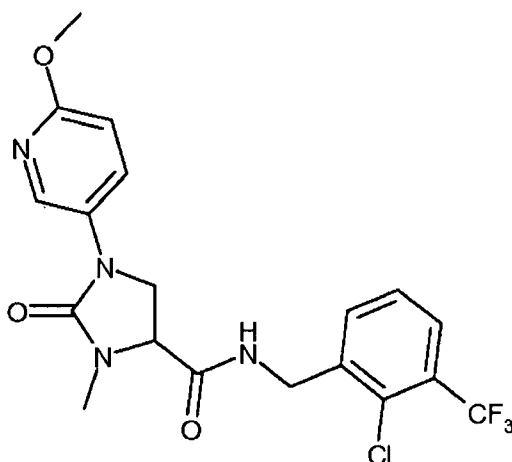
(ii) Se añade ácido trifluoroacético (1 ml) a una solución de 3-metil-1-[6-(metiloxi)-3-piridinil]-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (270 mg, 0.878 mmoles) en diclorometano (2 ml) y la solución se agita a temperatura ambiente toda la noche. La mezcla de reacción se reduce a sequedad bajo vacío y se forma en azeótropo con tolueno y se seca bajo vacío caliente toda la noche para proporcionar sal TFA del ácido 3-metil-1-[6-(metiloxi)-3-piridinil]-2-oxo-4-imidazolidinacarboxílico (asume ~0.88 mmoles).

LC/EM $[M+H]^+ = 252$.

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EJEMPLO 70**N-{{2-cloro-3-(trifluorometil)fenil}metil}-3-metil-1-[6-(metiloxi)-3-piridinil]-****2-oxo-4-imidazolidinacarboxamida (E70)****(en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-****5 {[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)**

10



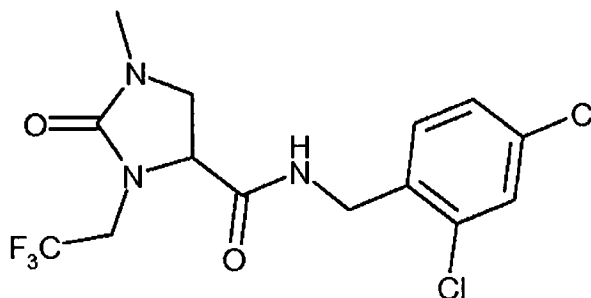
15

En una manera análoga a la que se describe en el ejemplo 69 anterior N-{{2-cloro-3-(trifluorometil)fenil}metil}-3-metil-1-[6-(metiloxi)-3-piridinil]-2-oxo-4-imidazolidinacarboxamida se prepara sustituyendo {[2-cloro-3-(trifluorometil)fenil]metil}amina por la 1-(2,4-diclorofenil)metanamina usada en el procedimiento anterior.

LC/EM $[M+H]^+ = 443$, tiempo de retención = 2.41 minutos.

EJEMPLO 72

N-[(2,4-diclorofenil)metil]-1-metil-2-oxo-3-(2,2,2-trifluoroetil)-4-
imidazolidinacarboxamida (E72) (en una forma obtenible o preparada a
partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil]-4-
imidazolidinacarboxílico)



Una mezcla de ácido 1-metil-2-oxo-3-(2,2,2-trifluoroetil)-4-imidazolidinacarboxílico (84 mg, 0.37 mmoles), hidrato de 1-hidroxibenzotriazol (68.0 mg, 0.444 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (85 mg, 0.444 mmoles) y N-etil morfolina (0.189 ml, 1.480 mmoles) en diclorometano (9 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de [1-(2,4-diclorofenil)metil]amina (65.1 mg, 0.37 mmoles) en diclorometano (1 ml) se añade y la mezcla de reacción se agita a temperatura ambiente durante 18 horas. La mezcla de reacción se diluye con diclorometano (10 ml) y la solución se lava con solución saturada de carbonato ácido de sodio (10 ml), agua (10 ml), solución de ácido cítrico (10 ml) y salmuera (10 ml), se seca y se evapora. El residuo se purifica mediante HPLC automatizada dirigida de masa. El residuo se tritura con éter y el sólido resultante se colecta y se seca para proporcionar N-[(2,4-

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diclorofenil)metil]-1-metil-2-oxo-3-(2,2,2-trifluoroetil)-4-imidazolidinacarboxamida (60 mg, 42%).

LC/EM $[M+H]^+ = 384$, tiempo de retención = 2.64 minutos.

El ácido 1-metil-2-oxo-3-(2,2,2-trifluoroetil)-4-

5 imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) Una solución de 1-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (180 mg, 0.9 mmoles) (preparada como se describe en la etapa (i) del ejemplo 49 a partir de 3-metil-2-oxo-1,5-imidazolidinadicarboxilato

10 de 5-(1,1-dimetiletil) 1-(fenilmetilo), por si misma preparada como se describe en la etapa (ii) del ejemplo 13, iniciando originalmente a partir del ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico en N,N-dimetilformamida (10 ml), bajo argón a -35°C , se trata con hidruro de sodio (60% de dispersión en aceite) (36.0 mg, 0.900 mmoles). La mezcla se agita a

15 -35°C durante 15 minutos y después triclorometanosulfonato de 2,2,2-trifluoroetilo (507 mg, 1.800 mmoles) se añade y la mezcla de reacción se agita a -35°C durante 2 horas (la temperatura se incrementa lentamente a -15°C). La reacción se templea con agua (5 ml) y se deja calentar a temperatura ambiente y la mezcla de reacción se extrae con acetato de etilo (2 x 20 ml). La

20 capa orgánica se separa, se lava con solución saturada de carbonato ácido de sodio (10 ml), agua (2 x 10 ml) y salmuera (20 ml) y se evapora. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 10-100% de acetato de etilo en isohexano para proporcionar 1-metil-2-oxo-3-(2,2,2-

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trifluoroetil)-4-imidazolidinacarboxilato de 1,1-dimetiletilo (107 mg, 42%).

LC/EM $[M+H]^+ = 283$.

(ii) Una solución de 1-metil-2-oxo-3-(2,2,2-trifluoroetil)-4-imidazolidinacarboxilato de 1,1-dimetiletilo (107 mg, 0.379 mmoles) en TFA/DCM (1:2, 3 ml) se agita a temperatura ambiente durante 4 horas. La solución se evapora y el residuo se co-evapora con diclorometano y se seca para proporcionar ácido 1-metil-2-oxo-3-(2,2,2-trifluoroetil)-4-imidazolidinacarboxílico crudo (asume ~ 0.38 mmoles) que se usa en la siguiente reacción.

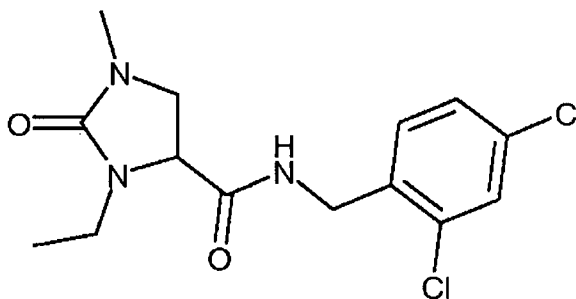
LC/EM $[M+H]^+ = 227$.

EJEMPLO 73

N-[(2,4-diclorofenil)metil]-3-etil-1-metil-2-oxo-4-imidazolidinacarboxamida

(E73) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-

{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)



20

Una mezcla de ácido 3-etil-1-metil-2-oxo-4-imidazolidinacarboxílico (138 mg, 0.800 mmoles), hidrato de 1-hidroxibenzotriazol (147 mg, 0.960 mmoles), clorhidrato de 1-etil-3-(3-

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dimetilaminopropil)carbodiimida (184 mg, 0.960 mmoles) y N-etil morfolina (0.409 ml, 3.20 mmoles) en diclorometano (9 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de [1-(2,4-diclorofenil)metil]amina (141 mg, 0.8 mmoles) en diclorometano (1 ml) se añade y la mezcla de
5 reacción se agita a temperatura ambiente durante 18 horas. La mezcla de reacción se diluye con diclorometano (10 ml) y la solución se lava con solución saturada de carbonato ácido de sodio (10 ml), agua (10 ml), solución de ácido cítrico (10 ml) y salmuera (10 ml), se seca y se evapora. El residuo se purifica mediante HPLC automatizada dirigida de masa. El residuo se tritura con éter y
10 el sólido resultante se colecta y se seca para proporcionar N-[(2,4-diclorofenil)metil]-3-etil-1-metil-2-oxo-4-imidazolidinacarboxamida (141 mg, 53%).

LC/EM $[M+H]^+ = 330$, tiempo de retención = 2.36 minutos.

El ácido 3-etil-1-metil-2-oxo-4-imidazolidinacarboxílico usado en
15 el método descrito anteriormente se prepara como sigue:

(i) Una solución agitada de 1-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (0.501 mg, 2.5 mmoles) (preparada como se describe en la etapa (i) del ejemplo 49 a partir de 3-metil-2-oxo-1,5-imidazolidinadicarboxilato de 5-(1,1-dimetiletil) 1-(fenilmetilo), por si misma
20 preparada como se describe en la etapa (ii) del ejemplo 13, iniciando originalmente a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico) en N,N-dimetilformamida (10 ml) se enfría a -10°C bajo argón y se trata con yodoetano (0.404 ml, 5.00 mmoles). Se añade a

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manera de porción hidruro de sodio (60% de dispersión en aceite) (0.100 g, 2.500 mmoles). La mezcla se deja calentar agitada a temperatura ambiente alrededor de 3 horas. El solvente se evapora *in vacuo* y el residuo se divide entre acetato de etilo (20 ml) y salmuera (10 ml). La capa acuosa se re-extrae con acetato de etilo (20 ml) y los extractos orgánicos se combinan, se lavan con solución saturada de carbonato ácido de sodio (20 ml), agua (2 x 20 ml) y salmuera (20 ml), se seca y se evaporan. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 25-100% de acetato de etilo en isohexano para proporcionar 3-etil-1-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (433 mg, 76%).

$$\text{LC/EM } [\text{M}+\text{H}]^+ = 229.$$

(ii) Una solución de 3-etil-1-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (433 mg, 1.897 mmoles) en TFA/DCM (1:2, 6 ml) se agita a temperatura ambiente durante 18 horas. La solución se evapora y el residuo se co-evapora con diclorometano y se seca para proporcionar ácido 3-etil-1-metil-2-oxo-4-imidazolidinacarboxílico crudo (asume ~ 1.9 mmoles).

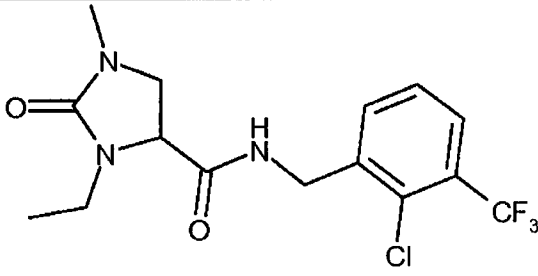
$$\text{LC/EM } [\text{M}+\text{H}]^+ = 173.$$

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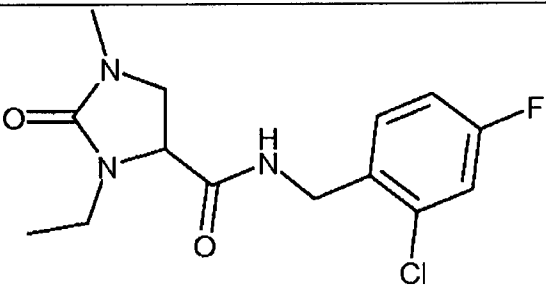
EJEMPLO 74-75**(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-****{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico**

- 5 En una manera análoga a la que se describe para el ejemplo 73 anterior los compuestos tabulados posteriormente (cuadro 11) se preparan mediante la sustitución de la amina apropiada (o su sal) por la [1-(2,4-diclorofenil)metil]amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 11 son disponibles de fuentes comerciales o se pueden
- 10 preparar usando rutas descritas previamente en la literatura química o métodos análogos.

CUADRO 11

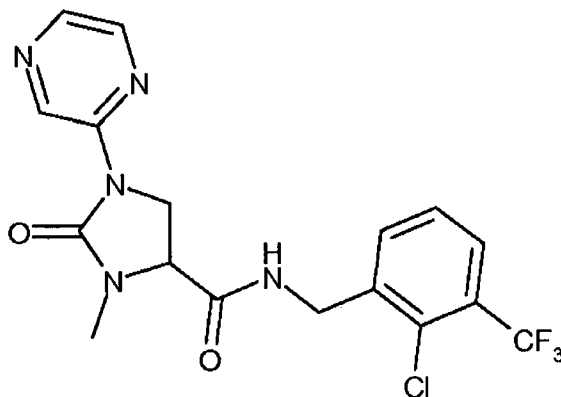
15	No. de ejemplo	Nombre químico	$[M+H]^+$	Tiempo de retención (minutos)
20	E74	 N-[[2-cloro-3-(trifluorometil)fenil]metil]- 3-etil-1-metil-2-oxo-4- imidazolidinacarboxamida	364	2.44

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No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E75	 N-[(2-cloro-4-fluorofenil)metil]-3-etil-1-metil-2-oxo-4-imidazolidinacarbamida	314	2.15

EJEMPLO 76

N-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-(2-pirazinil)-4-imidazolidinacarbamida (E76) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)



A una solución de ácido 3-metil-2-oxo-1-(2-pirazinil)-4-imidazolidinacarboxílico (145 mg, 0.561 mmoles) y N-etilmorfolina (0.426 ml, 3.36 mmoles) en diclorometano (5 ml) se añade hidrato de 1-

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hidroxibenzotriazol (86 mg, 0.561 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (107 mg, 0.561 mmoles) y la mezcla de reacción se agita durante 10 minutos a temperatura ambiente. Se añade 1-[2-cloro-3-(trifluorometil)fenil]metanamina (141 mg, 0.673 mmoles) y la mezcla de
5 reacción se agita a temperatura ambiente toda la noche. La mezcla de reacción se diluye con diclorometano y se lava con solución saturada de carbonato ácido de sodio, agua y salmuera y se separa mediante frita hidrófoba y la capa orgánica se reduce bajo vacío. El residuo se purifica mediante cromatografía en gel de sílice automatizada SP4 eluyendo con 10-
10 100% de acetato de etilo en isohexano para proporcionar N-[[2-cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-1-(2-pirazinil)-4-imidazolidinacarboxamida (45 mg, 19% de rendimiento).

LC/EM $[M+H]^+ = 413$, tiempo de retención = 2.21 minutos.

El ácido 3-metil-2-oxo-1-(2-pirazinil)-4-imidazolidinacarboxílico
15 usado en el método descrito anteriormente se prepara como sigue:

(i) A una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (400 mg, 1.998 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-
20 {{{(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico) y 2-cloropirazina (0.179 ml, 1.998 mmoles) en 1,4-dioxano (20 ml) se añade carbonato de cesio (2604 mg, 7.99 mmoles), tris(dibencilidenoacetona)dipaladio (0) (91 mg, 0.100 mmoles) y Xantphos™ (87 mg, 0.150 mmoles) y la mezcla de reacción se agita a reflujo toda la noche. La mezcla de reacción se deja enfriar a temperatura ambiente y

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el solvente se remueve bajo vacío y el residuo se divide entre diclorometano y agua. La capa orgánica se lava con solución saturada de carbonato ácido de sodio, agua y salmuera y se separa mediante frita hidrófoba. La solución se reduce bajo vacío y el residuo se purifica mediante cromatografía en gel de sílice eluyendo con 10-75% de acetato de etilo en isohexano para proporcionar el 3-metil-2-oxo-1-(2-pirazinil)-4-imidazolidinacarboxilato de 1,1-dimetiletilo (322 mg, 38.2% de rendimiento) que se usa en la siguiente etapa.

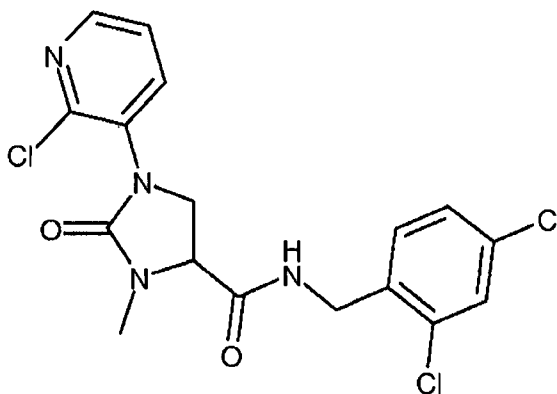
$$\text{LC/EM } [\text{M}+\text{H}]^+ = 279.$$

(ii) Se añade ácido trifluoroacético (1 ml) a una solución de 3-metil-2-oxo-1-(2-pirazinil)-4-imidazolidinacarboxilato de 1,1-dimetiletilo (290 mg, 0.709 mmoles) en diclorometano y la solución se agita a temperatura ambiente toda la noche. La mezcla de reacción se reduce a sequedad formando azeótropo con tolueno y se seca bajo vacío caliente. El residuo se toma en diclorometano y se extrae con solución saturada de carbonato ácido de sodio (x3) y la capa acuosa se reduce bajo vacío. El residuo se toma en agua y la solución se acidifica a pH 4 mediante la adición lenta de ácido clorhídrico 2N. La solución se lava con diclorometano (x2) y el solvente se reduce bajo vacío. El residuo se tritura con la cantidad mínima de metanol, el sólido se filtra y el filtrado se reduce bajo vacío para dejar un sólido blanco que se seca bajo vacío caliente para proporcionar ácido 3-metil-2-oxo-1-(2-pirazinil)-4-imidazolidinacarboxílico (242 mg, ~0.7 mmoles) que se usa en la siguiente etapa.

$$\text{LC/EM } [\text{M}+\text{H}]^+ = 223.$$

EJEMPLO 77

1-(2-cloro-3-piridinil)-N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (E77) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil}-4-imidazolidinacarboxílico)



A una solución de ácido 1-(2-cloro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxílico (179 mg, 0.484 mmoles) y N-etilmorfolina (0.368 ml, 2.91 mmoles) en diclorometano (5 ml) se añade hidrato de 1-hidroxibenzotriazol (111 mg, 0.726 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (139 mg, 0.726 mmoles) y la mezcla se agita durante 10 minutos a temperatura ambiente. Se añade 1-(2,4-diclorofenil)metanamina (128 mg, 0.726 mmoles) y la mezcla de reacción se agita a temperatura ambiente toda la noche. La mezcla de reacción se diluye con diclorometano y se lava con solución saturada de carbonato ácido de sodio, agua y salmuera y se separa mediante frita hidrófoba y la solución se reduce bajo vacío. El residuo se purifica por cromatografía en gel de sílice automatizada SP4 eluyendo con 10-100% de acetato de etilo en isohexano

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para proporcionar 1-(2-cloro-3-piridinil)-N-[[2,4-diclorofenil]metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (60 mg, 27.6% de rendimiento).

LC/EM $[M+H]^+ = 413$, tiempo de retención = 2.21 minutos.

El ácido 1-(2-cloro-3-piridinil)-3-metil-2-oxo-4-

5 imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) A una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (650 mg, 3.25 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-

10 [[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico) y 3-bromo-2-cloropiridina (625 mg, 3.25 mmoles) en 1,4-dioxano (30 ml) se añade carbonato de cesio (4231 mg, 12.98 mmoles), tris(dibencilidenoacetona)dipaladio (0) (149 mg, 0.162 mmoles) y Xantphos™ (141 mg, 0.243 mmoles) y la reacción se agita a reflujo toda a noche. La mezcla de reacción se deja enfriar y el solvente se

15 remueve bajo vacío y el residuo se divide entre acetato de etilo y agua. La capa orgánica se separa y se lava con solución saturada de carbonato ácido de sodio, agua y salmuera y se separa mediante una frita hidrófoba. La solución orgánica se reduce bajo vacío y el residuo se purifica mediante cromatografía en gel de sílice automatizada SP4 eluyendo con 10-80% de

20 acetato de etilo en iso-hexano para proporcionar 1-(2-cloro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (579 mg, 51.5% de rendimiento).

LC/EM $[M+H]^+ = 312$.

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(ii) Se añade ácido trifluoroacético (2.5 ml) a una solución de 1-(2-cloro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (579 mg, 1.857 mmoles) en diclorometano (10 ml) y la solución se agita a temperatura ambiente durante 36 horas. El solvente se evapora bajo vacío formando azeótropo con tolueno y el residuo se seca bajo vacío caliente toda la noche 1-(2-cloro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxílico (537 mg, 70.4% de rendimiento) que se usa crudo en la siguiente etapa.

LC/EM MH⁺ = 256.

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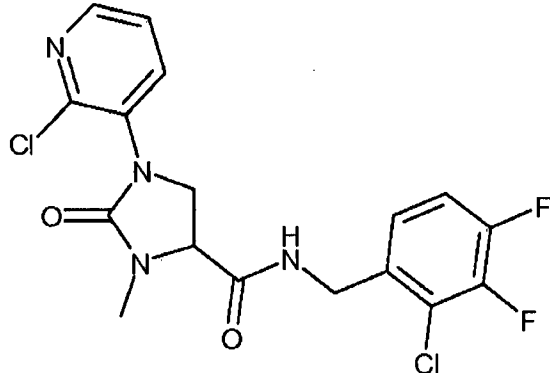
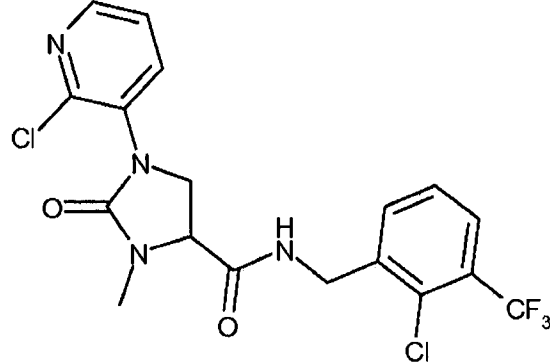
EJEMPLOS 78-79

(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

En una manera análoga a la que se describe para el ejemplo 77 anterior los compuestos tabulados posteriormente (cuadro 12) se preparan mediante la sustitución de la amina apropiada (o su sal) para la [1-(2,4-diclorofenil)metil]amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 12 son disponibles de fuentes comerciales o se pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

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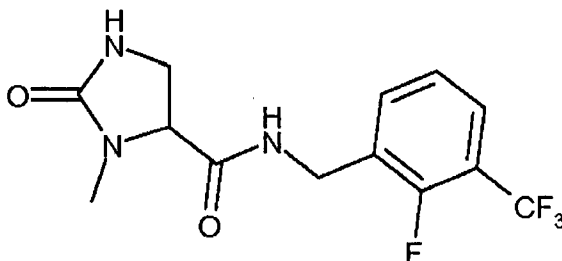
CUADRO 12

No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E78	 N-[(2-cloro-3,4-difluorofenil)metil]-1-(2-cloro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida	415	2.07
E79	 1-(2-cloro-3-piridinil)-N-[[2-cloro-3-(trifluorometil)fenil]metil]-3-metil-2-oxo-4-imidazolidinacarboxamida	447	2.29

30A

EJEMPLO 80

N-{[2-fluoro-3-(trifluorometil)fenil]metil}metil-3-metil-2-oxo-4-imidazolidinacarboxamida (E80) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)



Una mezcla de ácido 3-metil-2-oxo-4-imidazolidinacarboxílico (86 mg, 0.6 mmoles) (preparada como se describe en el ejemplo 28 a partir de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo, por si misma preparada como se describe en la etapa (iii) del ejemplo 13, iniciando originalmente a partir de ácido (4S)-2-oxo-3-{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico), N-etil morfolina (0.380 ml, 3.00 mmoles), hidrato de 1-hidroxibenzotriazol (110 mg, 0.720 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (138 mg, 0.720 mmoles) en diclorometano (9 ml) se agita a temperatura ambiente durante 10 minutos, bajo una atmósfera de argón. Se añade {[2-fluoro-3-(trifluorometil)fenil]metil}amina (0.1 ml, 0.684 mmoles) y la reacción se agita toda la noche bajo una atmósfera de argón. La mezcla de reacción se diluye con diclorometano (10 ml) y la solución se lava con solución saturada de carbonato ácido de sodio (10 ml), agua (10 ml), solución de ácido cítrico (10 ml) y salmuera (10 ml). La capa de ácido cítrico

se re-extrae con diclorometano y los extractos de diclorometano se combinan, se secan y se evaporan. El residuo se purifica mediante HPLC automatizada dirigida de masa. Las fracciones que contienen el producto se colectan y el solvente se evapora *in vacuo* para proporcionar N-{{2-fluoro-3-(trifluorometil)fenil}metil}-3-metil-2-oxo-4-imidazolidinacarboxamida (16 mg, 8% de rendimiento) como un sólido blanco.

LC/EM $[M+H]^+ = 320$, tiempo de retención = 1.85 minutos.

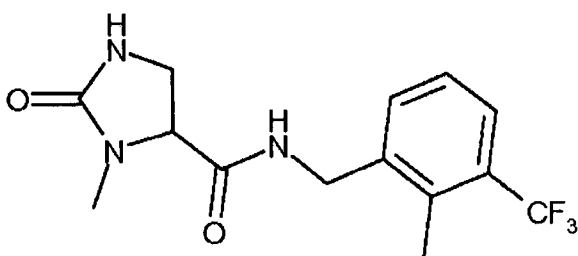
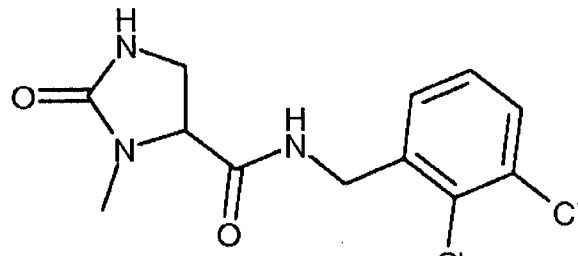
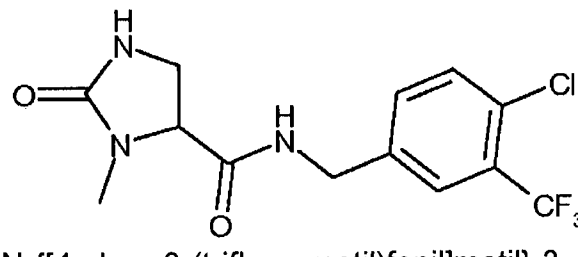
EJEMPLOS 81-83

10 (en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
{{(fenilmetil)oxi}carbonil}-4-imidazolidinacarboxílico)

En una manera análoga a la que se describe para el ejemplo 80 anterior los compuestos tabulados posteriormente (cuadro 13) se preparan mediante la sustitución de la amina apropiada (o su sal) por la {{2-fluoro-3-(trifluorometil)fenil}metil}amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 13 son disponibles de fuentes comerciales o se pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

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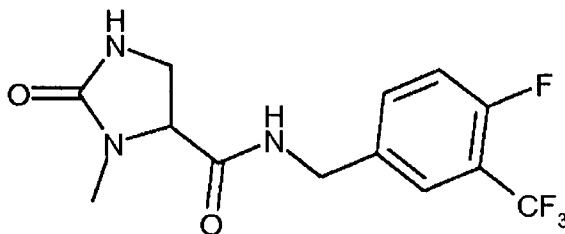
CUADRO 13

No. de ej.	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
5 E81	 3-metil-N-([2-metil-3-(trifluorometil)fenil]metil)-2-oxo-4-imidazolidinacarboxamida	316	1.94
10 E82	 N-([2,3-diclorofenil]metil)-3-metil-2-oxo-4-imidazolidinacarboxamida	302	1.78
15 E83	 N-([4-cloro-3-(trifluorometil)fenil]metil)-3-metil-2-oxo-4-imidazolidinacarboxamida	336	2.00

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EJEMPLO 84

N-{[4-fluoro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-4-imidazolidinacarboxamida (E84) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico)



Una mezcla de ácido 3-metil-2-oxo-4-imidazolidinacarboxílico (86 mg, 0.6 mmoles) (preparada como se describe en el ejemplo 28 a partir de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo, por si misma preparada como se describe en la etapa (iii) del ejemplo 13, iniciando originalmente a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico), N-etil morfolina (0.380 ml, 3.00 mmoles), hidrato de 1-hidroxibenzotriazol (110 mg, 0.720 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (138 mg, 0.720 mmoles) en diclorometano (9 ml) se agita a temperatura ambiente durante 10 minutos, bajo una atmósfera de argón. Se añade {[4-fluoro-3-(trifluorometil)fenil]metil}amina (127 mg, 0.660 mmoles) y la reacción se agita toda la noche bajo una atmósfera de argón. La mezcla de reacción se diluye con diclorometano (10 ml) y la solución se lava con solución saturada de carbonato ácido de sodio (10 ml), agua (10 ml) y salmuera (10 ml). La solución orgánica se seca y el solvente se evapora *in*

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vacuo. El residuo se purifica mediante HPLC automatizada dirigida de masa. Las fracciones que contienen el producto se colectan y el solvente se evapora *in vacuo* para proporcionar N-{[4-fluoro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-4-imidazolidinacarboxamida (8 mg, 4% de rendimiento) como un sólido

5 blanco.

LC/EM $[M+H]^+ = 320$, tiempo de retención = 1.87 minutos.

EJEMPLO 85-87

(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-

10 {[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

En una manera análoga a la que se describe para el ejemplo 84 anterior los compuestos tabulados posteriormente (cuadro 14) se preparan mediante la sustitución de la amina apropiada (o su sal) por la {[4-fluoro-3-

15 (trifluorometil)fenil]metil}amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 14 son disponibles de fuentes comerciales o se pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

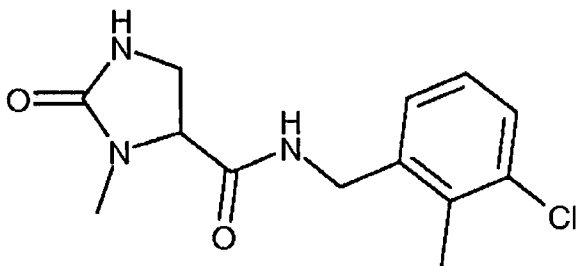
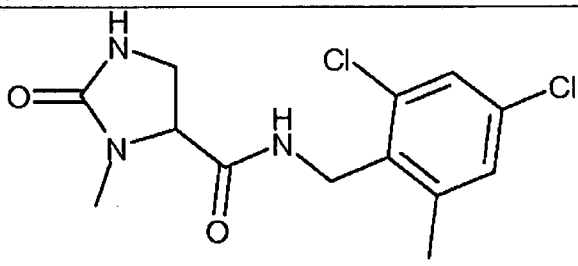
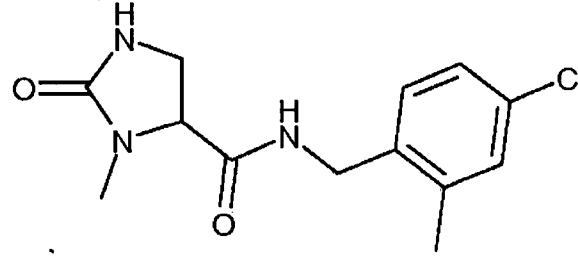
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CUADRO 14

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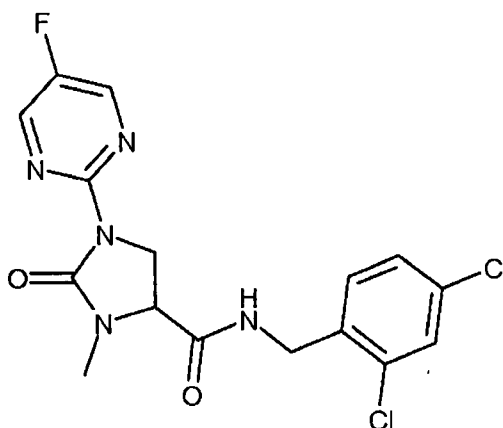
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No. de ej.	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E85	 N-[(3-cloro-2-metilfenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida	282	1.78
E86	 N-[(2,4-dicloro-6-metilfenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida	316	1.97
E87	 N-[(4-cloro-2-metilfenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida	282	1.87

EJEMPLO 88

N-[(2,4-diclorofenil)metil]-1-(5-fluoro-2-pirimidinil)-3-metil-2-oxo-4-
imidazolidinacarboxamida (E88) (en una forma obtenible o preparada a
partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil}-4-
imidazolidinacarboxílico



Se suspende ácido 1-(5-fluoro-2-pirimidinil)-3-metil-2-oxo-4-imidazolidinacarboxílico (211 mg, 0.878 mmoles) en diclorometano (5 ml) bajo argón y se trata con N-etilmorfolina (0.667 ml, 5.27 mmoles), hidrato de 1-hidroxibenzotriazol (161 mg, 1.054 mmoles), y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (202 mg, 1.054 mmoles) y se agita a temperatura ambiente durante ~5 minutos. La mezcla después se trata con 1-(2,4-diclorofenil)metanamina (0.117 ml, 0.878 mmoles) y se deja agitar toda la noche a temperatura ambiente. La mezcla se diluye con diclorometano (~10 ml) y se lava con solución saturada de carbonato ácido de sodio, agua, 10% de ácido cítrico acuoso, agua, y salmuera, después se filtra a través de una frita hidrófoba y se evapora. La trituración del aceite resultante con dietil éter proporciona N-[(2,4-diclorofenil)metil]-1-(5-fluoro-2-pirimidinil)-3-metil-2-oxo-4-

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imidazolidinacarboxamida (187 mg, 53.5% de rendimiento) como un sólido blanco que se colecta mediante filtración y se seca *in vacuo*.

LC/EM $[M+H]^+ = 398$, tiempo de retención = 2.12 minutos.

El ácido 1-(5-fluoro-2-pirimidinil)-3-metil-2-oxo-4-

5 imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (300 mg, 1.498 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-
10 {[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico y 2-cloro-5-fluoropirimidina (0.194 ml, 1.573 mmoles) en 1,4-dioxano (10 ml) se trata con carbonato de cesio (732 mg, 2.247 mmoles), Xantphos™ (65.0 mg, 0.112 mmoles), y tris(dibencilidenoacetona)dipaladio (0) (34.3 mg, 0.037 mmoles) y después se
15 calienta a reflujo durante ~3 horas. La mezcla se enfría a temperatura ambiente, se diluye con agua (~25 ml) y se extrae con acetato de etilo (3x). Las capas de acetato de etilo combinadas se lavan con agua y después con salmuera y se evaporan para proporcionar un residuo amarillo/café. Este se purifica mediante cromatografía de columna en gel de sílice automatizada (Biotage SP-4), eluyendo con un gradiente 0-100% de acetato de etilo en
20 isohexano (8 volúmenes de columna), para proporcionar 1-(5-fluoro-2-pirimidinil)-3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (232 mg, 52.3% de rendimiento) como un sólido blanco.

(ii) Se disuelve 1-(5-fluoro-2-pirimidinil)-3-metil-2-oxo-4-

imidazolidinacarboxilato de 1,1-dimetiletilo (232 mg, 0.783 mmoles) se disuelve en una mezcla de ácido trifluoroacético (2 ml, 26.0 mmoles) y diclorometano (4 ml) a 0°C y después se deja calentar a temperatura ambiente y se agita toda la noche. La mezcla se evapora (formando azeótropo con tolueno y después con diclorometano para remover todas las trazas de TFA) para proporcionar ácido 1-(5-fluoro-2-pirimidinil)-3-metil-2-oxo-4-imidazolidinacarboxílico (211 mg) como un sólido blanco que se usa sin purificación adicional en química posterior.

LC/EM MH⁺ = 240.85.

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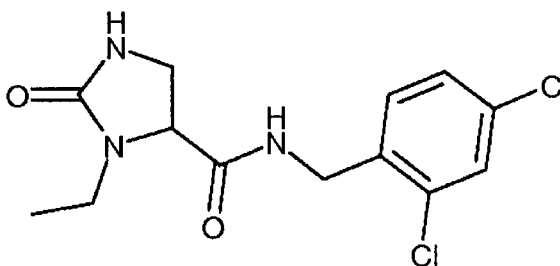
EJEMPLO 89

N-[(2,4-diclorofenil)metil]-3-etil-2-oxo-4-imidazolidinacarboxamida (E89)

(en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-

{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

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Una mezcla de ácido 3-etil-2-oxo-4-imidazolidinacarboxílico (127 mg, 0.800 mmoles), hidrato de 1-hidroxibenzotriazol (147 mg, 0.960 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (184 mg, 0.960 mmoles) y N-etil morfolina (0.409 ml, 3.20 mmoles) en diclorometano (9 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de [1-(2,4-

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diclorofenil)metil]amina (141 mg, 0.8 mmoles) en diclorometano (1 ml) se añade y la mezcla de reacción se agita a temperatura ambiente durante 18 horas. La mezcla de reacción se diluye con diclorometano (20 ml) y la mezcla se lava con solución de ácido cítrico 3N (10 ml). La fase orgánica se separa, se lava con salmuera (10 ml) y se evapora. El residuo se purifica mediante HPLC automatizada dirigida de masa. El residuo se tritura con éter y el sólido resultante se colecta y se seca para proporcionar el producto como un sólido blanco (45 mg, 18%).

LC/EM $[M+H]^+ = 316$, tiempo de retención 1.93 minutos.

El ácido 3-etil-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) A una solución agitada de 2-oxo-1,5-imidazolidinadicarboxilato de 5-(1,1-dimetiletil) 1-(fenilmetilo) (1602 mg, 5 mmoles) (preparada como se describe en la etapa (ii) del ejemplo 13, iniciando a partir del ácido (4S)-2-oxo-3-[[{(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico) en tetrahidrofurano (20 ml) bajo argón a 0°C se añade hidruro de sodio (60% de dispersión en aceite, 210 mg, 5.25 mmoles) (manera de porción). La mezcla de reacción se agita a 10°C durante 1 hora. Se añade gota a gota ácido acético (1 ml, 17.47 mmoles) y el solvente se evapora. El residuo se divide entre acetato de etilo (30 ml) y salmuera (15 ml). Los extractos orgánicos se combinan, se secan y se evaporan. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 50-100% en acetato de etilo en isohexano para proporcionar 2-oxo-1,4-imidazolidinadicarboxilato de 4-(1,1-dimetiletil) 1-(fenilmetilo) (780

mg, 49%).

LC/EM $[M+H]^+ = 321$.

(ii) Una solución agitada de 2-oxo-1,4-imidazolidinadicarboxilato de 4-(1,1-dimetiletil) 1-(fenilmetilo) (0.769 g, 2.4 mmoles) en N,N-dimetilformamida (10 ml) se enfría a -10°C bajo argón y se trata con yodoetano (0.194 ml, 2.400 mmoles). Se añade a manera de porción hidruro de sodio (60% de dispersión en aceite) (0.096 g, 2.400 mmoles). La mezcla se deja calentar a temperatura ambiente alrededor de 3 horas y se agita a temperatura ambiente durante 16 horas. El solvente se evapora y el residuo se divide entre acetato de etilo (20 ml) y salmuera (10 ml). La capa acuosa se re-extrae con acetato de etilo (20 ml) y los extractos orgánicos se combinan, se lavan con solución saturada de carbonato ácido de sodio (20 ml), agua (2 x 20 ml) y salmuera (20 ml), se seca y se evapora para proporcionar 3-etil-2-oxo-1,4-imidazolidinadicarboxilato de 4-(1,1-dimetiletil) 1-(fenilmetilo) (1.15 g) que se usa crudo en la siguiente reacción.

LC/EM $[M+H]^+ = 349$.

(ii) Una solución de 3-etil-2-oxo-1,4-imidazolidinadicarboxilato de 4-(1,1-dimetiletil) 1-(fenilmetilo) (836 mg, 2.4 mmoles) en metanol (15 ml) que contiene paladio en carbón (10% de pasta, 200 mg) se hidrogena a temperatura y presión ambiente durante 72 horas. La mezcla se filtra a través de una almohadilla de filtro y la almohadilla se lava con metanol. Los filtrados se combinan y se evaporan para proporcionar 3-etil-2-oxo-4-imidazolidinadicarboxilato de 1,1-dimetiletilo que se usa en la siguiente reacción

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(540 mg).

LC/EM $[M+H]^+ = 215$.

(iv) Una solución de 3-etil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (0.514 g, 2.4 mmoles) en ácido trifluoroacético/diclorometano (1:2, 6 ml) se agita a temperatura ambiente durante 18 horas. La solución se evapora y el residuo se co-evapora con diclorometano y se seca para proporcionar ácido 3-etil-2-oxo-4-imidazolidinacarboxílico (asume ~2.4 mmoles).

LC/EM $[M+H]^+ = 159$.

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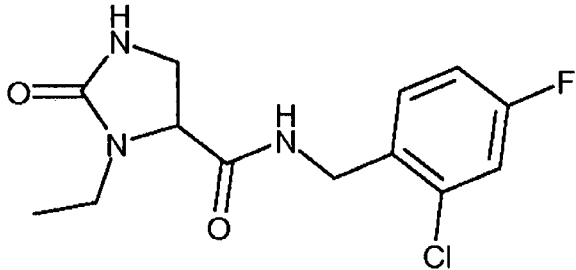
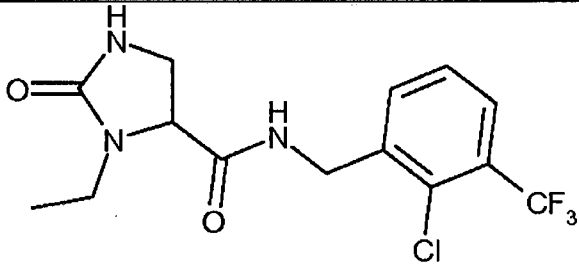
EJEMPLOS 90-91

(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

15 En una manera análoga a la que se describe para el ejemplo 89 anterior los compuestos tabulados posteriormente (cuadro 15) se preparan mediante la sustitución de la amina apropiada (o su sal) por la [1-(2,4-diclorofenil)metil]amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 15 son disponibles de fuentes comerciales o se pueden
20 preparar usando rutas descritas previamente en la literatura química o métodos análogos.

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CUADRO 15

No. de ej.	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E90	 N-[(2-cloro-4-fluorofenil)metil]-3-etil-2-oxo-4-imidazolidinacarboxamida	300	1.74
E91	 N-[[2-cloro-3-(trifluorometil)fenil]metil]-3-etil-2-oxo-4-imidazolidinacarboxamida	350	2.05

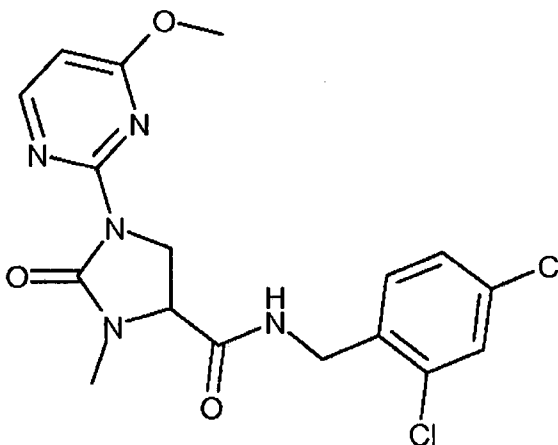
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EJEMPLO 92

N-[(2,4-diclorofenil)metil]-3-metil-1-[4-(metiloxi)-2-pirimidinil]-2-oxo-4-imidazolidinacarboxamida (E92) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil)-4-imidazolidinacarboxílico)



Se trata ácido 3-metil-1-[4-(metiloxi)-2-pirimidinil]-2-oxo-4-imidazolidinacarboxílico (76 mg, 0.3 mmoles) (~0.3 mmoles) en diclorometano (4 ml) se trata con los tamices moleculares 4A (200 mg, 0.300 mmoles), y la mezcla se agita a temperatura ambiente durante 5 minutos. Después se añade N-etilmorfolina (0.190 ml, 1.500 mmoles), hidrato de 1-hidroxibenzotriazol (55.1 mg, 0.360 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (82 mg, 0.360 mmoles) y la reacción se agita a temperatura ambiente bajo argón durante 10 minutos. Se añade [(2,4-diclorofenil)metil]amina (58.1 mg, 0.330 mmoles) y la reacción se deja agitar a temperatura ambiente bajo argón durante 4 horas. La mezcla de reacción se diluye con diclorometano (15 ml) y solución saturada de carbonato ácido de

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sodio (20 ml), y el producto se extrae en diclorometano (x2). Los extractos orgánicos combinados se lavan con agua (20 ml), salmuera (20 ml) y después se secan sobre sulfato de magnesio. El solvente se evapora *in vacuo* para proporcionar un sólido amarillo, que se purifica mediante HPLC automatizada
5 dirigida de masa. Las fracciones que contienen el producto se combinan y el solvente se evapora *in vacuo*, se co-evapora con dietil éter para proporcionar N-[(2,4-diclorofenil)metil]-3-metil-1-[4-(metiloxi)-2-pirimidinil]-2-oxo-4-imidazolidinacarboxamida como un sólido blanco (60 mg, 46.3% de rendimiento).

10 LC/EM $[M+H]^+ = 410$, tiempo de retención = 1.73 minutos.

El ácido 3-metil-1-[4-(metiloxi)-2-pirimidinil]-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) Una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de
15 1,1-dimetiletilo (500 mg, 2.497 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-imidazolidinacarboxílico) y 2-cloro-4-(metiloxi)pirimidina (361 mg, 2.497 mmoles) en 1,4-dioxano (20 ml) se trata con carbonato de cesio (1220 mg, 3.75 mmoles), Xantphos™ (108 mg, 0.187
20 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (57.2 mg, 0.062 mmoles) y la mezcla se calienta a reflujo bajo argón durante 3 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con agua (15 ml) y se extrae con acetato de etilo (x2, 20 ml). Las capas orgánicas

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se combinan, se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre sulfato de magnesio y después se evaporan *in vacuo*. El residuo se purifica mediante cromatografía instantánea en gel de sílice eluyendo con 0-10% de metanol en diclorometano. Las fracciones que contienen el producto se combinan y el solvente se evapora *in vacuo* para proporcionar un aceite amarillo. El residuo se purifica nuevamente mediante cromatografía instantánea en gel de sílice, eluyendo con 0-100% de acetato de etilo en isohexano para proporcionar 3-metil-1-[4-(metiloxi)-2-pirimidinil]-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetietilo como un aceite amarillo (100 mg, 13% de rendimiento).

LC/EM $[M+H]^+$ 309.

(ii) Una solución de 3-metil-1-[4-(metiloxi)-2-pirimidinil]-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetietilo (100 mg, 0.324 mmoles) en diclorometano (0.6 ml)/ácido trifluoroacético (0.300 ml) se agita a temperatura ambiente durante 24 horas. La solución se evapora y el residuo se co-evapora con tolueno (x3) y después diclorometano (x4). El producto después se seca en un horno *in vacuo* (50⁰C) para proporcionar ácido 3-metil-1-[4-(metiloxi)-2-pirimidinil]-2-oxo-4-imidazolidinacarboxílico crudo como una goma amarilla (95 mg, ~ 0.3 mmoles) que se usa en la siguiente reacción.

20 LC/EM $[M+H]^+$ 253.

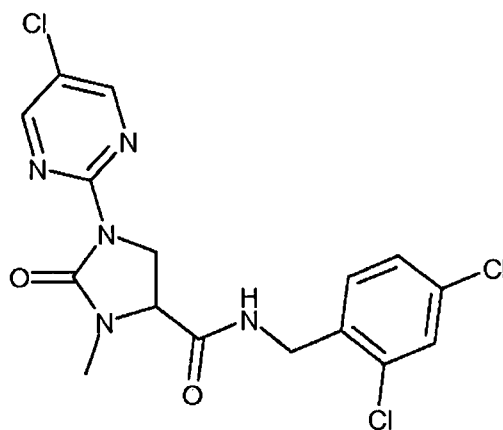
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EJEMPLO 93

1-(5-cloro-2-pirimidinil)-N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-
imidazolidinacarboxamida (E93) (en una forma obtenible o preparada a
partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil}-4-
imidazolidinacarboxílico)

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En una manera análoga a la que se describe en el ejemplo 88 anterior 1-(5-cloro-2-pirimidinil)-N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida se prepara sustituyendo 2,5-dicloropirimidina por 2-cloro-5-fluoropirimidina usada en la etapa (i) del procedimiento anterior.

LC/EM $[M+H]^+ = 412$, tiempo de retención = 2.34 minutos.

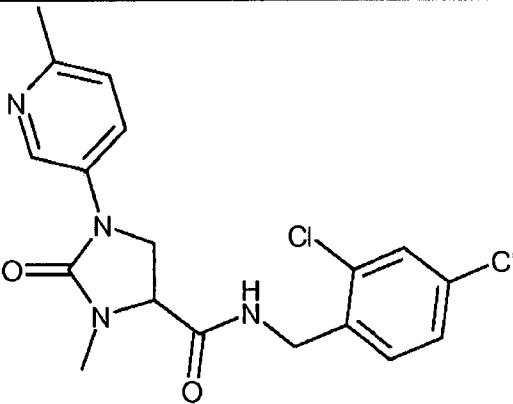
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EJEMPLOS 94-95

**(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)**

- 5 En una manera análoga a la que se describe para el ejemplo 13 anterior, los compuestos tabulados posteriormente (cuadro 16) se preparan mediante la sustitución de la amina apropiada (o su sal) por la {[2-cloro-3-(trifluorometil)fenil]metil}amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 16 son disponibles de fuentes comerciales o se
- 10 pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

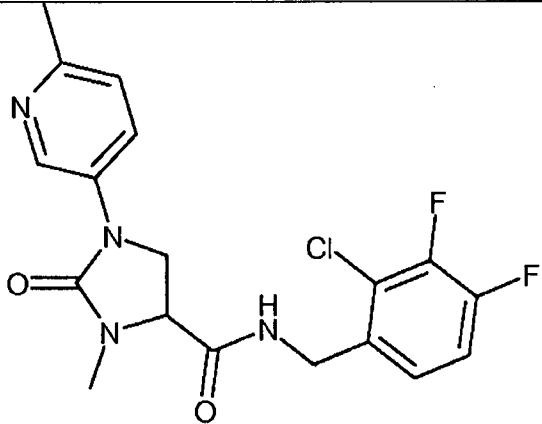
CUADRO 16

15	No. de ejemplo	Nombre químico	$[M+H]^+$	Tiempo de retención (minutos)
20	94	 N-[(2,4-diclorofenil)metil]-3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida	393	2.27

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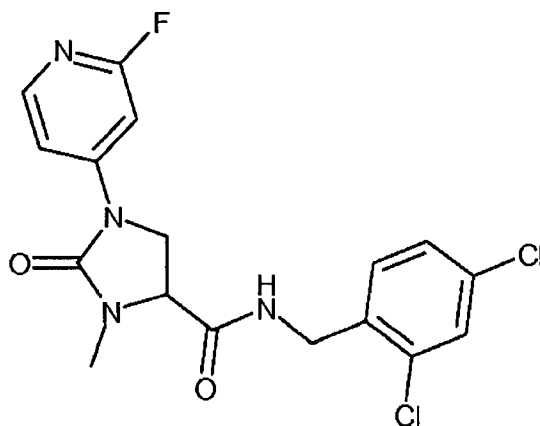
No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
95	 N-[(2-cloro-3,4-difluorofenil)metil]-3-metil-1-(6-metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida	395	2.11

EJEMPLO 96

N-[(2,4-diclorofenil)metil]-1-(2-fluoro-4-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida (E96) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil)-4-imidazolidinacarboxílico)

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Una solución de ácido 1-(2-fluoro-4-piridinil)-3-metil-2-oxo-4-

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- imidazolidinacarboxílico (200 mg, 0.521 mmoles) y N-etil morfolina (0.400 ml, 3.13 mmoles) en diclorometano (10 ml) se trata con hidrato de 1-hidroxibenzotriazol (80 mg, 0.521 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (100 mg, 0.521 mmoles) y la mezcla de
- 5 reacción se agita a temperatura ambiente durante 10 minutos. Después se añade [(2,4-diclorofenil)metil]amina (0.084 ml, 0.521 mmoles) y la reacción se agita toda la noche. La mezcla de reacción se diluye con diclorometano y se lava con solución saturada de carbonato ácido de sodio, agua y salmuera y se separa a través de una frita hidrófoba. La capa orgánica se reduce bajo vacío.
- 10 El residuo se purifica por HPLC automatizada dirigida de masa para proporcionar N-[(2,4-diclorofenil)metil]-1-(2-fluoro-4-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida (64 mg, 30.3 % de rendimiento).

LC/EM $[M+H]^+ = 397$, tiempo de retención = 2.45 minutos.

- El ácido 1-(2-fluoro-4-piridinil)-3-metil-2-oxo-4-
- 15 imidazolidinacarboxílico usado en el procedimiento anterior se prepara en una manera análoga a la que se describe en el ejemplo 67 anterior sustituyendo 4-bromo-2-fluoropiridina por 2-fluoro-3-yodopiridina usada en la etapa (i) del ejemplo 67 del procedimiento.

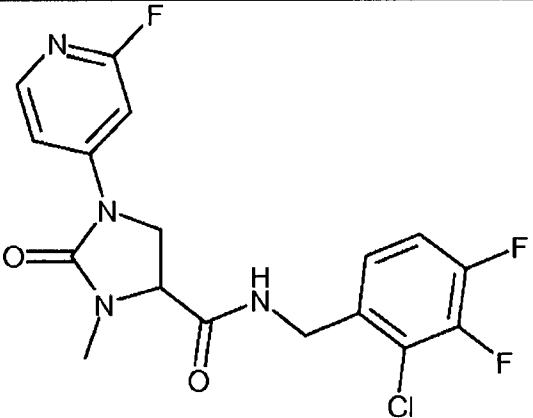
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EJEMPLOS 97-98

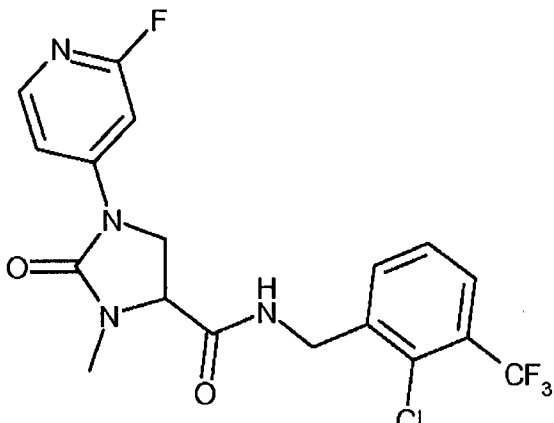
**(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)**

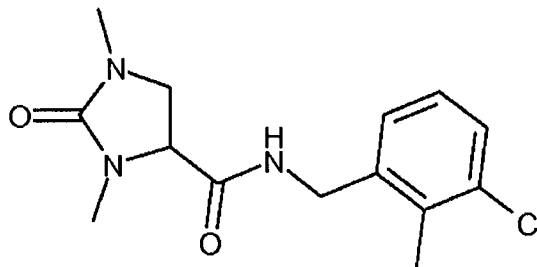
- 5 En una manera análoga a la que se describe para el ejemplo 96 anterior los compuestos tabulados posteriormente (cuadro 17) se preparan mediante la sustitución de la amina apropiada (o su sal) por la [(2,4-diclorofenil)metil]amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 17 son disponibles de fuentes comerciales o se pueden
- 10 preparar usando rutas descritas previamente en la literatura química o métodos análogos.

CUADRO 17

15	No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
20	97	 N-[(2-cloro-3,4-difluorofenil)metil]-1-(2-fluoro-4-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida	399	2.33

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No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
98	 N-[(2-cloro-3-(trifluorometil)fenil]metil}- 1-(2-fluoro-4-piridinil)-3-metil-2-oxo-4- imidazolidinacarboxamida	431	2.28

EJEMPLO 99**N-[(3-cloro-2-metilfenil)metil]-1,3-dimetil-2-oxo-4-****imidazolidinacarboxamida (E98) (en una forma obtenible o preparada a****partir de ácido (4S)-2-oxo-3-[[[(fenilmetil)oxi]carbonil]-4-****imidazolidinacarboxílico**

Se añade al ácido 1,3-dimetil-2-oxo-4-imidazolidinacarboxílico (6.000 ml, 0.600 mmoles) (solución 0.1M en diclorometano) la N-etilmorfolina (0.380 ml, 3.00 mmoles), hidrato de 1-hidroxibenzotriazol (110 mg, 0.720

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mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (138 mg, 0.720 mmoles), y la reacción se agita a temperatura ambiente bajo argón durante 10 minutos. Después se añade [(3-cloro-2-metilfenil)metil]amina (103 mg, 0.660 mmoles) y la reacción se deja agitar a temperatura ambiente bajo argón toda la noche. La mezcla de reacción se diluye con diclorometano (15 ml) y después la solución se lava con solución saturada de carbonato ácido de sodio (20 ml), agua (20 ml), solución de ácido cítrico 3N (20 ml), salmuera (20 ml) y después se seca sobre sulfato de magnesio. El solvente se evapora *in vacuo*. El residuo se purifica mediante HPLC automatizada dirigida de masa.

10 Las fracciones que contienen el producto se combinan y el solvente se evapora *in vacuo*, se co-evapora con éter dietílico para proporcionar la N-[(3-cloro-2-metilfenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida como un sólido blanco (50 mg, 26.8 % de rendimiento).

LC/EM $[M+H]^+ = 296$, tiempo de retención = 1.96 minutos.

15 El ácido 1,3-dimetil-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) Una solución agitada de 1-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (1.75 g, 8.74 mmoles) (preparada como se describe en la etapa (i) del ejemplo 49 a partir de 3-metil-2-oxo-1,5-imidazolidinadicarboxilato de 5-(1,1-dimetiletil) 1-(fenilmetilo), por si misma preparada como se describe en la etapa (ii) del ejemplo 13, iniciando originalmente a partir del ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil-4-imidazolidinacarboxílico) en N,N-dimetilformamida (22 ml) se enfría a -10°C

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bajo argón, y después se añade yoduro de metilo (2.186 ml, 35.0 mmoles). Después se añade a manera de porción hidruro de sodio (60% de dispersión en aceite) (0.329 g, 8.22 mmoles). La mezcla de reacción se deja calentar a temperatura ambiente mientras se agita bajo argón toda la noche. El solvente se evapora *in vacuo* y después el residuo se divide entre acetato de etilo (40 ml) y salmuera (30 ml). La capa acuosa se re-extrae con acetato de etilo (x2) y después los extractos orgánicos combinados se lavan con agua (x2, 50 ml), salmuera (50 ml) y se secan sobre sulfato de magnesio. El solvente se evapora *in vacuo*. El producto crudo se purifica mediante cromatografía instantánea en gel de sílice, eluyendo con 25-100% de acetato de etilo/iso-hexano. Las fracciones que contienen el producto se combinan y el solvente se evapora *in vacuo* para proporcionar un aceite amarillo, 1,3-dimetil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetietilo (1.48 g, 79% de rendimiento).

(ii) Una solución de 1,3-dimetil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetietilo (1.92 g, 8.96 mmoles) en diclorometano (12 ml)/ácido trifluoroacético (6.00 ml) se agita a temperatura ambiente durante 24 horas. La solución se evapora y el residuo se co-evapora con tolueno (x3) y después diclorometano (x2). El producto después se seca para proporcionar ácido 1,3-dimetil-2-oxo-4-imidazolidinacarboxílico crudo (1.65 g) que se disuelve en diclorometano (90 ml) para proporcionar una solución ~0.1M en diclorometano que se usa en reacciones subsecuentes.

$$\text{LC/EM } [\text{M}+\text{H}]^+ = 159.$$

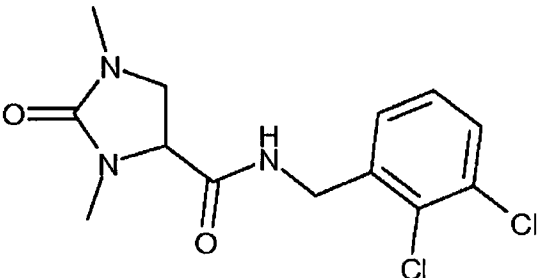
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EJEMPLOS 100-108

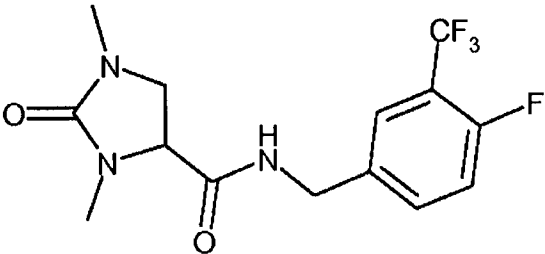
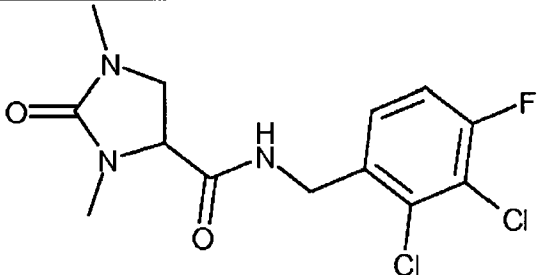
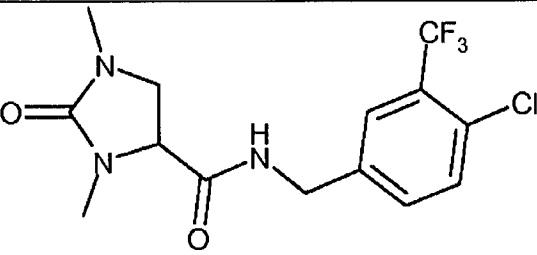
(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

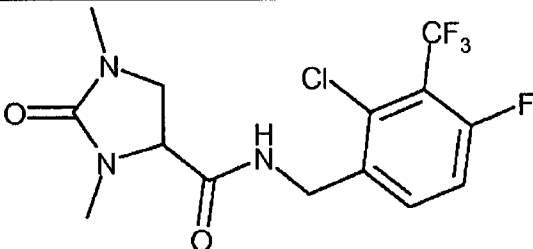
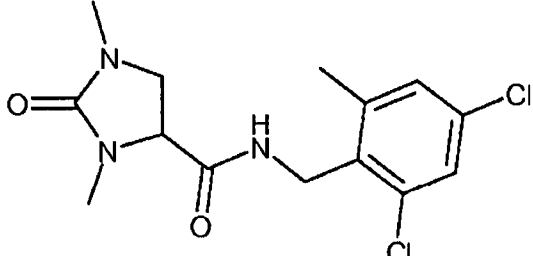
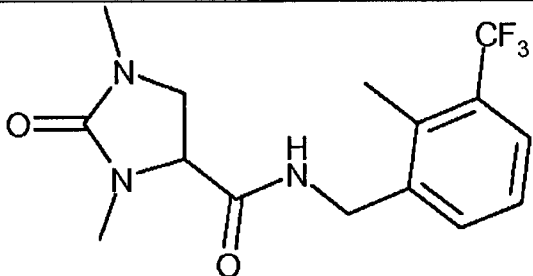
- 5 En una manera análoga a la que se describe para el ejemplo 99 anterior los compuestos tabulados posteriormente (cuadro 18) se prepara mediante la sustitución de la amina apropiada (o su sal) por la [(3-cloro-2-metilfenil)metil]amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 18 son disponibles de fuentes comerciales o se pueden
- 10 preparar usando rutas descritas previamente en la literatura química o métodos análogos.

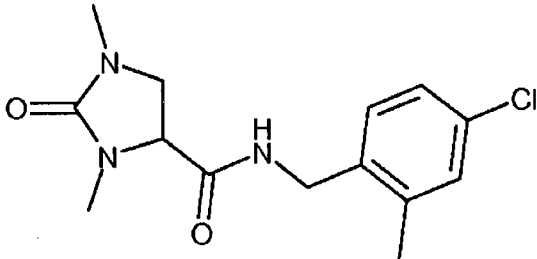
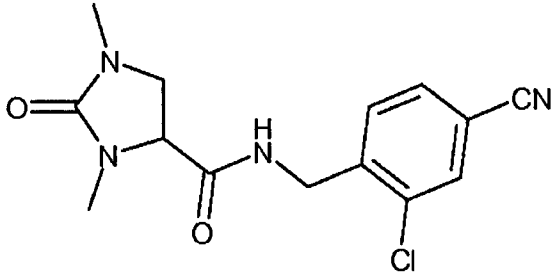
CUADRO 18

15	No. de ejemplo	Nombre químico	$[M+H]^+$	Tiempo de retención (minutos)
20	E100	 N-[(2,3-diclorofenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxiamida	316	1.97

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No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E101	 N-([4-fluoro-3-(trifluorometil)fenil]metil)- 1,3-dimetil-2-oxo-4- imidazolidinacarboxamida	334	2.06
E102	 N-((2,3-dicloro-4-fluorofenil)metil)-1,3- dimetil-2-oxo-4- imidazolidinacarboxamida	334	2.05
E103	 N-([4-cloro-3-(trifluorometil)fenil]metil)- 1,3-dimetil-2-oxo-4- imidazolidinacarboxamida	350	2.19

No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E104	 N-[(2-cloro-4-fluoro-3-(trifluorometil)fenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida	369	2.20
E105	 N-[(2,4-dicloro-6-metilfenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida	330	2.17
E106	 1,3-dimetil-N-[[2-metil-3-(trifluorometil)fenil]metil]-2-oxo-4-imidazolidinacarboxamida	330	2.17

No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E107	 N-[(4-cloro-2-metilfenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida	296	2.00
E108	 N-[(2-cloro-4-cianofenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida	307	1.68

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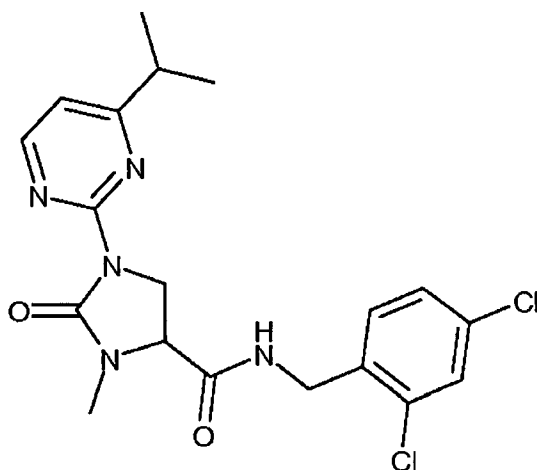
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EJEMPLO 109

N-[(2,4-diclorofenil)metil]-3-metil-1-[4-(1-metiletil)-2-pirimidinil]-2-oxo-4-imidazolidinacarboxamida (E109) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

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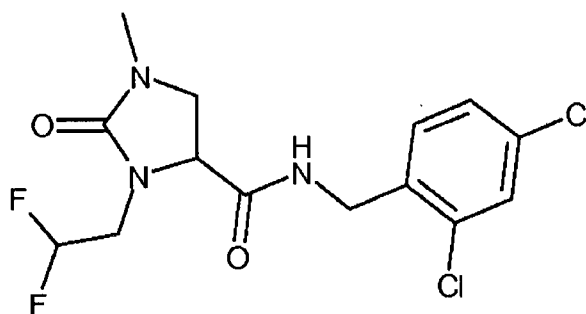
En una manera análoga a la que se describe en el ejemplo 92 anterior N-[(2,4-diclorofenil)metil]-3-metil-1-[4-(1-metiletil)-2-oxo-4-imidazolidinacarboxamida se prepara sustituyendo 2-cloro-4-(1-metiletil)pirimidina por la 2-cloro-4-(metiloxi)pirimidina usada en la etapa (i) del ejemplo 92 del procedimiento.

LC/EM $[M+H]^+ = 422$, tiempo de retención = 2.42 minutos.

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EJEMPLO 110

N-[(2,4-diclorofenil)metil]-3-(2,2-difluoroetil)-1-metil-2-oxo-4-
imidazolidinacarboxamida (E110) (en una forma obtenible o preparada a
partir del ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil)-4-
imidazolidinacarboxílico)



Una mezcla de ácido 3-(2,2-difluoroetil)-1-metil-2-oxo-4-imidazolidinacarboxílico (105 mg, 0.505 mmoles), hidrato de 1-hidroxibenzotriazol (93 mg, 0.606 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (116 mg, 0.606 mmoles) y N-etil morfolina (0.258 ml, 2.020 mmoles) en diclorometano (7 ml) se agita a temperatura ambiente durante 10 minutos. Se añade [1-(2,4-diclorofenil)metil]amina (89 mg, 0.505 mmoles), se añade un sólido precipitado y DMF (1 ml). La mezcla de reacción se agita a temperatura ambiente durante 18 horas, después se diluye con diclorometano (10 ml), se lava con solución saturada de carbonato ácido de sodio (10 ml), agua (10 ml), solución de ácido cítrico (10 ml) y salmuera (10 ml). La fase orgánica se seca (sulfato de magnesio) y se evapora. El residuo se purifica mediante cromatografía en gel de sílice usando 0-20% de metanol en diclorometano seguido por HPLC automatizada dirigida de masa. La

fracción que contiene el producto deseado se evapora y el residuo se tritura con éter dietílico y se seca para proporcionar un sólido blanco (10 mg).

LC/EM $[M+H]^+ = 366$, tiempo de retención 2.29 minutos.

El ácido 3-(2,2-difluorofenil)-1-metil-2-oxo-4-

5 imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

(i) A una solución de 1-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (200 mg, 0.999 mmoles) (preparada como se describe en la etapa (i) del ejemplo 49 a partir de 3-metil-2-oxo-1,5-imidazolidinadicarboxilato
10 de 5-(1,1-dimetiletil) 1-(fenilmetilo), por si misma preparada como se describe en la etapa (ii) del ejemplo 13, iniciando originalmente a partir del ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil-4-imidazolidinacarboxílico en N,N-dimetilformamida (10 ml) a -35°C bajo argón se añade hidruro de sodio (39.9 mg, 0.999 mmoles). La mezcla se agita durante 15 minutos, se añade
15 trifluorometanosulfonato de 2,2-difluoroetilo (428 mg, 1.998 mmoles) y la mezcla de reacción se agita a -35°C durante 30 minutos después se calienta lentamente a -15°C. Después de 1 hora la mezcla de reacción se templea con agua (10 ml), se calienta a temperatura ambiente y se extrae con acetato de etilo (20 ml, x2). Las capas orgánicas combinadas se lavan con solución
20 saturada de carbonato ácido de sodio (15 ml), agua (10 ml x2) y salmuera (15 ml). La capa orgánica después se seca (sulfato de magnesio), se filtra y se evapora. El residuo crudo se purifica mediante cromatografía en gel de sílice eluyendo con 10-100% de acetato de etilo en isohexano para proporcionar 3-

(2,2-difluoroetil)-1-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (178 mg).

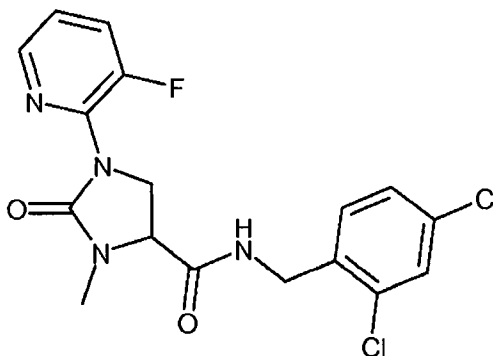
LC/EM $[M+H]^+ = 265$.

(ii) 3-(2,2-difluoroetil)-1-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (178 mg, 0.674 mmoles) se disuelve en diclorometano (3.00 ml) y se añade ácido trifluoroacético (1 ml). La solución se agita a temperatura ambiente durante 2 horas. El solvente se evapora y el residuo se co-evapora con diclorometano y tolueno para proporcionar un ácido 3-(2,2-difluoroetil)-1-metil-2-oxo-4-imidazolidinacarboxílico crudo (asume 0.674 mmoles) que se usa para la siguiente reacción.

LC/EM $[M+H]^+ = 209$.

EJEMPLO 111

N-[(2,4-diclorofenil)metil]-1-(3-fluoro-2-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida (E111) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[[fenilmetil]oxi]carbonil]-4-imidazolidinacarboxílico)



En una manera análoga a la que se describe en el ejemplo 67

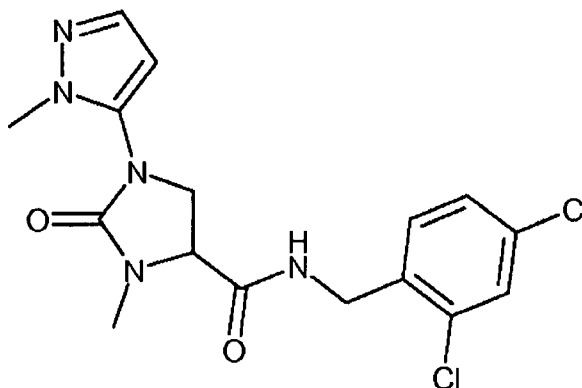
339

anterior N-[(2,4-diclorofenil)metil]-1-(3-fluoro-2-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida se prepara sustituyendo 2-bromo-3-fluoropiridina por 2-fluoro-3-yodopiridina usada en la etapa (i) del ejemplo 67 del procedimiento.

5 LC/EM $[M+H]^+ = 397$, tiempo de retención = 2.32 minutos.

EJEMPLO 112

N-[(2,4-diclorofenil)metil]-3-metil-1-(1-metil-1H-pirazol-5-il)-2-oxo-4-
imidazolidinacarboxamida (E112) (en una forma obtenible o preparada a
10 partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil}-4-
imidazolidinacarboxílico)



15

A una mezcla agitada de N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxílico (200 mg, 0.662 mmoles) (preparada como se describe en el ejemplo 30), 5-yodo-1-metil-1H-pirazol (165 mg, 0.794 mmoles) en 1,4-dioxano (20 ml) se añade fosfato de potasio (703 mg, 3.31 mmoles), yoduro de cobre (I) (126 mg, 0.662 mmoles) y trans-N,N-dimetilciclohexano-1,2-diamina (0.104 ml, 0.662 mmoles) y la mezcla de reacción se calienta a

20

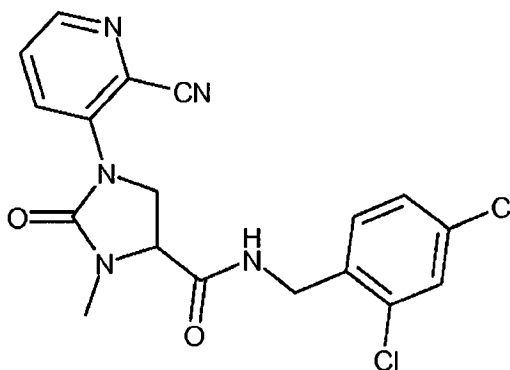
360

reflujo bajo argón durante 18 horas. Después del enfriamiento a temperatura ambiente, acetato de etilo (20 ml), agua (10 ml) y 0.880 de solución de amoníaco (5 ml) se añade. La capa orgánica se separa y la capa acuosa se extrae con acetato de etilo (2 x 20 ml). Los extractos orgánicos se combinan, se lavan con solución de ácido cítrico (20 ml), agua (10 ml) y salmuera (10 ml), se secan y se evaporan. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 0-10% de metanol en diclorometano seguido por HPLC automatizada dirigida de masa para proporcionar N-[(2,4-diclorofenil)metil]-3-metil-1-(1-metil-1H-pirazol-5-il)-2-oxo-4-imidazolidinacarboxamida (40 mg, 16%).

LC/EM $[M+H]^+ = 382$, tiempo de retención = 2.12 minutos.

EJEMPLO 113

1-(2-ciano-3-piridinil)-N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (E113) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil)-4-imidazolidinacarboxílico)



361

- Una suspensión de N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (200 mg, 0.662 mmoles) (preparada como se describe en el ejemplo 30) y 3-bromo-2-piridinacarbonitrilo (121 mg, 0.662 mmoles) en 1,4-dioxano (5 ml) se trata con carbonato de cesio (323 mg, 0.993 mmoles), Xantphos™ (28.7 mg, 0.050 mmoles) y tris(dibencilidenoacetona)dipaladio (0) (15.15 mg, 0.017 mmoles) y la mezcla se calienta a reflujo bajo argón durante toda la noche. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluye con solución saturada de carbonato ácido de sodio y se extrae con diclorometano.
- 10 Las capas orgánicas se combinan, se lavan con agua y salmuera y se evaporan *in vacuo*. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 10-100% de acetato de etilo en isohexano para proporcionar 1-(2-ciano-3-piridinil)-N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (212 mg, 78% de rendimiento).
- 15 LC/EM $[M+H]^+ = 404$, tiempo de retención = 2.32 minutos.

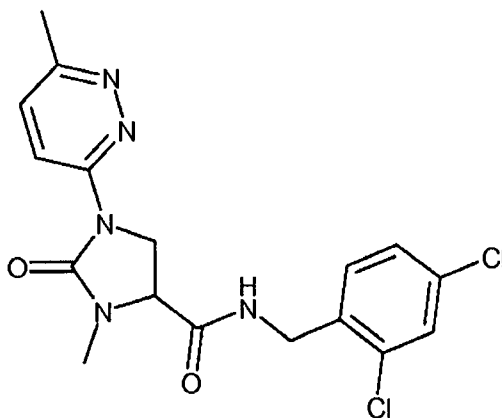
362

EJEMPLO 114

N-[(2,4-diclorofenil)metil]-3-metil-1-(6-metil-3-piridazinil)-2-oxo-4-imidazolidinacarboxamida (E114) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil}-4-imidazolidinacarboxílico)

5

10



En una manera análoga a la que se describe en el ejemplo 92 anterior N-[(2,4-diclorofenil)metil]-3-metil-1-(6-metil-3-piridazinil)-2-oxo-4-imidazolidinacarboxamida se prepara sustituyendo 3-cloro-6-metilpiridazina por 2-cloro-4-(metiloxi)pirimidina usada en la etapa (i) del ejemplo 92 del procedimiento.

15

LC/EM $[M+H]^+ = 394$, tiempo de retención = 1.96 minutos.

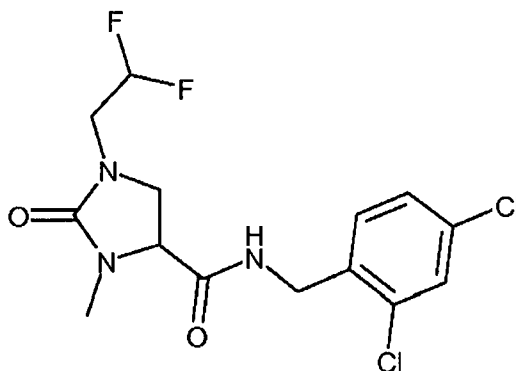
EJEMPLO 115

N-[(2,4-diclorofenil)metil]-1-(2,2-difluoroetil)-3-metil-2-oxo-4-

imidazolidinacarboxamida (E115) (en una forma obtenible o preparada a

partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil]-4-

imidazolidinacarboxílico)



Una mezcla de ácido 1-(2,2-difluoroetil)-3-metil-2-oxo-4-

imidazolidinacarboxílico (125 mg, 0.6 mmoles), hidrato de 1-hidroxibenzotriazol (110 mg, 0.720 mmoles), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (138 mg, 0.720 mmoles) y N-etil morfolina (0.305 ml, 2.400 mmoles) en diclorometano (5 ml) se agita durante 10 minutos. Se añade [(2,4-diclorofenil)metil]amina (106 mg, 0.600 mmoles) y la solución se agita a temperatura ambiente durante 3 días. La mezcla de reacción se diluye con diclorometano (10 ml), se lava con solución saturada de carbonato ácido de sodio (10 ml), agua (10 ml), y salmuera (10 ml). La fase orgánica se seca (sulfato de magnesio) y se evapora. El residuo se purifica mediante HPLC automatizada dirigida de masa. La fracción que contiene el producto deseado se evapora y el residuo se tritura con éter dietílico y se seca para proporcionar N-[(2,4-diclorofenil)metil]-1-(2,2-difluorofenil)-3-metil-2-oxo-4-

364

imidazolidinacarboxamida (25 mg).

LC/EM $[M+H]^+ = 366$, tiempo de retención = 2.09 minutos.

El ácido 1-(2,2-difluorofenil)-3-metil-2-oxo-4-

imidazolidinacarboxílico usado en el método descrito anteriormente se prepara

5 como sigue:

(i) A una solución de 3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (200 mg, 0.999 mmoles) (preparada como se describe en la etapa (iii) del ejemplo 13, iniciando a partir del ácido (4S)-2-oxo-3-
10 {{{(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico) y trifluorometanosulfonato de 2,2-difluoroetilo (428 mg, 1.998 mmoles) en N,N-dimetilformamida (4 ml) a -35°C bajo argón se añade hidruro de sodio (80 mg, 1.998 mmoles). La mezcla de reacción se calienta a 0°C alrededor de 2 horas, se templea con agua (10 ml) y se extrae con acetato de etilo (20 ml x 2). Las capas orgánicas combinadas se lavan con solución saturada de carbonato ácido de sodio (15
15 ml), agua (10 ml x 2) y salmuera (15 ml). La capa orgánica se seca (sulfato de magnesio), se filtra y se evapora. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con 10-100% de acetato de etilo en isohexano para proporcionar 1-(2,2-difluoroetil)-3-metil-2-oxo-4-
imidazolidinacarboxilato de 1,1-dimetiletilo (200 mg).

20 LC/EM $[M+H]^+ = 265$.

(ii) Se disuelve 1-(2,2-difluoroetil)-3-metil-2-oxo-4-imidazolidinacarboxilato de 1,1-dimetiletilo (200 mg, 0.757 mmoles) en diclorometano (3 ml) y ácido trifluoroacético (1 ml) se añade. La solución se

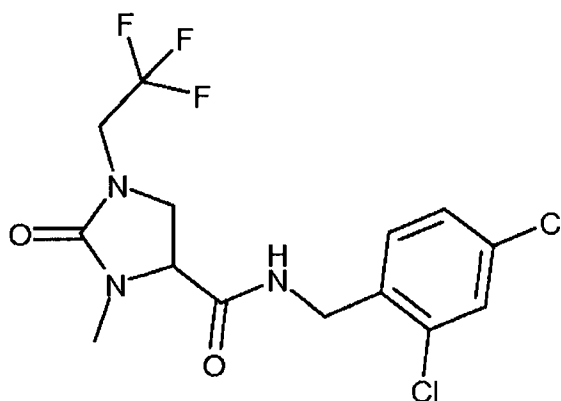
365

agita a temperatura ambiente durante 2 horas. El solvente se evapora y el residuo se co-evapora con tolueno (x2) para proporcionar ácido 1-(2,2-difluoroetil)-3-metil-2-oxo-4-imidazolidinacarboxílico (0.757 mmoles) que se usa en la siguiente etapa.

5 LC/EM $[M+H]^+ = 209$.

EJEMPLO 116

N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-1-(2,2,2-trifluoroetil)-4-imidazolidinacarboxamida (E116) (en una forma obtenible o preparada a
10 partir de ácido (4S)-2-oxo-3-[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)



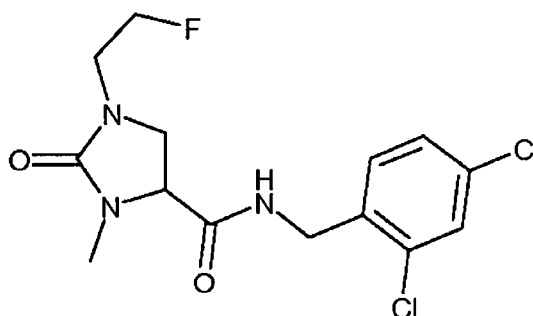
En una manera análoga a la que se describe en el ejemplo 115 anterior N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-1-(2,2,2-trifluoroetil)-4-imidazolidinacarboxamida se prepara sustituyendo triclorometanosulfonato de 2,2,2-trifluoroetilo por trifluorometanosulfonato de 2,2-difluoroetilo usado en la etapa (i) del ejemplo 115 del procedimiento.

LC/EM $[M+H]^+ = 384$, tiempo de retención = 2.41 minutos.

366

EJEMPLO 117

N-[(2,4-diclorofenil)metil]-1-(2-fluoroetil)-3-metil-2-oxo-4-
imidazolidinacarboxamida (E117) (en una forma obtenible o preparada a
partir de ácido (4S)-2-oxo-3-[[fenilmetil]oxi]carbonil]-4-
imidazolidinacarboxílico)



En una manera análoga a la que se describe en el ejemplo 115 anterior N-[(2,4-diclorofenil)metil]-1-(2-fluoroetil)-3-metil-2-oxo-4-imidazolidinacarboxamida se prepara sustituyendo 1-fluoro-2-yodoetano por trifluorometanosulfonato de 2,2-difluoroetilo usado en la etapa (i) del ejemplo 115 del procedimiento.

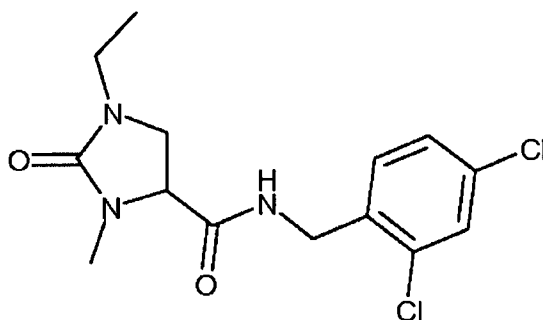
LC/EM $[M+H]^+ = 348$, tiempo de retención = 2.11 minutos.

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EJEMPLO 118

N-[(2,4-diclorofenil)metil]-1-etil}3-metil-2-oxo-4-imidazolidinacarboxamida
(E118) (en una forma obtenible o preparada a partir de ácido (4S)-2-oxo-
3-{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

5



10

En una manera análoga a la que se describe en el ejemplo 115 anterior N-[(2,4-diclorofenil)metil]-1-etil-3-metil-2-oxo-4-imidazolidinacarboxamida se prepara sustituyendo yodoetano por trifluorometanosulfonato de 2,2-difluoroetilo usado en la etapa (i) del ejemplo 115 del procedimiento.

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LC/EM $[M+H]^+ = 330$, tiempo de retención = 2.17 minutos.

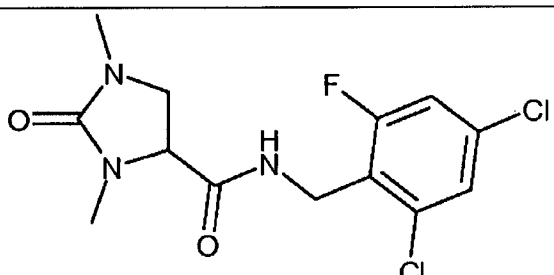
26

EJEMPLOS 119-121

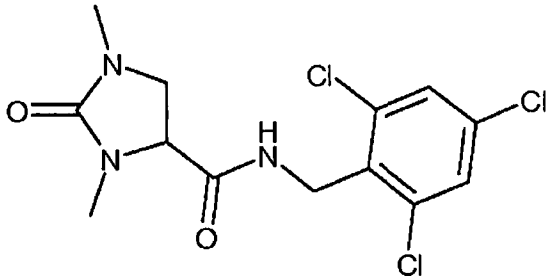
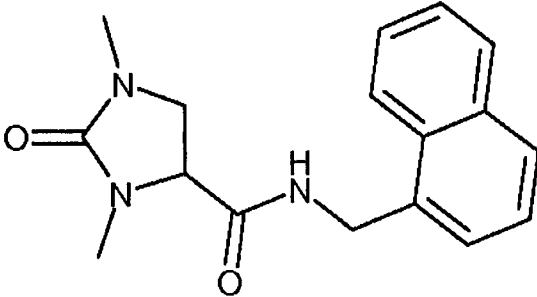
**(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
{[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)**

- 5 En una manera análoga a la que se describe para el ejemplo 99 anterior los compuestos tabulados posteriormente (cuadro 19) se preparan mediante la sustitución de la amina apropiada (o su sal) por la [(3-cloro-2-metilfenil)metil]amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 19 son disponibles de fuentes comerciales o se pueden
- 10 preparar usando rutas descritas previamente en la literatura química o métodos análogos.

CUADRO 19

15	No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
20	E119	 N-[(2,4-dicloro-6-fluorofenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida	334	2.01

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No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E120	 1,3-dimetil-2-oxo-N-[(2,4,6-triclorofenil)metil]-4-imidazolidinacarboxamida	352	2.16
E121	 1,3-dimetil-N-(1-naftalenilmetil)-2-oxo-4-imidazolidinacarboxamida	298	1.95

EJEMPLOS 122 Y 123

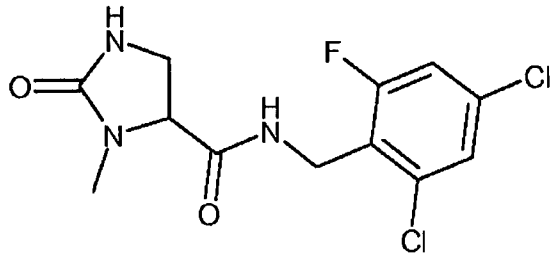
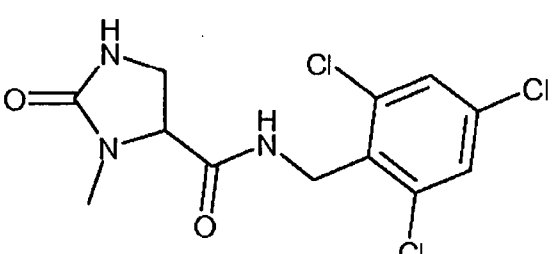
(en formas obtenibles o preparadas a partir de ácido (4S)-2-oxo-3-
 {[[(fenilmetil)oxi]carbonil}-4-imidazolidinacarboxílico)

En una manera análoga a la que se describe para el ejemplo 84 anterior los compuestos tabulados posteriormente (cuadro 20) se preparan mediante la sustitución de la amina apropiada (o su sal) por la {[4-fluoro-3-(trifluorometil)fenil]metil}amina usada en el procedimiento anterior. Todas las aminas usadas en el cuadro 20 son disponibles de fuentes comerciales o se

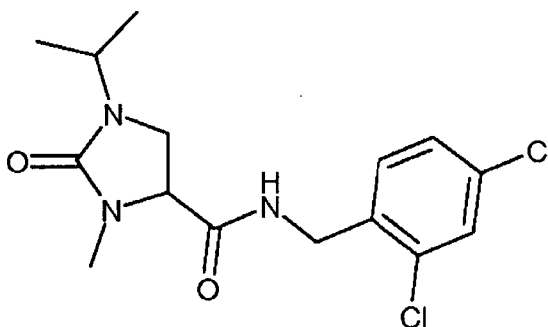
370

pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

CUADRO 20

No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E122	 N-[(2,4-dicloro-6-fluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida	320	1.88
E123	 3-metil-2-oxo-N-[(2,4,6-triclorofenil)metil]-4-imidazolidinacarboxamida	338	1.97

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EJEMPLO 124**N-[(2,4-diclorofenil)metil]-3-metil-1-(1-metiletil)-2-oxo-4-imidazolidinacarboxamida (E124)**

5

Una mezcla de ácido 3-metil-1-(1-metiletil)-2-oxo-4-

10 imidazolidinacarboxílico (100 mg, 0.537 mmoles), N-etilmorfolina (0.274 ml, 2.148 mmoles), hidrato de 1-hidroxibenzotriazol (99 mg, 0.644 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (124 mg, 0.644 mmoles) en diclorometano (9 ml) se agita a temperatura ambiente durante 10 minutos. Una solución de [1-(2,4-diclorofenil)metil]amina (95 mg, 0.537

15 mmoles) en diclorometano (1 ml) se añade y la mezcla de reacción se agita a temperatura ambiente durante 18 horas. La mezcla de reacción se diluye con diclorometano (10 ml) y la mezcla se lava con solución saturada de carbonato ácido de sodio (10 ml) y salmuera (10 ml), se seca y se evapora. El residuo se purifica mediante HPLC automatizada dirigida de masa. El residuo se tritura

20 con éter y el sólido resultante se colecta y se seca para proporcionar N-[(2,4-diclorofenil)metil]-3-metil-1-(1-metiletil)-2-oxo-4-imidazolidinacarboxamida (124 mg, 67%).

LC/EM $[M+H]^+ = 344$, tiempo de retención = 2.32 minutos.

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El ácido 3-metil-1-(1-metiletil)-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

Una solución agitada de 3-metil-2-oxo-4-imidazolidinacarboxilato de metilo (316 mg, 2 mmoles) (preparada como se describe en la etapa (ii) del ejemplo 8) en N,N-dimetilformamida (5 ml) se enfría a 0°C bajo argón y se trata con hidruro de sodio (60% de dispersión en aceite) (120 mg, 3.00 mmoles). Después de 10 minutos se añade 2-yodopropano (0.400 ml, 4.00 mmoles) y la mezcla de reacción se agita a temperatura ambiente durante 18 horas. Una solución de hidróxido de litio (57.5 mg, 2.400 mmoles) en agua (1 ml) se añade y la mezcla de reacción se agita a temperatura ambiente durante 30 minutos. Se añade ácido clorhídrico (2M) para ajustar el pH de la mezcla a pH 2 y el solvente se evapora. Se añade dimetilsulfóxido (3 ml) al residuo y la suspensión se filtra. El filtrado se purifica mediante HPLC automatizada dirigida de masa para proporcionar ácido 3-metil-1-(1-metiletil)-2-oxo-4-imidazolidinacarboxílico (100 mg, 27%, alrededor de 2 etapas).

LC/EM $[M+H]^+ = 187$.

EJEMPLOS 125 Y 126

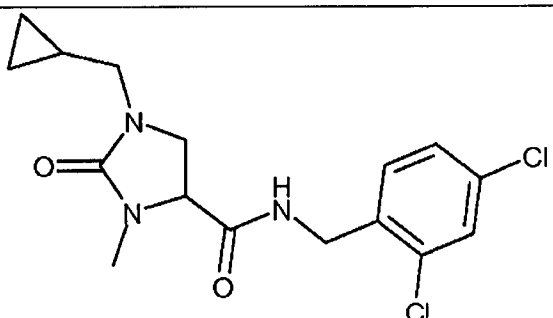
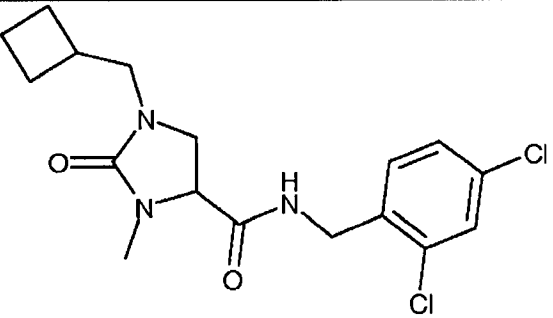
En una manera análoga a la que se describe para el ejemplo 124 anterior los compuestos tabulados posteriormente (cuadro 21) se preparan mediante la sustitución del bromuro de alquilo apropiado por el 2-yodopropano usado en el procedimiento anterior. Todos los bromuros de alquilo usados en

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el cuadro 21 son disponibles de fuentes comerciales o se pueden preparar usando rutas descritas previamente en la literatura química o métodos análogos.

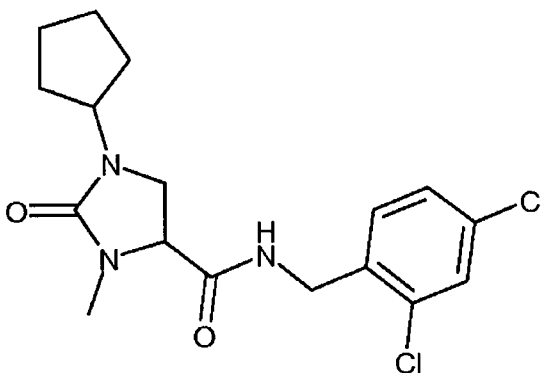
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CUADRO 21

No. de ejemplo	Nombre químico	[M+H] ⁺	Tiempo de retención (minutos)
E125	 1-(ciclopropilmetil)-N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida	356	2.41
E126	 1-(ciclobutilmetil)-N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida	370	2.60

20

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EJEMPLO 127**1-ciclopentil-N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (E127)**

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10 Una mezcla de ácido 1-ciclopentil-3-metil-2-oxo-4-imidazolidinacarboxílico (39 mg, 0.184 mmoles), N-etilmorfolina (0.094 ml, 0.735 mmoles), hidrato de 1-hidroxibenzotriazol (33.8 mg, 0.220 mmoles) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (42.3 mg, 0.220 mmoles) en diclorometano (9 ml) se agita a temperatura ambiente durante 10

15 minutos. Una solución de [1-(2,4-diclorofenil)metil]amina (32.3 mg, 0.184 mmoles) en diclorometano (1 ml) se añade y la mezcla de reacción se agita a temperatura ambiente durante 72 horas. La mezcla de reacción se diluye con diclorometano (10 ml) y la mezcla se lava con solución saturada de carbonato ácido de sodio (10 ml) y salmuera (10 ml), se seca y se evapora. El residuo se

20 purifica mediante HPLC automatizada dirigida de masa. El residuo se tritura con éter y el sólido resultante se colecta y se seca para proporcionar 1-ciclopentil-N-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida (42 mg, 62%).

375

LC/EM $[M+H]^+ = 370$, tiempo de retención = 2.28 minutos.

El ácido 1-ciclopentil-3-metil-2-oxo-4-imidazolidinacarboxílico usado en el método descrito anteriormente se prepara como sigue:

Una solución agitada de 3-metil-2-oxo-4-imidazolidinacarboxilato de metilo (316 mg, 2.0 mmoles) (preparada como se describe en la etapa (ii) del ejemplo 8) en N,N-dimetilformamida (5 ml) se enfría a 0°C bajo argón y se trata con hidruro de sodio (60% de dispersión en aceite) (80 mg, 2.0 mmoles). Después de 10 minutos bromociclopentano (298 mg, 2.0 mmoles) se añade y la mezcla de reacción se agita a temperatura ambiente durante 3 horas y después a 60°C durante 18 horas. Después del enfriamiento a temperatura ambiente se añade hidruro de sodio adicional (60% de dispersión en aceite) (80 mg, 2.0 mmoles) seguido por bromociclopentano (298 mg, 2.0 mmoles) y la mezcla de reacción se calienta a 60°C durante 48 horas. Después del enfriamiento a temperatura ambiente una solución de hidróxido de litio (0.057 g, 2.400 mmoles) en agua (1 ml) se añade y la mezcla de reacción se agita a temperatura ambiente durante 30 minutos. Se añade ácido clorhídrico (2M) para ajustar el pH de la mezcla a pH 2 y el solvente se evapora. Se añade dimetilsulfóxido (3 ml) al residuo y la suspensión se filtra. El filtrado se purifica mediante HPLC automatizada dirigida de masa para proporcionar ácido 1-ciclopentil-3-metil-2-oxo-4-imidazolidinacarboxílico (39 mg, 9%).

LC/EM $[M+H]^+ = 213$.

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HPLC automatizada dirigida de masa

Cuando se indica en los ejemplos anteriores, la purificación por HPLC automatizada dirigida de masa se lleva a cabo usando los siguientes aparatos y condiciones.

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Hardware

Modulo gradiente binario Waters 2525

Bomba de relleno Waters 515

Modulo de control de bomba Waters

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Colector de inyección Waters 2767

Administrador de fluidos de columna Waters

Detector de arreglo de fotodiodos Waters 2996

Espectrómetro de masa Waters ZQ

Colector de fracción Gilson 202

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Colector de residuos Gilson Aspec

Software

Waters MassLynx versión 4 SP2

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Columna

Las columnas usadas son Waters Atlantis, las dimensiones de las cuales son 19mm x 100 mm (escala pequeña) y 30 mm x 100 mm (escala grande). El tamaño de partícula de fase estacionaria es 5 μ m.

Solventes

A: Solvente acuoso = Agua + 0.1% de ácido fórmico

B: Solvente orgánico = acetonitrilo + 0.1% de ácido fórmico

Solvente de relleno = metanol : agua 80:20

5 Solvente de enjuagado de agujas = metanol

Métodos

Existen cinco métodos usados dependiendo del tiempo de retención analítico del compuesto de interés. Tienen un tiempo de corrida de 10 13.5 minutos, que comprende un gradiente de 10 minutos seguido por un purgado de la columna de 3.5 minutos y una etapa de re-equilibrio.

Escala grande/pequeña 1.0-1.5 = 5-30% de B

Escala grande/pequeña 1.5-2.2 = 15-55% de B

Escala grande/pequeña 2.2-2.9 = 30-85% de B

15 Escala grande/pequeña 2.9-3.6 = 50-99% de B

Escala grande/pequeña 3.6-5.0 = 80-99% de B (en 6 minutos seguido por 7.5 minutos de purgado y re-equilibrio).

Velocidad de flujo

20 Todos los métodos anteriores tienen una velocidad de flujo de 20 mls/min (escala pequeña) o 40 mls/min (escala grande).

376

HPLC quiral

Aparatos y condiciones usados para caracterizar la pureza enantiomérica de muestras seleccionadas son como sigue.

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Método (A)

Instrumento cromatograma líquido Agilent serie 1100.

Columna: Chiralpak AD (250 mm x 4.6 mm; tamaño de partícula 10 μ m).

10

bomba.

Fase móvil: heptano:etanol absoluto (70:30) v/v mezclado de

Velocidad de flujo: 1 ml/min

Temperatura: ambiente

Longitud de onda U.V.: 215 nm.

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Método (B)

Instrumento cromatograma líquido Agilent serie 1100

Columna: Chiralpak AD (250 mm x 4.6 mm; tamaño de partícula 10 μ m)

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bomba

Fase móvil: heptano:etanol absoluto (50:50) v/v mezclado de

Velocidad de flujo: 1 ml/min

Temperatura: ambiente

Longitud de onda U.V.: 215 nm

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Método (C)

Instrumento: cromatograma líquido Agilent serie 1100

Columna: Chiralpak AD (250 mm x 4.6 mm; tamaño de partícula

10 μ m)

5 Fase móvil: Heptano:etanol absoluto (80:20) v/v mezclado de
bomba

Velocidad de flujo: 1 ml/min

Temperatura: ambiente

Longitud de onda U.V.: 215 nm

10

Método (D)

Instrumento: cromatograma líquido Agilent serie 1100

Columna: Chiralpak AS (250 mm x 4.6 mm; tamaño de partícula

10 μ m)

15 Fase móvil: Heptano:etanol absoluto (80:20) v/v mezclado de
bomba

Velocidad de flujo: 1 ml/min

Temperatura: ambiente

Longitud de onda U.V.: 215 nm.

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Cromatografía líquida/espectrometría de masa

Los análisis de los ejemplos anteriores 1-71 y 74-78 por
cromatografía líquida/espectrometría de masa (LC/EM) se llevan a cabo

380

usando los siguientes aparatos y condiciones.

Hardware

	Bomba gradiente Agilent 1100
5	Auto-muestreador Agilent 1100
	Detector DAD Agilent 1100
	Desgasificador Agilent 1100
	Horno Agilent 1100
	Controlador Agilent 1100
10	Espectrómetro de masa Waters ZQ
	Sedere Sedex 85

Software

	Waters MassLynx versión 4.0 SP2
15	

Columna

La columna usada es una Waters Atlantis, las dimensiones de las cuales son 4.6 mm x 50 mm. El tamaño de partícula de fase estacionaria es 3 μm .

20

Solventes

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

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

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Método

El método genérico usado tiene un tiempo de corrida de 5 minutos.

5

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

El método anterior tiene una velocidad de flujo de 3 ml/mins.

10

El volumen de inyección para el método genérico es 5ul.

La temperatura de columna es 30 grados.

El intervalo de detección de UV es de 220 a 330 nm.

Los análisis de los ejemplos anteriores 72, 73 y 79-123 mediante cromatografía líquida/espectrometría de masa (LC/EM) se llevan a cabo

15 usando los siguientes aparatos y condiciones:

Hardware

Bomba gradiente Agilent 1100

Auto-muestreador Agilent 1100

20

Detector DAD Agilent 1100

Desgasificador Agilent 1100

Horno Agilent 1100

Controlador Agilent 1100

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Espectrómetro de masa Waters ZQ

Sedere Sedex 85

Software

5 Waters MassLynx versión 4.1

Columna

El análisis de HPLC se conduce en una columna C19 Sunfire (30 mm x 4.6 mm i.d. 3.5 μ m de diámetro empacado) a 30 grados centígrados.

10

Solventes

A: 0.1% de solución v/v de ácido fórmico en agua.

B: 0.1% de solución v/v de ácido fórmico en acetonitrilo.

15

Método

El método genérico usado tiene un tiempo de corrida de 5 minutos. El gradiente empleado es:

20

Tiempo (min)	Velocidad de flujo (ml/min)	%A	%B
0	3	97	3
0.1	3	97	3
4.2	3	0	100
4.8	3	0	100
4.9	3	97	3
5.0	3	97	3

383

La detección UV es una señal promedio de longitud de onda de 210 nm a 350 nm y el espectro de masa se registra en un espectrómetro de masa usando ionización por electroaspersión de modo positivo y negativo de exploración alterna.

5

Datos farmacológicos

Los compuestos de la invención se pueden analizar para actividad biológica *in vitro* en el receptor P2X7 de acuerdo con los siguientes estudios.

10

Ensayo de acumulación de etidio

Se realizan estudios usando regulador de pH de ensayo de NaCl de la composición siguiente (en mM): 140 mM de NaCl, HEPES 10, N-metil-D-glucamina 5, KCl 5.6, D-glucosa 10, CaCl₂ 0.5 (pH 7.4). Células HEK293, que expresan receptores P2X7 recombinantes humanos, se hacen crecer en placas de 96 pozos pre-tratadas con poli-L-lisina durante 18-24 h. (La clonación del receptor P2X7 humano se describe en US 6,133,434). Las células se lavan dos veces con 350 µl de regulador de pH de ensayo antes de la adición de 50 µl del antagonista. Las células después se incuban a temperatura ambiente (19-21°C) durante 30 minutos antes de la adición de ATP y etidio (concentración final de ensayo 100 µM). La concentración de ATP se elige para ser cerca de la EC₈₀ para el tipo receptor y es 1mM para estudios en el receptor P2X7 humano. Incubaciones se continúan durante 8 o

16 minutos y se terminan mediante la adición de 25 μ l de 1.3M de sucrosa que contiene 5 mM del reactivo de antagonista del receptor P2X7 negro 5 (Aldrich). Acumulación celular de etidio se determina por la medición de la fluorescencia (excitación de longitud de onda de 530 nm y emisión de longitud de onda de 620 nm) de debajo de la placa con un fluorocontador Canberra Packard (Pangbourne, UK). Valores de pIC_{50} de antagonista para el bloqueo de respuestas de ATP se determinan usando técnicas iterativas de ajuste de curva.

10 Ensayo Ca de lector de placa de formación de imagen
fluorescente (FLIPR)

Se realizan estudios usando regulador de pH de ensayo de NaCl de la siguiente composición (en mM) para P2X7 humano: 137 NaCl; 20 HEPES; 5.37 KCl; 4.17 $NaHCO_3$; 1 $CaCl_2$; 0.5 $MgSO_4$; y 1 g/l de D-glucosa (pH 7.4).

Células HEK293, que expresan receptores P2X7 recombinantes humanos, se hacen crecer en placas de 384 pozos pre-tratadas con poli-L-lisina durante 42-48 horas. (La clonación del receptor P2X7 humano se describe en US 6,133,434). Las células se lavan tres veces con 80 μ l de regulador de pH de ensayo, se cargan durante 1 hora a 37°C con 2 μ M de Fluo4 (Teflabs), se lavan tres veces nuevamente, y se dejan con 30 μ l de regulador de pH antes de la adición de 10 μ l de antagonista concentrado 4x.

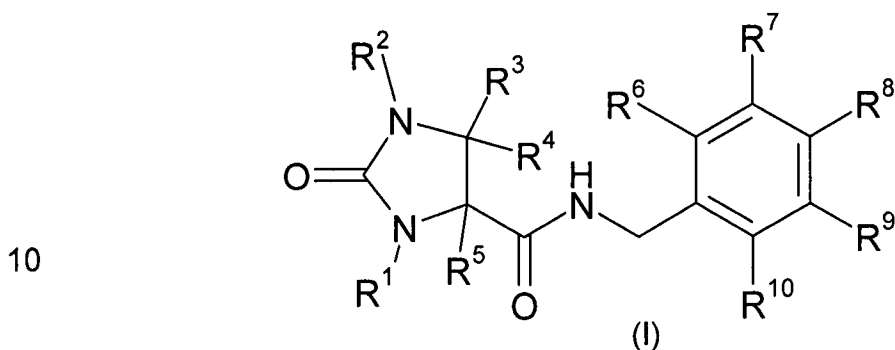
Las células después se incuban a temperatura ambiente durante 30 minutos antes de la adición (en línea, por instrumento FLIPR384 o FLIPR3 (Molecular Devices)) de concentración de ensayo final 60 μ M de benzoilbenzoil-ATP (BzATP). La concentración de BzATP se elige para ser cercana a EC_{50} para el tipo de receptor. Las incubaciones y lecturas se continúan por 90 segundos, y el incremento de calcio intracelular se determina por la medición de fluorescencia (excitación de longitud de onda de 488 nm y emisión de longitud de onda de 516 nm) debajo de la placa, con cámara de FLIPR CCD. Los valores de pIC_{50} del antagonista para bloquear respuestas de BzATP se determinan usando técnicas iterativas de ajuste de curva.

Los compuestos de los ejemplos 1-127 se analizan en el ensayo Ca FLIPR y/o el ensayo de acumulación de etidio para actividad del antagonista del receptor P2X7 humano y se encuentra que tiene valores de $pIC_{50} > 4.7$ en el ensayo Ca FLIPR y/o valores $pIC_{50} > 5.5$ en el ensayo de acumulación de etidio. Los compuestos de los ejemplos E1, a E5, E7, E8, E10 a E13, E15, E18, E19, E21, E23, E25 a E28, E30, E32 a E35, E39, E41, E42, E45, E51, E52, E54, E55, E57 a E61, E64, a E70, E72, a E79, E81, E82, E85, E86, E88, E89, E91 a E97, E99, E100, E102, E104 a E108, E110 a E113, E115 a E120, y E122 a E127 se encuentra que tienen valores de pIC_{50} de aproximadamente 7.5 o más en el ensayo de acumulación de etidio.

NOVEDAD DE LA INVENCION

REIVINDICACIONES

- 5 1.- Un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo:



- en donde: R¹ representa hidrógeno, alquilo de C₁₋₆, alquenilo de C₂₋₆, alquinilo de C₂₋₆, cicloalquilo de C₃₋₆, cicloalquilmetilo- C₃₋₆, piridinilmetilo- o bencilo, y en donde cualquiera de dichos alquilo de C₁₋₆, alquenilo de C₂₋₆, alquinilo de C₂₋₆, cicloalquilo de C₃₋₆, cicloalquilmetilo-C₃₋₆, piridinilmetilo- o bencilo es
- 15 opcionalmente sustituido con 1, 2 o 3 átomos de halógeno; o un fenilo no sustituido; R² representa hidrógeno, alquilo de C₁₋₆, alquenilo de C₂₋₆, alquinilo de C₂₋₆, cicloalquilo de C₃₋₆, cicloalquilmetilo-C₃₋₆, -(CR^xR^y)_n-NR¹¹R¹², arilmetilo-C₆₋₁₀, heterociclilo-(CR^xR^y)_n- o heteroarilo-(CR^xR^y)_n; y en donde
- 20 cualquiera de dichos alquilo de C₁₋₆, alquenilo de C₂₋₆, alquinilo de C₂₋₆, cicloalquilo de C₃₋₆, cicloalquilmetilo-C₃₋₆, arilmetilo-C₆₋₁₀, heterociclilo-(CR^xR^y)_n- o heteroarilo-(CR^xR^y)_n- se sustituye opcionalmente con 1, 2 o 3 átomos de halógeno o grupos alquilo de C₁₋₆, o el heteroarilo-(CR^xR^y)_n- se

sustituye opcionalmente en el anillo heteroarilo con un alcoxi de C_{1-3} (por ejemplo, metoxi), ciano o grupo trifluorometilo; R^3 , R^4 y R^5 independientemente representan hidrógeno, flúor o metilo; y R^6 , R^7 , R^8 , R^9 y R^{10} independientemente representan hidrógeno, halógeno, ciano, alquilo de C_{1-6} , alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} o fenilo, y cualquiera de dichos alquilo de C_{1-6} , alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} o fenilo se sustituye opcionalmente con 1, 2 o 3 átomos de halógeno; o R^9 y R^{10} junto con los átomos de carbono a los cuales se unen forman un anillo de benceno que se sustituye opcionalmente con 1, 2 o 3 átomos de halógeno; R^x y R^y representan independientemente hidrógeno o alquilo de C_{1-6} ; R^{11} y R^{12} representan independientemente hidrógeno o alquilo de C_{1-6} ; n representa un número entero de 0 a 4; con la condición de que cuando R^6 y R^{10} representan independientemente hidrógeno o flúor, al menos uno de R^7 , R^8 y R^9 sea un átomo de halógeno, o solo uno de R^7 , R^8 y R^9 sea un grupo CF_3 .

2.- El compuesto o sal de conformidad con la reivindicación 1, caracterizado además porque R^1 representa alquilo de C_{1-6} , alquenilo de C_{2-8} , alquinilo de C_{2-8} , cicloalquilo de C_{3-6} , cicloalquilmetilo- C_{3-6} , piridinilmetilo- o bencilo, cualquiera de los cuales es opcionalmente sustituido con 1, 2 o 3 átomos de halógeno, o un fenilo no sustituido.

3.- El compuesto o sal de conformidad con la reivindicación 2, caracterizado además porque R^1 representa metilo, etilo o etilo sustituido con 1, 2, o 3 átomos de flúor.

4.- El compuesto o sal de conformidad con la reivindicación 2, caracterizado además porque R^1 representa alquilo de C_{1-6} no sustituido.

5.- El compuesto o sal de conformidad con la reivindicación 4, caracterizado además porque R^1 representa metilo.

5 6.- El compuesto o sal de conformidad con la reivindicación 1, 2, 3, 4 o 5 caracterizado además porque R^2 representa hidrógeno, alquilo de C_{1-6} , alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} , cicloalquilmetilo- C_{3-6} , - $(CR^xR^y)_n-NR^{11}R^{12}$, arilmetilo- C_{6-10} , heterociclilo- $(CR^xR^y)_n$ - o heteroarilo- $(CR^xR^y)_n$ -; y en donde cualquiera de dichos alquilo de C_{1-6} , alquenilo de C_{2-6} , alquinilo de C_{2-6} , cicloalquilo de C_{3-6} , cicloalquilmetilo- C_{3-6} , arilmetilo- C_{6-10} , heterociclilo- $(CR^xR^y)_n$ - o heteroarilo- $(CR^xR^y)_n$ - se sustituye opcionalmente con 1, 2 o 3 átomos de halógeno o grupos alquilo de C_{1-6} .

15 7.- El compuesto o sal de conformidad con la reivindicación 1, 2, 3, 4 o 5 caracterizado además porque R^2 representa hidrógeno, alquilo de C_{1-6} , o heteroarilo- $(CR^xR^y)_n$ - en donde n representa 0; y en donde cualquiera de dichos alquilo de C_{1-6} o heteroarilo- $(CR^xR^y)_n$ - es opcionalmente sustituido con 1, 2 o 3 átomos de halógeno o grupos metilo; o el heteroarilo- $(CR^xR^y)_n$ - es opcionalmente sustituido en el anillo heteroarilo por un alcoxi de C_{1-3} , ciano o grupo trifluorometilo.

20 8.- El compuesto o sal de conformidad con la reivindicación 7, caracterizado además porque R^2 representa piridinilo, pirimidinilo, imidazolilo o pirazolilo, en donde cualquiera de dichos grupos son opcionalmente sustituidos con 1 o 2 átomos de flúor o cloro, con 1 o 2 grupos metilo, o con

un metoxi, ciano o grupo trifluorometilo.

9.- El compuesto o sal de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizado además porque R^2 representa hidrógeno o alquilo de C_{1-6} no sustituido.

5 10.- El compuesto o sal de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizado además porque R^2 representa hidrógeno, metilo, etilo o etilo sustituido con 1, 2, o 3 átomos de flúor.

10 11.- El compuesto o sal de conformidad con cualquiera de las reivindicaciones anteriores, caracterizado además porque R^1 y R^2 ambos no representan hidrógeno.

12.- El compuesto o sal de conformidad con cualquiera de las reivindicaciones anteriores, caracterizado además porque R^1 y R^2 ambos representan metilo o R^1 representa metilo y R^2 representa hidrógeno.

15 13.- El compuesto o sal de conformidad con cualquiera de las reivindicaciones anteriores, caracterizado además porque R^3 , R^4 y R^5 todos representan hidrógeno.

14.- El compuesto o sal de conformidad con cualquiera de las reivindicaciones anteriores, caracterizado además porque R^6 , R^7 , R^8 , R^9 y R^{10} representan independientemente hidrógeno, halógeno, metilo o trifluorometilo.

20 15.- El compuesto o sal de conformidad con cualquiera de las reivindicaciones anteriores, caracterizado además porque R^6 y R^7 ambos representan hidrógeno, R^8 representa hidrógeno, cloro o flúor, R^9 representa hidrógeno, cloro, flúor o trifluorometilo y R^{10} representa cloro, flúor, metilo o

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trifluorometilo.

16.- El compuesto o sal de conformidad con la reivindicación 15, caracterizado además porque R^6 y R^7 ambos representan hidrógeno, R^8 representa hidrógeno, cloro o flúor, R^9 representa hidrógeno, cloro, flúor o trifluorometilo y R^{10} representa cloro o metilo, en donde uno o ambos de R^8 y R^9 es/son diferentes de hidrógeno.

17.- El compuesto o sal de conformidad con la reivindicación 16, caracterizado además porque R^6 y R^7 ambos representan hidrógeno, R^8 representa hidrógeno o flúor, R^9 representa trifluorometilo y R^{10} representa cloro o metilo.

18.- El compuesto o sal de conformidad con cualquiera de las reivindicaciones 1 a 14, caracterizado además porque R^6 representa hidrógeno, cloro, flúor o metilo, R^7 representan hidrógeno, R^8 representa cloro o flúor, R^9 representa hidrogeno y R^{10} representa cloro o metilo.

19.- El compuesto o sal de conformidad con la reivindicación 18, caracterizado además porque R^6 representa hidrógeno, cloro, flúor o metilo, R^7 representan hidrógeno, R^8 representa cloro, R^9 representa hidrogeno y R^{10} representa cloro o metilo.

20.- El compuesto o sal de conformidad con cualquiera de las reivindicaciones 1 a 14, caracterizado además porque R^6 , R^7 y R^8 cada uno representa hidrógeno, R^9 representa trifluorometilo, y R^{10} representa cloro; R^6 , R^7 y R^9 cada uno representa hidrógeno y R^8 y R^{10} ambos representan cloro; R^6 y R^7 ambos representan hidrógeno, R^8 y R^9 ambos representan flúor, y R^{10}

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- representa cloro; R^6 , R^7 y R^8 cada uno representa hidrógeno, R^9 representa trifluorometilo, y R^{10} representa metilo; R^6 y R^7 ambos representan hidrógeno, R^8 representa flúor, R^9 representa trifluorometilo, y R^{10} representa cloro; R^6 es metilo, R^7 y R^9 ambos representan hidrógeno, y R^8 y R^{10} ambos representan
- 5 cloro; R^6 , R^8 y R^{10} cada uno representa cloro; y R^7 y R^9 ambos representan hidrógeno; R^6 , R^7 y R^8 cada uno representa hidrógeno, R^9 representa trifluorometilo, y R^{10} representa flúor; R^6 , R^7 y R^9 cada uno representa hidrógeno, R^8 representa flúor y R^{10} representa cloro; R^6 , R^7 y R^9 cada uno
- 10 representa hidrógeno, R^8 representa cloro, y R^{10} representa metilo; R^6 , R^7 y R^8 cada uno representa hidrógeno, R^9 representa cloro, y R^{10} representa metilo; R^6 y R^7 ambos representan hidrógeno, R^8 representa flúor, y R^9 y R^{10} ambos representan cloro; R^6 , R^7 y R^8 cada uno representa hidrógeno y R^9 y R^{10} ambos representan cloro; o R^6 es flúor, R^7 y R^9 ambos representan hidrógeno, y R^8 y R^{10} ambos representan cloro.
- 15 21.- El compuesto o sal de conformidad con la reivindicación 20, caracterizado además porque R^6 , R^7 y R^8 cada uno representa hidrógeno, R^9 representa trifluorometilo, y R^{10} representa cloro; R^6 , R^7 y R^9 cada uno
- 20 cloro; R^6 , R^7 y R^8 cada uno representa hidrógeno, R^9 representa trifluorometilo, y R^{10} representa metilo; R^6 y R^7 ambos representa hidrógeno, R^8 representa flúor, R^9 representa trifluorometilo, y R^{10} representa cloro; R^6 es metilo, R^7 y R^9 ambos representan hidrógeno, y R^8 y R^{10} ambos representan cloro; o R^6 ,

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R^8 y R^{10} cada uno representa cloro; y R^7 y R^9 ambos representan hidrógeno.

22.- El compuesto o sal de conformidad con la reivindicación 21, caracterizado además porque R^6 , R^7 y R^8 cada uno representa hidrógeno, R^9 representa trifluorometilo, y R^{10} representa cloro; R^6 , R^7 y R^9 cada uno
5 representa hidrógeno y R^8 y R^{10} ambos representan cloro; o R^6 y R^7 ambos representan hidrógeno, R^8 y R^9 ambos representan flúor, y R^{10} representa cloro.

23.- El compuesto o sal de conformidad con la reivindicación 1, caracterizado además porque es un compuesto seleccionado de los ejemplos
10 E1 a E50 o una sal farmacéuticamente aceptable del mismo.

24.- El compuesto o sal de conformidad con la reivindicación 1, caracterizado además porque es un compuesto seleccionado de los ejemplos E51 a E123 o una sal farmacéuticamente aceptable del mismo.

25.- Un compuesto o una sal farmacéuticamente aceptable del
15 mismo, el cual es *N*-{[2-cloro-3-(trifluorometil)fenil]metil}-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-diclorofenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2-cloro-3,4-difluorofenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-fluoro-3-(trifluorometil)fenil]metil}-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida, 1,3-dimetil-2-oxo-*N*-[(2,3,4-
20 trifluorofenil)metil]-4-imidazolidinacarboxamida, *N*-[(2-cloro-4-fluorofenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-(2-pirimidinil)-4-

- imidazolidinacarboxamida, *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-2-
 oxo-1-(4-piperidinil)-4-imidazolidinacarboxamida, *N*-{[2-Cloro-3-
 (trifluorometil)fenil]metil}-3-metil-2-oxo-1-(3-piridinil)-4-
 imidazolidinacarboxamida, *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-1-(6-
 5 metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-Cloro-3-
 (trifluorometil)fenil]metil}-3-metil-1-(2-metil-4-piridinil)-2-oxo-4-
 imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-3-metil-1-(2-metil-3-
 piridinil)-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-Cloro-3-
 (trifluorometil)fenil]metil}-3-metil-1-(2-metil-4-piridinil)-2-oxo-4-
 10 imidazolidinacarboxamida, *N*-[(2-Cloro-3,4-difluorofenil)metil]-3-metil-1-(2-
 metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-Cloro-3-
 (trifluorometil)fenil]metil}-3-metil-2-oxo-1-(2-piridinil)-4-
 imidazolidinacarboxamida, *N*-[(2-Cloro-3,4-difluorofenil)metil]-3-metil-1-(3-
 metil-2-piridinil)-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-Cloro-3-
 15 (trifluorometil)fenil]metil}-3-metil-1-(3-metil-2-piridinil)-2-oxo-4-
 imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-3-metil-1-(3-metil-2-
 piridinil)-2-oxo-4-imidazolidinacarboxamida, *N*-[(2-Cloro-3,4-difluorofenil)metil]-
 3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-3-metil-2-
 oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-3-metil-2-oxo-1-(2-
 20 pirimidinil)-4-imidazolidinacarboxamida, *N*-[(2-Cloro-4-fluorofenil)metil]-3-metil-
 2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida, *N*-[(2-Cloro-3,4-
 difluorofenil)metil]-3-metil-2-oxo-1-(2-pirimidinil)-4-imidazolidinacarboxamida,
N-[(3-Cloro-2-metilfenil)metil]-3-metil-2-oxo-1-(2-pirimidinil)-4-

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imidazolidinacarboxamida, $N-[(2\text{-Cloro-3,4-difluorofenil})\text{metil}]-3\text{-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida}$, $N-[(2\text{-Cloro-3,4-difluorofenil})\text{metil}]-3\text{-metil-1-(1-metil-1H-pirazol-5-il)-2-oxo-4-imidazolidinacarboxamida}$, $N-[[2\text{-Cloro-3-(trifluorometil)fenil}]\text{metil}]-3\text{-metil-1-[2-(4-morfolinil)etil]-2-oxo-4-imidazolidinacarboxamida}$, o $N-[[2\text{-Cloro-3-(trifluorometil)fenil}]\text{metil}]-3\text{-metil-2-oxo-1-(5-pirimidinil)-4-imidazolidinacarboxamida}$; o una sal farmacéuticamente aceptable del mismo.

26.- Un compuesto o una sal farmacéuticamente aceptable del mismo, el cual es $N-[[2\text{-Cloro-3-(trifluorometil)fenil}]\text{metil}]-3\text{-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxamida}$, $N-[(2,4\text{-Diclorofenil})\text{metil}]-3\text{-metil-2-oxo-1-[4-(trifluorometil)-2-pirimidinil]-4-imidazolidinacarboxamida}$, $N-[[2\text{-Cloro-3-(trifluorometil)fenil}]\text{metil}]-1-(2,6\text{-dimetil-3-piridinil})-3\text{-metil-2-oxo-4-imidazolidinacarboxamida}$, $N-[(2,4\text{-Diclorofenil})\text{metil}]-1-(2,6\text{-dimetil-3-piridinil})-3\text{-metil-2-oxo-4-imidazolidinacarboxamida}$, $N-[[2\text{-Cloro-3-(trifluorometil)fenil}]\text{metil}]-3\text{-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida}$, $N-[(2,4\text{-Diclorofenil})\text{metil}]-3\text{-metil-1-(1-metil-1H-imidazol-4-il)-2-oxo-4-imidazolidinacarboxamida}$, $N-[[2\text{-Cloro-3-(trifluorometil)fenil}]\text{metil}]-3\text{-metil-1-(1-metil-1H-imidazol-2-il)-2-oxo-4-imidazolidinacarboxamida}$, $N-[(2,4\text{-Diclorofenil})\text{metil}]-3\text{-metil-1-(1-metil-1H-imidazol-5-il)-2-oxo-4-imidazolidinacarboxamida}$, $N-[[2\text{-Cloro-3-(trifluorometil)fenil}]\text{metil}]-3\text{-metil-1-(1-metil-1H-imidazol-5-il)-2-oxo-4-imidazolidinacarboxamida}$, $N-[[2\text{-Cloro-3-(trifluorometil)fenil}]\text{metil}]-3\text{-metil-2-oxo-1-[6-(trifluorometil)-4-pirimidinil]-4-imidazolidinacarboxamida}$.

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- imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-1-(6-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-1-(2-fluoro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-3-metil-1-[6-(metiloxi)-3-piridinil]-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-1-[6-(metiloxi)-3-piridinil]-2-oxo-4-imidazolidinacarboxamida, *N*-{[(2,4-Diclorofenil)metil]-1-metil-2-oxo-3-(2,2,2-trifluoroetil)-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-3-etil-1-metil-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-etil-1-metil-2-oxo-4-imidazolidinacarboxamida, *N*-{[(2-Cloro-4-fluorofenil)metil]-3-etil-1-metil-2-oxo-4-imidazolidinacarboxamida, *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-1-(2-pirazinil)-4-imidazolidinacarboxamida, 1-(2-Cloro-3-piridinil)-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2-Cloro-3,4-difluorofenil)metil]-1-(2-cloro-3-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida, 1-(2-Cloro-3-piridinil)-*N*-{[2-cloro-3-(trifluorometil)fenil]metil}-3-metil-2-oxo-4-imidazolidinacarboxamida, 3-Metil-*N*-{[2-metil-3-(trifluorometil)fenil]metil}-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,3-Diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(3-Cloro-2-metilfenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Dicloro-6-metilfenil)metil]-3-metil-2-oxo-4-

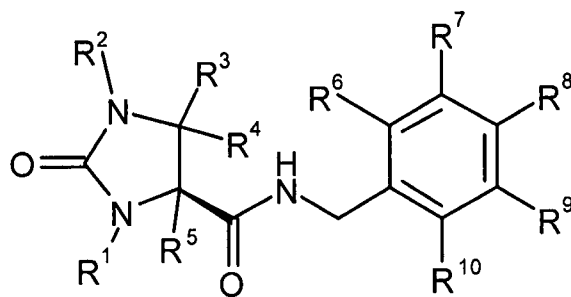
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- imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-1-(5-fluoro-2-pirimidinil)-
 3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-3-etil-2-
 oxo-4-imidazolidinacarboxamida, *N*-{[2-Cloro-3-(trifluorometil)fenil]metil}-3-etil-
 2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-3-metil-1-[4-
 5 (metiloxi)-2-pirimidinil]-2-oxo-4-imidazolidinacarboxamida, 1-(5-Cloro-2-
 pirimidinil)-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida,
N-[(2,4-Diclorofenil)metil]-3-metil-1-(6-metil-3-piridinil)-2-oxo-4-
 imidazolidinacarboxamida, *N*-[(2-Cloro-3,4-difluorofenil)metil]-3-metil-1-(6-
 metil-3-piridinil)-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-
 10 1-(2-fluoro-4-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2-Cloro-
 3,4-difluorofenil)metil]-1-(2-fluoro-4-piridinil)-3-metil-2-oxo-4-
 imidazolidinacarboxamida, *N*-[(3-Cloro-2-metilfenil)metil]-1,3-dimetil-2-oxo-4-
 imidazolidinacarboxamida, *N*-[(2,3-Diclorofenil)metil]-1,3-dimetil-2-oxo-4-
 imidazolidinacarboxamida, *N*-[(2,3-Dicloro-4-fluorofenil)metil]-1,3-dimetil-2-
 15 oxo-4-imidazolidinacarboxamida, *N*-{[2-Cloro-4-fluoro-3-
 (trifluorometil)fenil]metil}-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida, *N*-
 [(2,4-Dicloro-6-metilfenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida,
 1,3-Dimetil-*N*-{[2-metil-3-(trifluorometil)fenil]metil}-2-oxo-4-
 imidazolidinacarboxamida, *N*-[(4-Cloro-2-metilfenil)metil]-1,3-dimetil-2-oxo-4-
 20 imidazolidinacarboxamida, *N*-[(2-Cloro-4-cianofenil)metil]-1,3-dimetil-2-oxo-4-
 imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-3-(2,2-difluoroetil)-1-
 metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-1-(3-fluoro-
 2-piridinil)-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-

- Diclorofenil)metil]-3-metil-1-(1-metil-1*H*-pirazol-5-il)-2-oxo-4-imidazolidinacarboxamida, 1-(2-Ciano-3-piridinil)-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-1-(2,2-difluoroetil)-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-3-metil-2-oxo-1-(2,2,2-trifluoroetil)-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-1-(2-fluoroetil)-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-1-etil-3-metil-2-oxo-4-imidazolidinacarboxamida, *N*-[(2,4-Dicloro-6-fluorofenil)metil]-1,3-dimetil-2-oxo-4-imidazolidinacarboxamida, 1,3-Dimetil-2-oxo-*N*-[(2,4,6-triclorofenil)metil]-4-imidazolidinacarboxamida, *N*-[(2,4-Dicloro-6-fluorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida, 3-Metil-2-oxo-*N*-[(2,4,6-triclorofenil)metil]-4-imidazolidinacarboxamida, *N*-[(2,4-Diclorofenil)metil]-3-metil-1-(1-metiletil)-2-oxo-4-imidazolidinacarboxamida, 1-(Ciclopropilmetil)-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida, 1-(Ciclobutilmetil)-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida, o 1-Ciclopentil-*N*-[(2,4-diclorofenil)metil]-3-metil-2-oxo-4-imidazolidinacarboxamida; o una sal farmacéuticamente aceptable del mismo.

27.- El compuesto o sal de conformidad con cualquiera de las reivindicaciones anteriores, caracterizado además porque es un compuesto de fórmula (IA) o una sal farmacéuticamente aceptable del mismo:

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(IA)

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en donde: R¹ representa alquilo de C₁₋₄ o cicloalquilo de C₃₋₄, cualquiera de los cuales se sustituye opcionalmente con 1, 2 o 3 átomos de flúor y R², R^x, R^y, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² y n son como se definen en cualquiera de las reivindicaciones anteriores, y en donde más del 50% en molaridad del compuesto de fórmula (IA) o la sal farmacéuticamente aceptable del mismo tiene la estereoquímica indicada en el átomo de carbono del anillo unido a R⁵.

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28.- El compuesto o sal de conformidad con la reivindicación 27, caracterizado además porque R¹ representa metilo o etilo.

29.- Una composición farmacéutica que comprende un compuesto o una sal farmacéuticamente del mismo como se define en cualquiera de las reivindicaciones anteriores, y un portador o excipiente farmacéuticamente aceptable.

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30.- El compuesto o sal farmacéuticamente aceptable del mismo, de conformidad con cualquiera de las reivindicaciones 1 a 28, para el uso en terapia.

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31.- Un método para tratar a un sujeto humano o animal que sufre de dolor, inflamación o una enfermedad neurodegenerativa, cuyo método comprende administrar a dicho sujeto una cantidad efectiva de un

compuesto o su sal farmacéuticamente aceptable como se define en cualquiera de las reivindicaciones 1 a 28.

32.- El uso de un compuesto o su sal farmacéuticamente aceptable como se define en cualquiera de las reivindicaciones 1 a 28 para la
5 fabricación de un medicamento para el tratamiento o prevención de dolor, inflamación o una enfermedad neurodegenerativa.

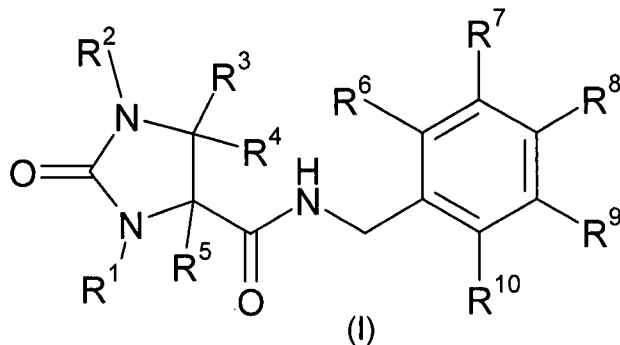
33.- El uso de un compuesto o su sal farmacéuticamente aceptable como se define en cualquiera de las reivindicaciones 1 a 28 para la
fabricación de un medicamento para el tratamiento o prevención de dolor
10 inflamatorio, dolor neuropático o dolor visceral.

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RESUMEN DE LA INVENCIÓN

La presente invención se refiere a un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo:

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- 10 los compuestos o sales modulan la función del receptor P2X7 y son capaces de antagonizar los efectos de ATP en el receptor P2X7 (antagonistas del receptor P2X7); la invención también provee el uso de dichos compuestos o sales, o composiciones farmacéuticas de los mismos, en el tratamiento o
- 15 prevención de trastornos/enfermedades mediadas por el receptor P2X7, por ejemplo dolor, inflamación o una enfermedad neurodegenerativa, en particular dolor tal como dolor inflamatorio, dolor neuropático o dolor visceral.

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P09-1363F

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: GLAXOSMITHKLINE Attn. Breen, Anthony Paul Corporate International Property 980 Great West Road Brentford Middlesex TW8 9GS GRANDE BRETAGNE	GlaxoSmithKline Corporate IP Received BRENTFORD 08 OCT 2008	NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION ATTY: <i>ABB</i> ADMIN: <i>h/10/mm</i> (PCT Rule 44.1) IPM: N/A ON UPLOADED ON: <i>2/10</i> ATTY CHECKED/FILED: <i>2/10</i> 09/10/2008
Applicant's or agent's file reference APB/PB62390		FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/EP2008/053962		International filing date (day/month/year) 02/04/2008
Applicant GLAXO GROUP LIMITED		

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

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

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

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

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

2. ☐ The applicant is hereby notified that no International search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices,

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

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

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

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

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

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

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Eva Brell
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1b(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference APB/PB62390	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/EP2008/053962	International filing date (day/month/year) 02/04/2008	(Earliest) Priority Date (day/month/year) 03/04/2007
Applicant GLAXO GROUP LIMITED		

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

This international search report consists of a total of 3 sheets.

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

1. Basis of the report

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

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

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6b/s(a)).

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

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

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

4. With regard to the **title**,

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

5. With regard to the **abstract**,

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

6. With regard to the **drawings**,

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

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/053962

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D233/36 C07D401/04 C07D401/06 C07D403/04 A61K31/4166
A61P29/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/026916 A1 (SHUM PATRICK [US] ET AL) 3 February 2005 (2005-02-03) the whole document	1-33
A	WO 99/29686 A (ASTRA PHARMA PROD [GB]; ASTRA AB [SE]; BAXTER ANDREW [GB]; CHESHIRE DA) 17 June 1999 (1999-06-17) the whole document	1-33

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

☒ See patent family annex.

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

9 September 2008

Date of mailing of the international search report

09/10/2008

Name and mailing address of the ISA/

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

Authorized officer

Grassi, Damian

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/053962

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005026916 A1	03-02-2005	US 2008132550 A1	05-06-2008
WO 9929686 A	17-06-1999	AU 1791599 A	28-06-1999
		BR 9813378 A	10-10-2000
		CA 2312357 A1	17-06-1999
		CN 1284074 A	14-02-2001
		EE 200000321 A	15-08-2001
		EP 1037889 A1	27-09-2000
		HU 0100731 A2	29-05-2002
		JP 2001525406 T	11-12-2001
		NO 20002787 A	01-08-2000
		PL 340837 A1	26-02-2001
		SK 8442000 A3	18-01-2001
		TR 200001544 T2	21-11-2000

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WOKS

To:		see form PCT/ISA/220		WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1) Date of mailing 09/10/2008 (day/month/year) see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220			FOR FURTHER ACTION See paragraph 2 below		
International application No. PCT/EP2008/053962	International filing date (day/month/year) 02.04.2008	Priority date (day/month/year) 03.04.2007			
International Patent Classification (IPC) or both national classification and IPC INV. C07D233/36 C07D401/04 C07D401/06 C07D403/04 A61K31/4166 A61P29/00					
Applicant GLAXO GROUP LIMITED					
1. This opinion contains indications relating to the following items: ☒ Box No. I Basis of the opinion ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application 2. FURTHER ACTION If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered. If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. For further options, see Form PCT/ISA/220. 3. For further details, see notes to Form PCT/ISA/220.					
Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Date of completion of this opinion see form PCT/ISA/210		Authorized Officer Grassi, Damian Telephone No. +49 89 2399-8499	

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2008/053962

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2008/053962

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

1. Statement

Novelty (N)	Yes: Claims	<u>1-33</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-33</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-33</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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

International application No. *W10*

PCT/EP2008/053962

Reference is made to the following documents:

D1: US 2005/026916

Re Item V

- 1) Claim 31 relates to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT.
The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.
- 2) The subject-matter of present claims 1-33 is new (Article 33(2) PCT).
- 3) The subject-matter of claims 1-33 involves an inventive step (Article 33(3) PCT).

The closest prior art is represented by D1 relating to dihydro-imidazole derivatives which are modulators of P2X₇ receptor activity.

The presently claimed group of compounds differs considerably from the disclosure of the above cited document (e.g. in the linking group between the phenyl ring and the imidazole ring, in the oxo group of the imidazole ring and in the point of attachment of the imidazole ring to the linker).

The technical problem underlying the present claims is seen in the provision of alternative modulators of P2X₇ receptor activity

In view of the test results disclosed on page 134, the problem appears to be solved.

The prior art does not prompt the skilled person to the above mentioned modifications, therefore, the subject-matter of present claim 1 appears to involve an inventive step.

The claims relating to the use of the compounds of claim 1 as well as the claims relating to a pharmaceutical composition containing the said involve an inventive step for the same reasons.

REMARKS

- 4) The claims 23 and 24 must not refer to the content of the description (cf. Guidelines Part II, 5.10).
- 5) The claim 27 appears to relate to a composition containing at least 50% of a compound of formula (IA). However, the wording is not clear.
- 5.1) The residues R^2 to R^{12} are not present in claims 25 and 26, therefore, the claim 27 should not refer to these claims.
- 5.2) The residues R^x , R^y , R^{11} and R^{12} do not appear to be present in the compounds of formula (IA).

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
9 October 2008 (09.10.2008)

PCT

(10) International Publication Number
WO 2008/119825 A3

(51) International Patent Classification:

C07D 233/36 (2006.01) C07D 403/04 (2006.01)
C07D 401/04 (2006.01) A61K 31/4166 (2006.01)
C07D 401/06 (2006.01) A61P 29/00 (2006.01)

(74) Agents: BREEN, Anthony, Paul et al.; GlaxoSmithKline,
Corporate Intellectual Property CN925.1, 980 Great West
Road, Brentford Middlesex TW8 9GS (GB).

(21) International Application Number:

PCT/EP2008/053962

(22) International Filing Date: 2 April 2008 (02.04.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0706501.4 3 April 2007 (03.04.2007) GB
0720653.5 22 October 2007 (22.10.2007) GB
0805272.2 20 March 2008 (20.03.2008) GB
0805504.8 26 March 2008 (26.03.2008) GB

(71) Applicant (for all designated States except US): GLAXO
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(72) Inventors; and

(75) Inventors/Applicants (for US only): BESWICK, Paul,
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line, New Frontiers Science Park South, Third Avenue,
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James [GB/GB]; GlaxoSmithKline, New Frontiers Sci-
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5AW (GB). MOSES, Andrew, Peter [GB/GB]; Glaxo-
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Avenue, Harlow Essex CM19 5AW (GB). WALTER,
Daryl, Simon [GB/GB]; GlaxoSmithKline, New Frontiers
Science Park South, Third Avenue, Harlow Essex CM19
5AW (GB).

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

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SI, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL,
NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG,
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

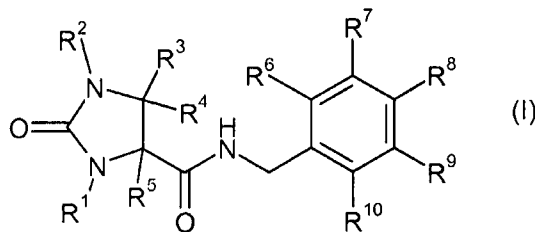
- as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

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

(88) Date of publication of the international search report:
11 December 2008

(54) Title: IMIDAZOLIDINE CARBOXAMIDE DERIVATIVES AS P2X7 MODULATORS



(57) Abstract: The present invention relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The compounds or salts modulate P2X7 receptor function and are capable of antagonizing the effects of ATP at the P2X7 receptor (P2X7 receptor antagonists). The invention also provides the use of such compounds or salts, or pharmaceutical compositions thereof, in the treatment or prevention of disorders / diseases mediated by the P2X7 receptor, for example pain, inflammation or a neurodegenerative disease, in particular pain such as inflammatory pain, neuropathic pain or visceral pain.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/053962

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D233/36 C07D401/04 C07D401/06 C07D403/04 A61K31/4166
A61P29/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/026916 A1 (SHUM PATRICK [US] ET AL) 3 February 2005 (2005-02-03) the whole document	1-33
A	WO 99/29686 A (ASTRA PHARMA PROD [GB]; ASTRA AB [SE]; BAXTER ANDREW [GB]; CHESHIRE DA) 17 June 1999 (1999-06-17) the whole document	1-33

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

☒ See patent family annex.

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

9 September 2008

Date of mailing of the international search report

09/10/2008

Name and mailing address of the ISA/

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

Authorized officer

Grassi, Damian

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/053962

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005026916 A1	03-02-2005	US 2008132550 A1	05-06-2008
WO 9929686 A	17-06-1999	AU 1791599 A	28-06-1999
		BR 9813378 A	10-10-2000
		CA 2312357 A1	17-06-1999
		CN 1284074 A	14-02-2001
		EE 200000321 A	15-08-2001
		EP 1037889 A1	27-09-2000
		HU 0100731 A2	29-05-2002
		JP 2001525406 T	11-12-2001
		NO 20002787 A	01-08-2000
		PL 340837 A1	26-02-2001
		SK 8442000 A3	18-01-2001
		TR 200001544 T2	21-11-2000



No. 09-107972- -00000-0000

Fecha: 2009-10-01 16:14:37 Dep. 2020 NUECREACION
Tra. 11 PATENTE IYII Eve: 378 FASENACIONAL I
Act. 411 PRESENTACION Folios: 414



Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE PCT

PATENTE DE INVENCION ☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☐
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☐

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Claudia M New Cortes
Firma Responsable

Fecha _____

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