



Industria y Comercio

S U P E R I N T E N D E N C I A

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No. 04-22055.

54. TÍTULO Compuestos - Urea Activos como antagonistas
del receptor Vanilloide.

51. CLASIFICACIÓN INTERNACIONAL C07D 207/10; A61K31/40

71. SOLICITANTE Smithkline Beecham P.LC.

DOMICILIO 980 Great west Road, Brentford, Middlesex
Tw28 9BS - Gran Bretaña.

74. APODERADO Carlos B. Olaree.

22. BOGOTÁ, D. C., Marzo 10, 2004

Industria y Comercio
SUPERINTENDENCIA

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Radicación : 04022953 00000000

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Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

① SOLICITUD DE :

☒ Patente de Invención ☐ Patente de Modelo de Utilidad
☐ Capítulo I. ☒ Capítulo II.

② SOLICITANTE
(71)

Nombre: SMITHKLINE BEECHAM P.L.C.

Dirección: 980 Great West Road, Brentford, Middlesex TW8 9GS.
Gran Bretaña.

Nacionalidad o Domicilio: BRITANICA

Lugar de Constitución: Reino Unido.

Teléfono:

Fax

E-Mail

IDENTIFICACION

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

③ REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre C, Calle 100 No. 8A-55 Piso 10.

Teléfono: 6386200

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IDENTIFICACION

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79.782.747 Bta TP 74.295

④ INVENTOR (ES)
(72)

Nombre: HARSHAD KANTILAL RAMI, MERVYN THOMPSON, PAUL ADRIAN WYMAN.

Dirección: New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW, Gran Bretaña.

Nacionalidad o Domicilio: BRITANICA

⑤ PCT (85)

Solicitud Internacional No. PCT/GB02/04206

Fecha Septiembre 13, 2002

Publicación Internacional No. WO 03/022809

Fecha Marzo 20, 2003

⑥ Título (54)

COMPUESTOS - UREA ACTIVOS COMO ANTAGONISTAS DEL RECEPTOR VANILOIDE.

⑦ Clasificación Internacional (51)

C07D 107/20 ; A61K31/40

⑧ Prioridad

SI ☒ NO ☐

(33) País de Origen

GB

GB

GB

GB

(32) Fecha

Septiembre 13, 2001

Diciembre 20, 2001

Diciembre 20, 2001

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0122156.3

0130547.3

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0130505.1

⑨ Comprobante de pago No. 12.959

Fecha 18-02-04

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

10

ANEXOS

2

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

11

FIGURA CARACTERISTICA

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA: 

C.C. 74.782.747 de Bú T.P. 74.295

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

3
SUPERINDUSTRIA Y COMERCIO
Radicación : 04022853 00000000 Folios: 151
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Trámite : 011 PCT-PATENT 379 FASE NNCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 12,959
FECHA : FEBRERO 19 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	13594217	16/02/2004	3,302,000.00

***** CONCEPTO *****

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

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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

PODER DE REPRESENTACION

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

Certificado de Notario De Pinna en español certificando que Peter John Giddings es apoderado de Smithkline Beecham p.l.c. firmado por James Kerr Milligan

APOSTILLA

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

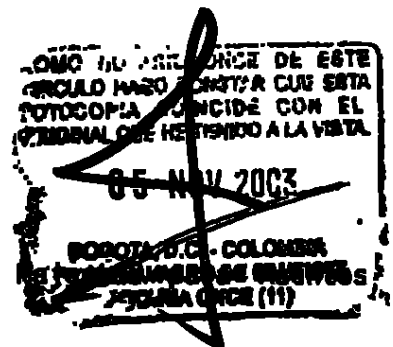
1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su exteriores y de la Mancomunidad
8. No. G229471
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

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

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



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

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

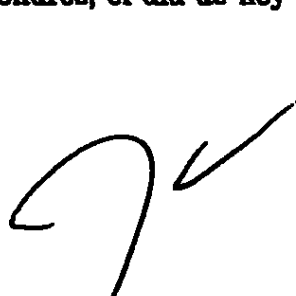
CERTIFICO:

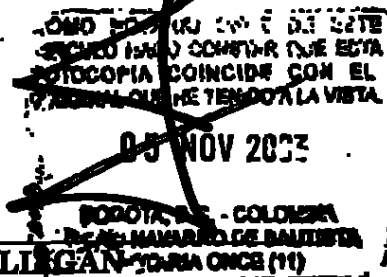
QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada "**SMITHKLINE BEECHAM p.l.c.**", Sociedad legalmente constituida y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **2387959**, con domicilio social en **980 Great West Road, Brentford, Middlesex TW8 9GS, Inglaterra;**

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

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

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


JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

This public document / Le présent acte public

2. Has been signed by James Kerr Milligan
a été signé par
3. Acting in the capacity of Notary Public
agissant en qualité de
4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de

5. at London/à Londres
6. Certified/Attesté
the/le 14 August 2003
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Étrangères et du Commonwealth.

8. Number/sous No **G229471**

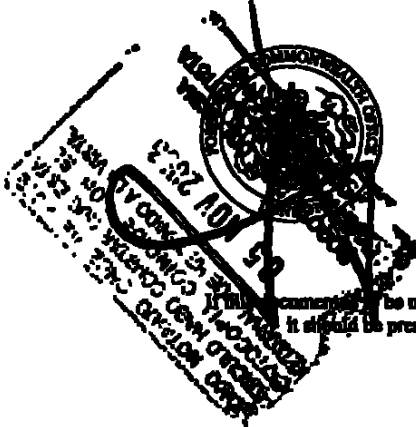
9. Stamp:
timbre:

10. Signature: J. Garbush



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

This document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
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: +57-1 838-8200
Fax: +57-1 838-8201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

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.

El suscrito,
SmithKline Beecham p.l.c.

domiciliado en

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

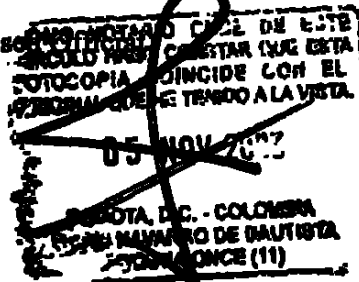
por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistirse 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 Signatory

Date/Fecha: 13 August 2003

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



(19) World Intellectual Property Organization
International Bureau



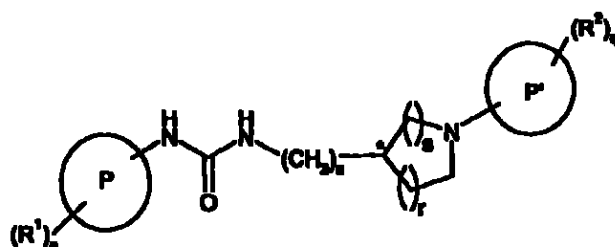
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20 March 2003 (20.03.2003)

PCT

(10) International Publication Number
WO 03/022809 A2

- (51) International Patent Classification⁷: C07D 207/00 (74) Agent: GIDDINGS, Peter, John; GlaxoSmithKline, Corporate Intellectual Property_CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9HP (GB).
- (21) International Application Number: PCT/GB02/04206
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0130503.6 20 December 2001 (20.12.2001) GB
0130505.1 20 December 2001 (20.12.2001) GB
- (71) Applicant (for all designated States except US):
SMITHKLINE BEECHAM P.L.C. [GB/GB]; 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).
- (72) Inventors; and
- (73) Inventor/Applicants (for US only): RAMU, Hamed, Kamil [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). THOMPSON, Mervyn [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). WYMAN, Paul, Adrian [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).
- (81) Designated States (national): AR, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GR, GU, HK, HN, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL COMPOUNDS



(I)

WO 03/022809 A2

(57) Abstract: Certain compounds of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein R¹, R², P, P', n, p, q, r and s are as defined in the specification, a process for preparing such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds and composition in medicine.

NOVEL COMPOUNDS

This invention relates to novel compounds, especially urea derivatives,
5 having pharmacological activity, processes for their preparation, to compositions containing them and to their use in medicine, especially in the treatment of various disorders.

Vanilloids are a class of natural and synthetic compounds that are characterised by the presence of a vanillyl (4-hydroxy 3-methoxybenzyl) group or a
10 functionally equivalent group. Vanilloid Receptor (VR-1), whose function is modulated by such compounds, has been widely studied and is extensively reviewed by Szallasi and Blumberg (The American Society for Pharmacology and Experimental Therapeutics, 1999, Vol. 51, No. 2.).

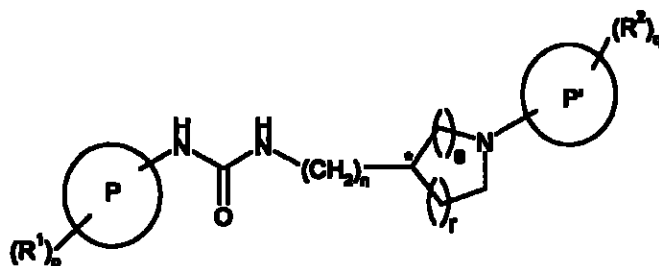
A wide variety of Vanilloid compounds of different structures are known
15 in the art, for example those disclosed in European Patent Application Numbers, EP 0 347 000 and EP 0 401 903, UK Patent Application Number GB 2226313 and International Patent Application, Publication Number WO 92/09285. Particularly notable examples of vanilloid compounds or vanilloid receptor modulators are capsaicin or trans 8-methyl-N-vanillyl-8-nonenamide which is
20 isolated from the pepper plant, capsaizapine (*Tetrahedron*, 53, 1997, 4791) and olvanil or - N-(4-hydroxy-3-methoxybenzyl)oleamide (*J. Med. Chem.*, 36, 1993, 2595).

US Patent Numbers, US 3,424,760 and US 3,424,761 both describe a series of 3-Ureidopyrrolidines that are said to exhibit analgesic, central nervous
25 system, and psychopharmacologic activities. These patents specifically disclose the compounds 1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea and 1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea respectively.

International Patent Applications, Publication Numbers WO 02/08221, WO 02/16317, WO 02/16318 and WO 02/16319 each disclose certain vanilloid
30 receptor antagonists and their use in the treatment of diseases associated with the activity of the vanilloid receptor.

Co-pending International Patent Application Number PCT/EP02/04802 discloses a series of urea derivatives and their use in the treatment of diseases associated with the activity of the vanilloid receptor.

According to a first aspect of the present invention, there is provided a compound of formula (I),



(I)

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

- 10 P and P' are independently selected from aryl and heteroaryl;
 R¹ and R² are independently selected from -H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO₂, -OH, -OCF₃, -CF₃, -NR⁴R⁵, -S(O)ₘR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)ₓNR⁴R⁵, -C(O)CF₃, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -C(O)(CH₂)ₓOR⁶, -
 15 C(O)(CH₂)ₓNR⁴R⁵, -C(O)alkoxy, -C(O)NR⁴R⁵, -(CH₂)ₓC(O)alkoxy, -(CH₂)ₓOC(O)R⁶, -(CH₂)ₓOR⁶, -(CH₂)ₓR⁴R⁵, -(CH₂)ₓC(O)NR⁴R⁵, -(CH₂)ₓN(R⁴)C(O)R⁶, -(CH₂)ₓS(O)₂NR⁴R⁵, -(CH₂)ₓN(R⁴)S(O)₂R⁶, -ZAr, -(CH₂)ₓS(O)₂R⁶, -(OCH₂)ₓS(O)₂R⁶, -N(R⁴)S(O)₂R⁶, -N(R⁴)C(O)R⁶, -(CH₂)ₓN(R⁴)S(O)₂R⁶, -(CH₂)ₓN(R⁴)C(O)R⁶ or -(CH₂)ₓC(O)alkyl;
 20 R⁴ and R⁵ may be the same or different and represent H or alkyl or R⁴ and R⁵ together with the atoms to which they are attached form a C₃-8 azacycloalkane, C₃-8(2-oxo)azacycloalkane ring or C₃-8 polymethylene chain optionally interrupted by heteroatoms such as O or -NR⁷.
 Z is O, S or NR⁷;
 25 R⁶ is alkyl or aryl;
 R⁷ is hydrogen, alkyl or aryl;
 m is 1 or 2;
 n is 0, 1, 2 or 3;

p and q are independently 0, 1, 2, 3 or 4;

r is 1, 2 or 3;

s is 0, 1 or 2; and

x is 0, 1, 2, 3, 4, 5 or 6;

- 5 with the proviso that said compound of formula (I) is not a compound selected from:

1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea;

1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea;

N-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

- 10 *N*-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

N-(4-Fluorophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

N-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

N-(4-Fluorophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

- 15 *N*-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(1-Naphthyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

- 20 *N*-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(4-fluoro-3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl)]urea;

- 25 *N*-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2,5-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(2,5-Dichlorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

- 30 *N*-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;

N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;

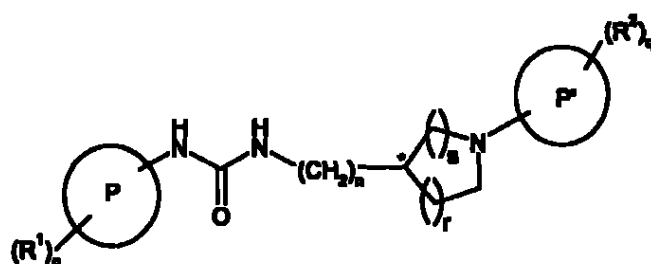
N-(2,5-Dichlorophenyl)-*N'*-[[(*R*)-1-(3,4-difluorophenyl)pyrrolidin-3-yl]]urea;
N-(3-Chloro-2-methylphenyl)-*N'*-[[(*R*)-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl]]urea; and
N-(2,3-Dichlorophenyl)-*N'*-[[(*R*)-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl]]urea.

5

Suitably, P and P' are independently selected from phenyl and heteroaryl.

In a preferred aspect of the present invention there is provided a subset of compounds of formula (I), of formula (IA),

10



(IA)

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

P is phenyl, naphthyl, quinoliny or isoquinoliny;

P' is phenyl or pyridyl;

R¹ and R² are independently selected from -H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO₂, -OH, -OCF₃, -CF₃,
 20 -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)_xNR⁴R⁵,
 -C(O)CF₃, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -C(O)(CH₂)_xOR⁶, -
 C(O)(CH₂)_xNR⁴R⁵, -C(O)alkoxy, -C(O)NR⁴R⁵, -(CH₂)_xC(O)alkoxy, -
 (CH₂)_xOC(O)R⁶, -(CH₂)_xOR⁶, -(CH₂)_xR⁴R⁵, -(CH₂)_xC(O)NR⁴R⁵, -
 (CH₂)_xN(R⁴)C(O)R⁶, -(CH₂)_xS(O)₂NR⁴R⁵, -(CH₂)_xN(R⁴)S(O)₂R⁶, -ZAr, -
 25 (CH₂)_xS(O)₂R⁶, -(OCH₂)_xS(O)₂R⁶, -N(R⁴)S(O)₂R⁶, -N(R⁴)C(O)R⁶, -
 (CH₂)_xN(R⁴)S(O)₂R⁶, -(CH₂)_xN(R⁴)C(O)R⁶ or -(CH₂)_xC(O)alkyl;

R⁴ and R⁵ may be the same or different and represent H or alkyl or R⁴ and R⁵ together with the atoms to which they are attached form a C₃₋₆azacycloalkane,

12

C₃₋₈(2-oxo)azacycloalkane ring or C₃₋₈ polymethylene chain optionally interrupted by heteroatoms such as O or -NR⁷.

Z is O, S or NR⁷;

R⁶ is alkyl or aryl;

5 R⁷ is hydrogen, alkyl or aryl;

m is 1 or 2;

n is 0, 1, 2 or 3;

p and q are independently 0, 1, 2, 3 or 4;

r is 1, 2 or 3;

10 s is 0, 1 or 2; and

x is 0, 1, 2, 3, 4, 5 or 6;

with the proviso that said compound of formula (IA) is not a compound selected from:

1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea;

15 1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea;

N-(4-Fluorophenyl)-*N'*-{[(*R*)-1-(3-methylphenyl)pyrrolidin-2-ylmethyl]}urea;

N-(2-Bromophenyl)-*N'*-{[(*R*)-1-(3-methylphenyl)pyrrolidin-3-yl]}urea;

N-(2-Bromophenyl)-*N'*-{[(*R*)-1-(3-methylphenyl)pyrrolidin-2-ylmethyl]}urea;

N-(4-Fluorophenyl)-*N'*-{[(*S*)-1-(3-methylphenyl)pyrrolidin-2-ylmethyl]}urea;

20 *N*-(2-Bromophenyl)-*N'*-{[(*S*)-1-(3-methylphenyl)pyrrolidin-2-ylmethyl]}urea;

N-(4-Fluorophenyl)-*N'*-{[(*S*)-1-(3-methylphenyl)pyrrolidin-3-yl]}urea;

N-(2-Bromophenyl)-*N'*-{[(*S*)-1-(3-methylphenyl)pyrrolidin-3-yl]}urea;

N-(4-Fluorophenyl)-*N'*-{[(*R*)-1-(3-methylphenyl)pyrrolidin-3-yl]}urea;

N-(4-Fluorophenyl)-*N'*-{[(*R*)-1-(3-fluorophenyl)pyrrolidin-3-yl]}urea;

25 *N*-(2-Bromophenyl)-*N'*-{[(*R*)-1-(3-fluorophenyl)pyrrolidin-3-yl]}urea;

N-(1-Naphthyl)-*N'*-{[(*R*)-1-(3-methylphenyl)pyrrolidin-3-yl]}urea;

N-(2,3-Dichlorophenyl)-*N'*-{[(*R*)-1-(3-methylphenyl)pyrrolidin-3-yl]}urea;

N-(2-Bromophenyl)-*N'*-{[(*S*)-1-(3-fluorophenyl)pyrrolidin-3-yl]}urea;

N-(2-Bromophenyl)-*N'*-{[(*R*)-1-(4-fluoro-3-methylphenyl)pyrrolidin-3-yl]}urea;

30 *N*-(2-Bromophenyl)-*N'*-{[(*R*)-1-(3,4-difluorophenyl)pyrrolidin-3-yl]}urea;

N-(2-Bromophenyl)-*N'*-{[(*R*)-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl]}urea;

N-(3-Chloro-2-methylphenyl)-*N'*-{[(*R*)-1-(3-methylphenyl)pyrrolidin-3-yl]}urea;

N-(2,3-Dichlorophenyl)-*N'*-{[(*R*)-1-(3-methylphenyl)pyrrolidin-3-yl]}urea;

- N -(2,5-Dichlorophenyl)- N' -[$((R)$ -1-(3-methylphenyl)pyrrolidin-3-yl)]urea;
 N -(2,3-Dichlorophenyl)- N' -[$((R)$ -1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;
 N -(2,5-Dichlorophenyl)- N' -[$((R)$ -1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;
 N -(3-Chloro-2-methylphenyl)- N' -[$((R)$ -1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;
5 N -(3-Chloro-2-methylphenyl)- N' -[$((R)$ -1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;
 N -(2,3-Dichlorophenyl)- N' -[$((R)$ -1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;
 N -(2,5-Dichlorophenyl)- N' -[$((R)$ -1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;
 N -(3-Chloro-2-methylphenyl)- N' -[$((R)$ -1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl)]urea; and
10 N -(2,3-Dichlorophenyl)- N' -[$((R)$ -1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl)]urea.

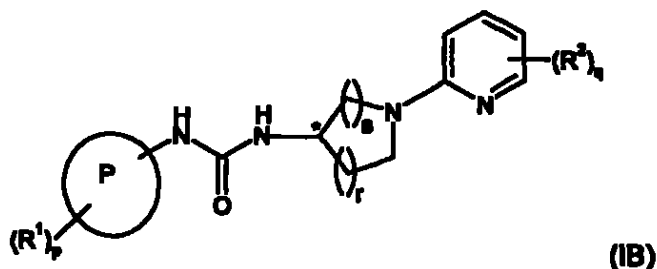
Suitably, P is phenyl, quinoliny or isoquinoliny. More suitably P is phenyl, 5-quinoliny, 7-quinoliny or 5-isoquinoliny. Preferably, P is phenyl or 5-isoquinoliny.

- 15 Suitably, P' is phenyl. Suitably, P'' is pyridyl.
 Suitably, R^1 is halo, $-CF_3$ or alkyl. Preferably, R^1 is fluoro, chloro, bromo, $-CF_3$, methyl or *tert*-butyl.
 When p is 2 or 3 the groups R^1 may be the same or different.
 Suitably, p is 1 or 2. Preferably, p is 1.
20 Suitably, m is 1.
 Suitably, n is 0 or 1. Preferably, n is 0.
 Suitably, R^2 is halo, alkyl, alkoxy, $-CN$ or $-CF_3$. Preferably, R^2 is fluoro, chloro, bromo, methyl, OMe or CF_3 .
 Suitably, q is 1 or 2. Preferably, q is 1.
25 Suitably, x is 1, 2 or 3.
 When q is 2 or 3 the groups R^2 may be the same or different.
 When q is 2, particularly preferred examples of R^2 are 3,4-difluoro, 3-fluoro-4-methyl, 3-methyl-4-fluoro, 3-chloro-5-trifluoromethyl, 3-cyano-5-trifluoromethyl and 3-cyano-6-trifluoromethyl.
30 Suitably, r and s have values such that they define a 4 - 7 membered ring.
 Preferably, r and s have values such that they define a 5 or 6 membered ring.
 Most preferably r and s have values such that they define a 5 membered ring.

11

According to a further preferred aspect of the present invention, there is provided a subset of compounds of formula (I), of formula (IB),

5



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

P is phenyl, naphthyl, quinoliny or isoquinoliny;

- 10 R¹ and R² are independently selected from -H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO₂, -OH, -OCF₃, -CF₃, -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)_xNR⁴R⁵, -C(O)CF₃, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -C(O)(CH₂)_xOR⁶, -C(O)(CH₂)_xNR⁴R⁵, -C(O)alkoxy, -C(O)NR⁴R⁵, -(CH₂)_xC(O)alkoxy, -
- 15 (CH₂)_xOC(O)R⁶, -(CH₂)_xOR⁶, -(CH₂)_xR⁴R⁵, -(CH₂)_xC(O)NR⁴R⁵, -(CH₂)_xN(R⁴)C(O)R⁶, -(CH₂)_xS(O)₂NR⁴R⁵, -(CH₂)_xN(R⁴)S(O)₂R⁶, -ZAr, -(CH₂)_xS(O)₂R⁶, -(OCH₂)_xS(O)₂R⁶, -N(R⁴)S(O)₂R⁶, -N(R⁴)C(O)R⁶, -(CH₂)_xN(R⁴)S(O)₂R⁶, -(CH₂)_xN(R⁴)C(O)R⁶ or -(CH₂)_xC(O)alkyl;

R⁴ and R⁵ may be the same or different and represent H or alkyl or R⁴ and R⁵

- 20 together with the atoms to which they are attached form a C₃₋₈azacycloalkane, C₃₋₈(2-oxo)azacycloalkane ring or C₃₋₈ polymethylene chain optionally interrupted by heteroatoms such as O or -NR⁷.

Z is O, S or NR⁷;

R⁶ is alkyl or aryl;

- 25 R⁷ is hydrogen, alkyl or aryl;

m is 1 or 2;

n is 0, 1, 2 or 3;

p and q are independently 0, 1, 2, 3 or 4;

r is 1, 2 or 3;

s is 0, 1 or 2; and

x is 0, 1, 2, 3, 4, 5 or 6.

Suitably, R^1 is halo, hydroxy, alkyl, alkoxy, $-CF_3$, $-NO_2$, $-CN$, $-OCF_3$, amino or mono- or dialkylamino. Preferably, R^1 is halo, $-CF_3$ or alkyl. More preferably, R^1 is bromo, chloro, fluoro, $-CF_3$, methyl or *tert*-butyl;

Suitably, R^2 is halo, hydroxy, alkyl, alkoxy, $-CF_3$, $-NO_2$, $-CN$, $-OCF_3$, amino or mono- or dialkylamino. Preferably, R^2 is halo, alkyl, alkoxy, $-CN$, or $-CF_3$. Preferably, R^2 is bromo, chloro, fluoro, methyl, $-OMe$ or $-CF_3$;

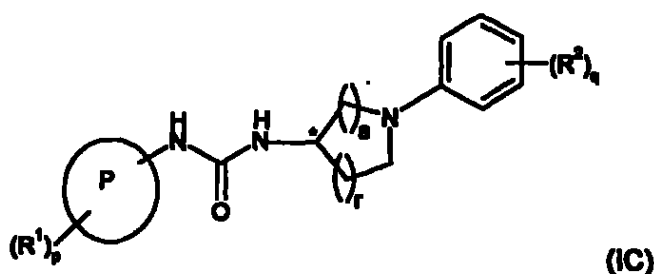
Suitably, p and q are independently 0, 1 or 2; and

Suitably, r and s are independently 1 or 2.

Suitably, x is 1, 2 or 3.

Compounds of formula (IB) of particular interest according to the present invention are Example numbers 1-23, 28, 29, 34-39, 44-50 and 55-76 (presented in Table 1 below) or pharmaceutically acceptable salts or solvates thereof.

According to a further aspect of the present invention, there is provided a subset of compounds of formula (I), of formula (IC),



20

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

P is phenyl, naphthyl, quinoliny or isoquinoliny;

R^1 and R^2 are independently selected from halo, hydroxy, alkyl, alkoxy, $-CF_3$, $-NO_2$, $-CN$, $-OCF_3$, amino or mono- or dialkylamino

25 n is 0, 1, 2 or 3;

p and q are independently 0, 1, 2, 3 or 4;

r is 1, 2 or 3; and

s is 0, 1 or 2;

16

with the proviso that said compound of formula (I) is not a compound selected from:

- 1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea;
 1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea;
- 5 *N*-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;
N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;
N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;
N-(4-Fluorophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;
N-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;
- 10 *N*-(4-Fluorophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;
N-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;
N-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;
N-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;
N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;
- 15 *N*-(1-Naphthyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;
N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;
N-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;
N-(2-Bromophenyl)-*N'*-[*((R)*-1-(4-fluoro-3-methylphenyl)pyrrolidin-3-yl)]urea;
N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;
- 20 *N*-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl)]urea;
N-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;
N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;
N-(2,5-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;
N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;
- 25 *N*-(2,5-Dichlorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;
N-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;
N-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;
N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;
N-(2,5-Dichlorophenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;
- 30 *N*-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl)]urea; and
N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl)]urea.

14.

Suitably, P is phenyl, quinoliny or isoquinoliny.

Suitably, R¹ is alkyl. Preferably R¹ is methyl.

Suitably, R² is halo or alkyl. Suitably, R² is fluoro or methyl.

5 Suitably, p and q are independently 0, 1 or 2.

Suitably, r and s are independently 1 or 2.

Compounds of formula (IC) of particular interest according to the present invention are Example numbers 24-27, 30-33, 40-43 and 51-54 (illustrated in Table 1 below) or pharmaceutically acceptable salts or solvates thereof.

10 Certain of the carbon atoms of formula (I) are chiral carbon atoms, such as the carbon atom marked with an "*", and therefore compounds of formula (I) may exist as stereoisomers. The invention extends to all optical isomers such as stereoisomeric forms of the compounds of formula (I) including enantiomers and mixtures thereof, such as racemates. The different stereoisomeric forms may be
15 separated or resolved one from the other by conventional methods or any given isomer may be obtained by conventional stereospecific or asymmetric syntheses.

Preferred compounds of formula (I) have the C* carbon in the R-configuration.

20 Certain of the compounds herein can exist in various tautomeric forms and it is to be understood that the invention encompasses all such tautomeric forms.

As indicated above, the compounds of formula (I) can form salts, especially pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts are those use conventionally in the art and include those
25 described in *J. Pharm. Sci.*, 1977, 66, 1-19, such as acid addition salts.

Suitable pharmaceutically acceptable salts include acid addition salts.

Suitable pharmaceutically acceptable acid addition salts include salts with inorganic acids such, for example, as hydrochloric acid, hydrobromic acid, orthophosphoric acid or sulphuric acid, or with organic acids such, for example
30 as methanesulphonic acid, toluenesulphonic acid, acetic acid, propionic acid, lactic acid, citric acid, fumaric acid, malic acid, succinic acid, salicylic acid, maleic acid, glycerophosphoric acid or acetylsalicylic acid.

18

The salts and/or solvates of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts and/or solvates of compounds of formula (I) or the compounds of the formula (I) themselves, and as such form another aspect of the present invention.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and if crystalline, may be optionally hydrated or solvated. This invention includes in its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

10 Suitable solvates include pharmaceutically acceptable solvates, such as hydrates.

Solvates include stoichiometric solvates and non-stoichiometric solvates.

As used herein the term "alkyl" as a group or part of a group refers to a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms. Such alkyl groups in particular include methyl ("Me"), ethyl ("Et"), n-propyl ("Prⁿ"), *iso*-propyl ("Prⁱ"), n-butyl ("Buⁿ"), *sec*-butyl ("Bu^s"), *tert*-butyl ("Bu^t"), pentyl and hexyl. Where appropriate, such alkyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, -CF₃, -OH, -OCF₃, C₂₋₆ alkenyl, C₃₋₆ alkynyl, C₁₋₆ alkoxy, aryl and di-C₁₋₆ alkylamino.

As used herein, the term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, *iso*-propoxy, n-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. Where appropriate, such alkoxy groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, -CF₃, -OH, -OCF₃, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ alkynyl, aryl and di-C₁₋₆ alkylamino.

As used herein, the term "aryl" as a group or part of a group refers to a carbocyclic aromatic radical ("Ar"). Suitably such aryl groups are 5-6 membered monocyclic groups or 8-10 membered fused bicyclic groups, especially phenyl ("Ph"), biphenyl and naphthyl, particularly naphthyl and phenyl.

As used herein, the term "heteroaryl" as a group or part of a group refers to a stable 5- 7-membered monocyclic or 7- to 10-membered bicyclic

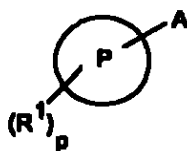
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heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4, suitably from 1 to 2, heteroatoms independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of suitable heteroaryl groups include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H, 6H-1,5,2-dithiazinyl, dihydrobenzofuranyl, furanyl, furazanyl, imidazolyl, 1H-
 10 indazolyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolyl, pyrimidinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridooxazolyl, pyridolimidazolyl, pyridothiazolyl, pyridyl, pyrrolyl, quinazolinyl, quinolinyl,
 15 quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienolimidazolyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

The term "halo" is used herein to describe, unless otherwise stated, a
 20 group selected from fluorine ("fluoro"), chlorine ("chloro"), bromine ("bromo") or iodine ("iodo").

The term "naphthyl" is used herein to denote, unless otherwise stated, both naphth-1-yl and naphth-2-yl groups.

The present invention also provides a process for the preparation of a
 25 compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises coupling a compound of formula (II):

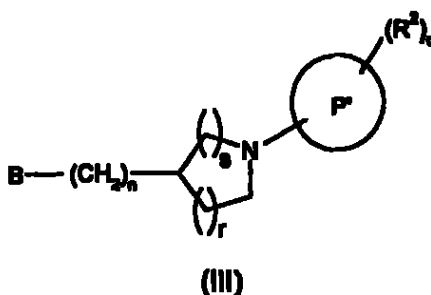


30

(II)

In which R^1 , P and p are as defined in formula (I) with a compound of formula (III):

5



- 10 In which P , R^2 , n , q , r and s are as defined in formula (I) and A and B contain appropriate functional groups which are capable of reacting together to form the urea moiety;
and thereafter, as necessary, carrying out one or more of the following reactions:
(I) converting one compound of formula (I) into another compound of formula (I);
15 (II) removing any protecting group;
(III) preparing a salt or a solvate of the compound so formed.

Suitable examples of appropriate A and B groups include:

- (a) A is $-N=C=O$ and B is NH_2 ; or A is NH_2 and B is $N=C=O$ or
(b) A is NH_2 and B is NH_2 together with an appropriate urea forming agent.
20 In process (a) the reaction is carried out in an inert solvent such as dichloromethane or acetonitrile.

- In process (b) the urea forming agent can be carbonyl diimidazole or phosgene or triphosgene, and carried out in an inert organic solvent such as diethyl ether, tetrahydrofuran or dichloromethane at ambient or elevated
25 temperature in the presence of a base such as triethylamine or pyridine.

An alternative method of synthesis of the unsymmetrical urea compounds of formula (I) is from a diaryl carbonate, via the corresponding carbamate. Such a methodology is described by Freer et al. (Synthetic

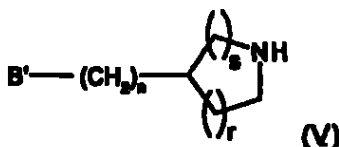
Communications, 26(2), 331 - 349, 1996). It would be appreciated by those skilled in the art that such a methodology could be readily adapted for preparation of the compounds of formula (I).

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above-mentioned procedures. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection of such groups is achieved using conventional procedures well known in the art.

A compound of formula (III) may be prepared by reaction of a compound of formula (IV):



wherein, P' is as defined in relation to formula (I) and R^{2'} is R² as defined above or a protected form thereof, L¹ is a leaving group and q is as defined above, with a compound of formula (V):



wherein B' is B as defined above or a protected form thereof and n, r and s are as defined above.

Suitably L¹ is a halogen, such as chlorine.

22

Suitably, the compound of formula (V) is in an activated form, for example an ionic form. Such activated forms are prepared using conventional coupling reaction methodology, as for example by reacting compounds (IV) and (V) in the presence of an alkali carbonate, such as potassium carbonate, in an aprotic solvent such as dimethylformamide using reaction conditions appropriate to the particular methodology chosen, for example at an elevated temperature, such as 100°C.

Compounds of formulae (IV) and (V) are commercially available, or are prepared by known procedures, such as those disclosed in: *Heterocycles*, 1984, 22(1), 117 and *J. Chem. Soc., Perkin 1*, 1988, 4, 921 for compounds of formula (IV) and *J. Med. Chem.*, 1992, 35(10), 1764 for compounds of formula (V), or by methods analogous to these disclosed methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have Vanilloid receptor antagonist (VR1) activity and are believed to be of potential use for the treatment or prophylaxis of certain disorders, or treatment of the pain associated with them, such as: pain, chronic pain, neuropathic pain, postoperative pain, post-rheumatoid arthritic pain, osteoarthritic pain, back pain, visceral pain, cancer pain, algosia, neuralgia, dental pain, headache, migraine, neuropathies, carpal tunnel syndrome, diabetic neuropathy, HIV-related neuropathy, post-herpetic neuralgia, fibromyalgia, neuritis, sciatica, nerve injury, ischaemia, neurodegeneration, stroke, post stroke pain, multiple sclerosis, respiratory diseases, asthma, cough, COPD, broncho constriction, inflammatory disorders, oesophagitis, heart burn, Barrett's metaplasia, dysphagia, gastroesophageal reflux disorder (GERD), stomach and duodenal ulcers, functional dyspepsia, irritable bowel syndrome, inflammatory bowel disease, colitis, Crohn's disease, pelvic hypersensitivity, pelvic pain, menstrual pain, renal colic, urinary incontinence, cystitis, burns, itch, psoriasis, pruritis, emesis (hereinafter referred to as the "Disorders of the Invention").

Accordingly, the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, for use as an active

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therapeutic substance, in particular in the treatment and/or prophylaxis of the Disorders of the Invention.

In particular, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment or
5 prophylaxis of pain.

The invention further provides a method for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, in particular the Disorders of the Invention, in mammals including humans, which comprises administering to a mammal in need thereof a therapeutically effective
10 amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The invention provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment or prophylaxis of disorders in which an antagonist
15 of the Vanilloid (VR1) receptor is beneficial, particularly the Disorders of the Invention.

In order to use the compounds of the invention in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. Thus, the present invention also provides a
20 pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier or excipient therefor.

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

30 Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets

24

may be coated according to methods well known in normal pharmaceutical practice.

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.

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

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. For systemic administration, dosage levels from 0.01mg to 100mg per kilogramme of body weight are useful in the treatment of pain. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20, 20 to 250, or 0.1 to 500.0 mg, for example 0.2 to 5 and 0.1 to 250 mg; and such unit doses may be administered

more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 1000 mg; and such therapy may extend for a number of weeks or months.

No unacceptable toxicological effects are indicated with compounds of the invention when administered in accordance with the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

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

Abbreviations

BINAP – 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
HPLC – High Performance Liquid Chromatography
MgSO₄ - Magnesium sulfate
TFA – Trifluoroacetic acid
DCM - dichloromethane

Description 1

[(*R*)-1-(5-Trifluoromethylpyridin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (D1)

To a solution of 2-chloro-5-trifluoromethylpyridine (7.3g, 0.04mol) and 3*R*-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine (7.5g, 0.04mol) in dry dimethylformamide (100ml) was added powdered potassium carbonate (6.8g, 0.05mol) and the reaction heated at 100°C for 7h and cooled. Solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic phase was separated, dried (MgSO₄) and filtered. Removal of solvent under reduced pressure gave a solid.

26

Chromatography on silica gel eluting with ethyl acetate and DCM (gradient elution, 20% maximum) afforded the title compound as a white solid.

Description 2

5 (R)-1-(5-Trifluoromethylpyridin-2-yl)-pyrrolidin-3-ylamine (D2)

A solution of D1 (11.5g, 0.04mol) in DCM (80ml) was cooled (ice-bath) and trifluoroacetic acid (excess, 50ml) was added. Reaction was warmed to ambient temperature, stirred for 3h and partitioned between ethyl acetate and
10 aqueous sodium hydroxide. The organic phase was separated, dried (MgSO₄) and filtered. Removal of solvent under reduced pressure afforded the crude product as a yellow oil. Bulb to bulb distillation under reduced pressure initially afforded the title compound as an oil which crystallised on standing.

15 Description 3

1,3-Dimethyl-5-nitroisoquinoline (D3)

1,3-Dimethylisoquinoline [(*Chem. Lett.*, 1983, p.791), 2.39g, 15.20mM], in concentrated sulfuric acid, (15ml), was cooled to <4°C. A solution of potassium
20 nitrate, (1.69g, 16.72mM), in concentrated sulfuric acid was added dropwise, maintaining the temperature below 4°C. After complete addition the solution was stirred at this temperature for a further 2h then warmed to room temperature for 1h. The reaction mixture was poured into ice water and the solution basified with sodium hydroxide and extracted with DCM. The extract was washed with brine,
25 dried and concentrated to a yellow solid. Purification by silica gel chromatography afforded the title compound as a yellow crystalline solid.

Description 4

5-Amino-1,3-dimethylisoquinoline (D4)

30

A solution of D3 (2.01g, 9.94mM) and 10% palladium on charcoal (1g) in methanol was hydrogenated at atmospheric pressure for 1h. The catalyst was

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filtered off and the filtrate concentrated under reduced pressure to afford the title compound as an off white solid.

Description 5

5 3-Methyl-5-nitroisoquinoline (D5)

A solution of 3-methylisoquinoline (5.4g, 0.038mol) in concentrated sulfuric acid (30ml) was cautiously added to a solution of potassium nitrate (4.25g, 1.1eq) in concentrated sulfuric acid (23ml) whilst maintaining the
10 temperature below 4°C (ice bath). Stirring was continued for 2h and then temperature raised to ambient. Reaction was further stirred for 3h and then poured into ice-water slurry (500ml). Neutralisation using solid potassium carbonate afforded a yellow solid which was filtered and washed with water. The crude product was dissolved in ethanol (200ml), filtered and concentrated under
15 reduced pressure to afford the title compound as a yellow solid.

Description 6

5-Amino-3-methylisoquinoline (D6)

20 The title compound was prepared from D5 using the procedure outlined for Description 4.

Description 7

N-(2,2-Dimethoxyethyl)-(1-phenyl)ethylamine (D7)

25

A solution of α -methylbenzylamine (8.37g, 0.07mol) and bromoacetaldehyde dimethylacetal (11.67g, 0.07mol) in acetonitrile (150ml) containing potassium carbonate (12.39g, 0.09mol) was heated at reflux for 2d and cooled. The solid was filtered off and the filtrate was concentrated under
30 reduced pressure to leave an oil. Chromatography on silica gel eluting with ethyl acetate afforded the title compound as an oil.

28

Description 8**1-Methylisoquinoline (D8)**

To cooled chlorosulfonic acid (16ml, -10°C) was cautiously added D7 (5g, 0.024mol) over a period of 2h. Reaction was allowed to warm to ambient temperature and stirring continued for 3d. The reaction was then poured into ice-water slurry (500ml), basified using solid potassium carbonate followed by extraction using DCM. Organic phase was separated, dried over MgSO₄, filtered and concentrated under reduced pressure to leave an oil. Chromatography on silica gel eluting with ethyl acetate afforded the title compound as yellow oil.

Description 9**1-Methyl-5-nitroisoquinoline (D9)**

A solution D8 (1g, 7mmol) in sulfuric acid (2.5ml) was cooled (<4°C) and concentrated nitric acid (1ml) added over 10min. Reaction was stirred for 30min and then heated at 60°C for 2h. After cooling the reaction mixture was poured into ice water slurry (100ml) and basified using solid potassium carbonate followed by extraction using DCM. Organic phase was separated, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the title compound as a white solid.

Description 10**5-Amino-1-methylisoquinoline (D10)**

The title compound was prepared from (D9) using the procedure outlined for Description 4.

29

Description 11**((R)-1-(3-Methylphenyl)pyrrolidin-3-yl)carbamic acid tert-butyl ester (D11)**

A suspension of BINAP 1.25g, 2mmol), palladium acetate (0.3g, 1.3mmol)
5 cesium carbonate (6.6g, 0.02mol), 3-bromotoluene (4.6g, 0.027mol) and (3R)-
(+)-3-(tert-butyloxycarbonylamino)pyrrolidine (2.5g, 0.013mol) in 1,4-dioxane
(anhydrous, 50ml) was heated at reflux under an argon atmosphere for 18h.
After cooling, solvent was removed under reduced pressure and residue
partitioned between DCM and water. Organic phase was separated, dried over
10 MgSO₄, filtered and concentrated under reduced pressure to leave an oil.
Chromatography on silica gel eluting with ethyl acetate and hexane (gradient
elution, maximum 4%) afforded the title compound as an off-white solid.

Description 12**15 (R)-1-(3-Methylphenyl)pyrrolidin-3-amine (D12)**

A solution of D11 (2.07g, 7.5mmol) in TFA (1.2ml) and DCM (20ml) was
stirred at ambient temperature for 18h. Solvent was removed under reduced
pressure and the residue partitioned between DCM and aqueous sodium
20 hydrogen carbonate. Organic phase was separated, dried over MgSO₄, filtered
and concentrated under reduced pressure to afford the title compound as an oil.

Description 13**25 (R)-1-(3-Fluorophenylpyrrolidin-3-yl)carbamic acid tert-butyl ester (D13)**

The title compound was prepared from (3R)-(+)-3-(tert-
butyloxycarbonylamino)pyrrolidine and 1-bromo-3-fluorobenzene using the
procedure outlined in Description 11.

30

30

Description 14**(R)-1-(3-Fluorophenyl)pyrrolidin-3-ylamine (D14)**

5 The title compound was prepared from D13 using the procedure outlined for Description 12.

Description 15**(R)-1-(3,4-Difluorophenyl)pyrrolidine-3-carbamic acid tert-butyl ester (D15)**

10 The title compound was prepared from (3R)-(+)-3-(tert-butoxycarbonylamino)pyrrolidine and 4-bromo-1,2-difluorobenzene using the procedure outlined for Description 11.

Description 16**15 (R)-1-(3,4-Difluorophenyl)-pyrrolidin-3-ylamine(D16)**

The title compound was prepared from D15 using the procedure outlined for Description 12.

20 Description 17**(R)-1-(3-Fluoro-4-methylphenyl)pyrrolidine-3-carbamic acid tert-butyl ester (D17)**

25 The title compound was prepared from (3R)-(+)-3-(tert-butoxycarbonylamino)pyrrolidine and 4-bromo-2-fluorotoluene using the procedure outlined for Description 11.

Description 18**(R)-1-(3-Fluoro-4-methylphenyl)-pyrrolidin-3-ylamine(D18)**

30 The title compound was prepared from D17 using the procedure outlined for Description 12.

31

Description 19**(2,2-Diethoxyethyl)-(2-fluorobenzylidene)amine (D19)**

2-Fluorobenzaldehyde (7.45g), was added to aminoacetaldehyde
5 diethylacetal (9.16g) and the reaction heated to 100°C for 3h. After cooling, the
mixture was transferred to a separating funnel and partitioned between diethyl
ether and water. The ether layer was separated, dried over magnesium sulfate,
filtered and concentrated under reduced pressure to leave an oil. Distillation at
0.6-0.8mm collecting the fraction boiling at 102-106°C afforded the title
10 compound as a colourless oil.

Description 20**8-Fluoroisoquinoline (D20)**

15 A solution of phosphorus pentoxide, (18g), in concentrated sulfuric acid, (5
ml), was heated to 160°C was treated cautiously with a solution of D19 (11.5g)
concentrated sulfuric acid, (75ml) over a period of 5 mins. After heating for 25
mins the reaction was cooled and poured into ice-water slurry (1l). Basification
with solid sodium hydroxide to pH 10 was followed by extraction with ethyl
20 acetate. The organic phase was dried over magnesium sulfate, filtered and
concentrated under reduced pressure to afford the crude product.
Chromatography on silica gel eluting with ethyl acetate and hexane (gradient,
max 10%) afforded the product as a pale yellow crystalline solid.

25 Description 21**8-Fluoro-5-nitroisoquinoline (D21)**

D20, (0.278g), in concentrated sulfuric acid, (2ml), was cooled to 0°C.
Potassium nitrate, (0.21g), was added portionwise whilst maintaining the
30 temperature below 0°C. After complete addition the solution was stirred at 0°C
for a further 1.5h and then stirred at ambient temperature for 24h. The reaction
mixture was poured into ice-water slurry, basified with sodium hydroxide and

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extracted with ethyl acetate. The ethyl acetate solution was dried over magnesium sulfate, filtered and concentrated under reduced pressure to leave the crude product. Purification by silica gel chromatography eluting with ethyl acetate afforded the title compound as a yellow crystalline solid.

5

Description 22**5-Amino-8-fluoroisoquinoline (D22)**

D21, (0.283g), in ethanol (2ml), was treated with concentrated
10 hydrochloric acid, (2ml). Reaction mixture cooled in an ice bath and a solution of tin (II) chloride dihydrate, (1.45g), in ethanol, (2ml), was added portionwise over 10 mins. After a further 20mins the reaction mixture was basified with sodium hydroxide and extracted with DCM. The DCM solution was dried over
15 magnesium sulfate, filtered and concentrated under reduced pressure to leave the crude product. Chromatography on silica gel eluting with ethyl acetate gave the title compound as a cream solid.

Description 23**(1-Benzyl-piperidin-4-yl)-carbamic acid tert-butyl ester (D23)**

20

To a solution of 1-benzyl-4-aminopiperidine (30g, 0.16mol) in DCM (200ml) was added dropwise a solution of di-tert-butyl dicarbonate (1.1eq., 37.9g) in DCM (100ml) over a period of 2h. Reaction was stirred at ambient temperature for 18h and then solvent was removed under reduced pressure to
25 afford the title compound as a white solid.

Description 24**Piperidin-4-yl-carbamic acid tert-butyl ester (D24)**

30

A solution of D23 (10g, 3.4mmol) in methanol (150ml) was hydrogenated at 50psi in a Parr hydrogenator using 10% Palladium on carbon catalyst (800mg)

37

for 18h. Catalyst was filtered off and the filtrate concentrated under reduced pressure to afford the title compound as a white solid.

Description 25

- 5 **1-(((5-Trifluoromethylpyridin-2-yl)piperidin-4-yl)amino)-carbamic acid tert-butyl ester (D25)**

The title compound was prepared from D24 and 2-chloro-5-trifluoromethylpyridine using the procedure outlined for Description 1.

10

Description 26

- 1-(5-Trifluoromethylpyridin-2-yl)-piperidin-4-ylamine (D26)**

- 15 The title compound was prepared from D25 using the procedure outlined for Description 2.

Description 27

- 3-(3'-Isoquinolin-5-yl-ureido)-piperidine-1-carboxylic acid tert-butyl ester (D27)**

20

- To a suspension of 1-(tert-butoxycarbonyl)-3-piperidine carboxylic acid (1g, 4.4mmol) in toluene (10ml) and triethylamine (0.68ml) was added diphenylphosphoryl azide (1.1eq., 1.33g). Reaction was heated at reflux for 1h and cooled. 5-Aminoisoquinoline (629mg, 4.4mmol) was added and reaction
25 stirred at ambient temperature for 56h. Solvent was removed under reduced pressure and the residue chromatographed on silica gel eluting with hexane/ethyl acetate (gradient elution, maximum 50%) to afford the title compound as a foam.

30

34

Description 28***N*-(isoquinolin-5-yl)-*N'*-(piperidin-3-yl)-urea (D28)**

5 The title compound was prepared from D27 using the procedure outlined for Description 2.

Description 29**[(*R*)-1-(3-Trifluoromethylpyridin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (D29)**

10

 The title compound was prepared from 2-chloro-3-trifluoromethylpyridine and 3*R*-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine using the procedure outlined for Description 1.

15 **Description 30****(*R*)-1-(3-Trifluoromethylpyridin-2-yl)-pyrrolidin-3-ylamine(D30)**

 The title compound was prepared from D29 using the procedure outlined for Description 2.

20

Description 31**[(*R*)-1-(4-Trifluoromethylpyridin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (D31)**

25 The title compound was prepared from 2-chloro-4-trifluoromethylpyridine and 3*R*-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine using the procedure outlined for Description 1.

30

25

Description 32**(*R*)-1-(4-Trifluoromethylpyridin-2-yl)-pyrrolidin-3-ylamine (D32)**

5 The title compound was prepared from D31 using the procedure outlined for Description 2.

Description 33**[(*R*)-1-(6-Trifluoromethylpyridin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (D33)**

10

The title compound was prepared from 2-chloro-6-trifluoromethylpyridine and 3*R*-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine using the procedure outlined for Description 1.

15 **Description 34****(*R*)-1-(6-Trifluoromethylpyridin-2-yl)-pyrrolidin-3-ylamine(D34)**

The title compound was prepared from D33 using the procedure outlined for Description 2.

20

Description 35**[(*R*)-1-(3-Chloropyridin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (D35)**

25 The title compound was prepared from 2,3-dichloropyridine and 3*R*-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine using the procedure outlined for Description 1.

30

36

Description 36**(R)-1-(3-Chloropyridin-2-yl)-pyrrolidin-3-ylamine(D36)**

5 The title compound was prepared from D35 using the procedure outlined for Description 2.

Description 37**[(R)-1-(5-Chloropyridin-2-yl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester (D37)**

10

 The title compound was prepared from 2,5-dichloropyridine and 3R-(+)-3-(tert-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Description 1.

15 Description 38**(R)-1-(5-Chloropyridin-2-yl)-pyrrolidin-3-ylamine (D38)**

 The title compound was prepared from D37 using the procedure outlined for Description 2

20

Description 39**[(R)-1-(5-Bromopyridin-2-yl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester (D39)**

25 The title compound was prepared from 2-chloro-5-bromopyridine and 3R-(+)-3-(tert-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Description 1.

30

37

Description 40**(R)-1-(5-Bromopyridin-2-yl)-pyrrolidin-3-ylamine (D40)**

5 The title compound was prepared from D39 using the procedure outlined for Description 2.

Description 41**[(R)-1-(6-Methylpyridin-2-yl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester (D41)**

10

The title compound was prepared from 2-chloro-6-methylpyridine and 3R-(+)-3-(tert-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Description 1.

15 Description 42**(R)-1-(6-Methylpyridin-2-yl)-pyrrolidin-3-ylamine (D42)**

The title compound was prepared from D41 using the procedure outlined for Description 2

20

Description 43**1-(((3-Trifluoromethylpyridin-2-yl)piperidin-4-yl)amino)-carbamic acid tert-butyl ester (D43)**

25

The title compound was prepared from D24 and 2-chloro-3-trifluoromethylpyridine using the procedure outlined for Description 1.

Description 44**1-(3-Trifluoromethylpyridin-2-yl)-piperidine-4-ylamine (D44)**

30

The title compound was prepared from D43 using the procedure outlined for Description 2.

36

Description 45

1-(((6-Trifluoromethylpyridin-2-yl)piperidin-4-yl)amino]-carbamic acid tert-butyl ester (D45)

- 5 The title compound was prepared from D24 and 2-chloro-6-trifluoromethylpyridine using the procedure outlined for Description 1.

Description 46

1-(6-Trifluoromethylpyridin-2-yl)-piperidin-4-ylamine (D46)

10

The title compound was prepared from D45 using the procedure outlined for Description 2.

Description 47

- 15 **1-(((4-Trifluoromethylpyridin-2-yl)piperidin-4-yl)amino)-carbamic acid tert-butyl ester (D47)**

The title compound was prepared from D24 and 2-chloro-4-trifluoromethylpyridine using the procedure outlined for Description 1.

20

Description 48

1-(4-Trifluoromethylpyridin-2-yl)-piperidin-4-ylamine(D48)

- 25 The title compound was prepared from D47 using the procedure outlined for Description 2.

Description 49

1-(((3-Chloro-5-trifluoromethylpyridin-2-yl)piperidin-4-yl)amino)-carbamic acid tert-butyl ester (D49)

30

The title compound was prepared from D24 and 2,3-dichloro-5-trifluoromethylpyridine using the procedure outlined for Description 1.

2A

Description 50**1-(3-Chloro-5-trifluoromethylpyridin-2-yl)-piperidin-4-ylamine (D50)**

The title compound was prepared from D49 using the procedure outlined
5 for Description 2.

The following amines were prepared using methods to those described above.

10 **(R)-1-(3-Methylpyridin-2-yl)-pyrrolidin-3-ylamine (D51).**

(R)-1-(4-Methylpyridin-2-yl)-pyrrolidin-3-ylamine (D52).

(R)-1-(5-Methylpyridin-2-yl)-pyrrolidin-3-ylamine (D53).

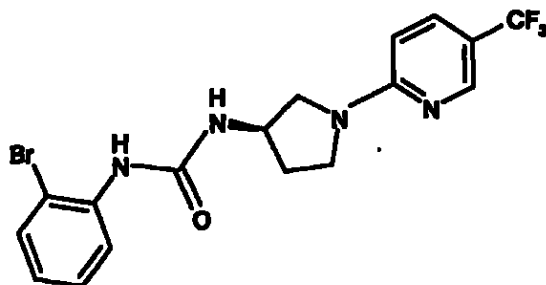
15 **(R)-1-(6-Methoxypyridin-2-yl)-pyrrolidin-3-ylamine (D54).**

1-(3-Cyano-5-trifluoromethylpyridin-2-yl)-piperidin-4-ylamine (D55).

20 **(3R)-(+)-3-(tert-butyloxycarbonylamino)pyrrolidine, 5-aminoisoquinoline, 1-aminoisoquinoline, 5-aminoquinoline and 7-aminoquinoline are available commercially from TCI (Japan), Aldrich Chemical Company and Specs and BloSpecs B.V. respectively. Di-tert-butyl tricarboxylate was prepared according to the procedure outlined in the literature (Org. Synth., 1978, 57, p.45). 2-methyl-7-aminoquinoline was prepared according to the procedure outlined in the literature**
25 **(J Med. Chem., 1977, 20(11), p.1528).**

30

40

Example 1***N*-(2-Bromophenyl)-*N'*-[*((R)*-1-(5-trifluoromethyl-2-pyridyl)pyrrolidin-3-yl)]urea (E1)**

5

A solution of 2-bromophenyl isocyanate (Aldrich Chemical Company) (27.4ml, 0.222mol) in dry diethyl ether (65ml) was added dropwise over 0.5h to an efficiently stirred solution of D2 (51.4g, 0.222mol) in dry diethyl ether (0.8L) under argon at ambient temperature. After stirring for 18h, a white precipitate was filtered off and washed with dry diethyl ether (2 x 150ml). The solid was crushed to a fine powder and then re-stirred with diethyl ether (470ml) for 4h at ambient temperature. The insoluble product was filtered off, washed with diethyl ether (100ml) and dried at 50°C/vacuum/24h to afford title compound as a white solid.

15

¹H NMR (d₆-DMSO, 400MHz) δ 1.94-1.98 (1H, m), 2.19-2.28 (1H, m), 3.31-3.41 (1H, m), 3.58 (2H, br, s), 3.67-3.71 (1H, m), 4.34-4.36 (1H, m), 6.62 (1H, d, J 9.0Hz), 6.89 (1H, t, J 7.8Hz), 7.28 (1H, t, J 8.5Hz), 7.47 (1H, d, J 6.7Hz), 7.55 (1H, dd, J 8.0, 1.4Hz), 7.76-7.79 (2H, m), 8.12 (1H, dd, J 8.3, 1.4Hz), 8.41 (1H, s). MH⁺ 429, 431.

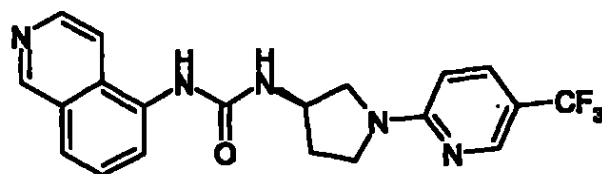
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Example 2

***N*-(isoquinolin-5-yl)-*N'*-[(*R*)-1-(5-trifluoromethyl-2-pyridyl)pyrrolidin-3-yl]urea (E2)**



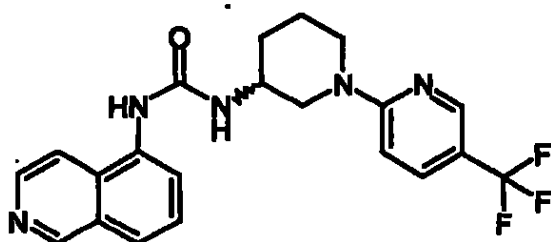
5

To a solution of di-*tert*-butyl tricarboxylate, (0.681g, 2.595mmol), in dry DCM (1ml) was added a solution of D2, (0.5g, 2.162mmol) in dry DCM (1ml) in one portion. After the initial effervescence, the solution was stirred at room temperature for 0.3h. A solution of 5-aminoisoquinoline, (0.312g, 2.162mmol) in dry DCM (1ml) was added. The reaction mixture was stirred at room temperature overnight. The resultant precipitate was removed by centrifugation, and the solid washed with ether and dried to give the title compound as a white solid.

¹H NMR (d₆-DMSO, 250MHz) δ 9.26 (1H, s), 8.57 (1H, s), 8.52 (1H, d), 8.41(1H,s), 8.31 (1H,d), 7.88 (1H, d), 7.78 (1H,dd), 7.70 (1H, d), 7.60 (1H, t), 6.99 (1H, d), 6.64 (1H, d), 4.41 (1H, m), 3.73 (1H, dd), 3.59 (2H, m), 3.42 (1H, m), 2.28 (1H, m) and 2.02 (1H, m). MH⁺ 402

Example 3

(+)-*N*-(isoquinolin-5-yl)-*N'*-[(1-(5-trifluoromethyl-2-pyridyl)piperidin-3-yl)]urea (E3)



42
#2

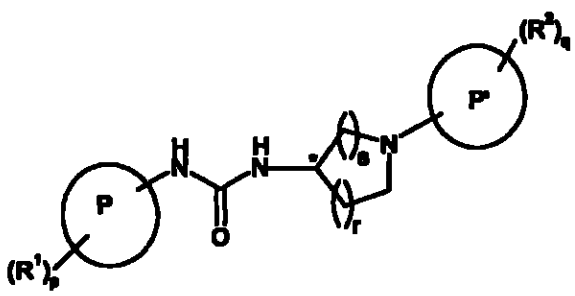
D28 (0.2g, 0.74mmol), 2-chloro-5-trifluoromethylpyridine (3eq., 0.4g) in dimethylformamide (10ml) and finely powdered potassium carbonate (3eq. 0.31g) were heated at 90°C for 18h and cooled. Solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic phase was separated, dried (MgSO₄) and filtered. Removal of solvent under reduced pressure afforded the crude product. This was chromatographed on silica gel eluting with ethyl acetate to give the title compound as an off-white solid which was converted into a hydrochloride salt. MH⁺ (free base) 416.

The two enantiomers (E3A and E3B) were separated by HPLC using Chiralpak AD column (250x19mm id), and eluting with n-hexane:ethanol (80:20 v/v) at a flow rate of 1ml/min with UV detection at 215nm.

Examples presented in Table 1 were prepared in accordance with the procedures described herein and similar to those of E1 to E3.

43 183

Table 1

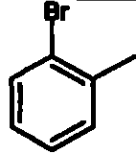
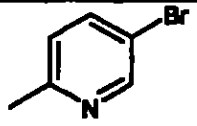
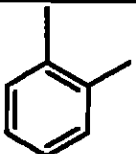
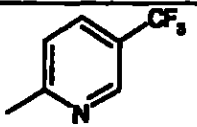
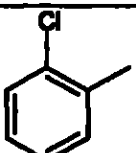
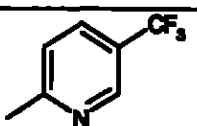
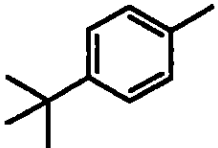
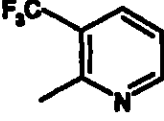
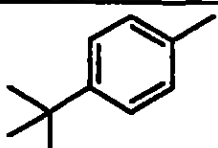
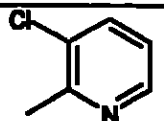
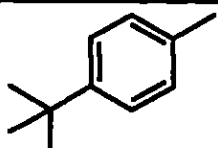
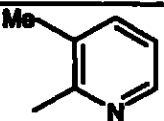
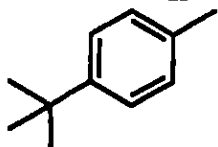
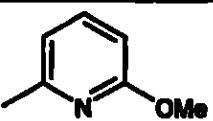
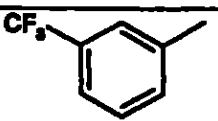
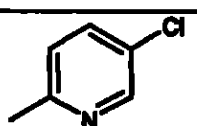
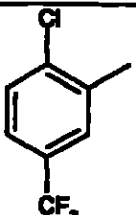
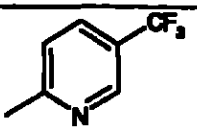


(I)

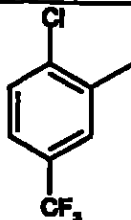
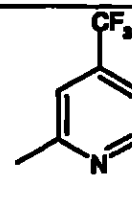
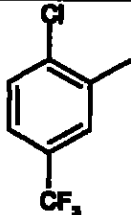
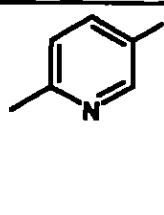
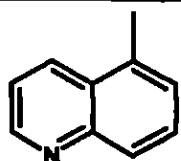
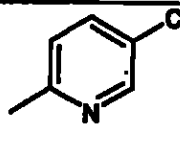
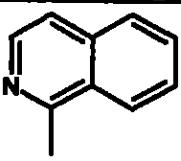
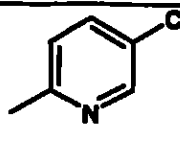
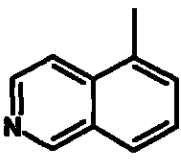
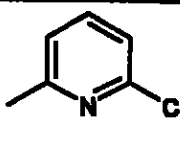
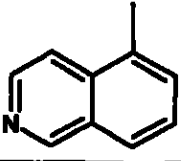
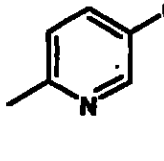
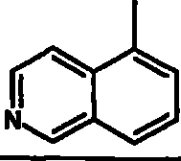
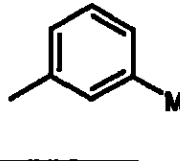
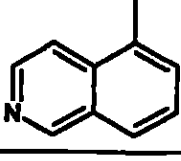
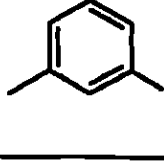
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6		R	1	1		428, 431
7		R	1	1		398, 398
8		R	1	1		398, 398

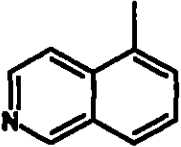
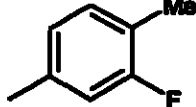
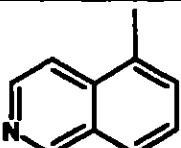
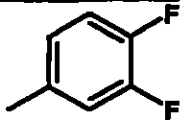
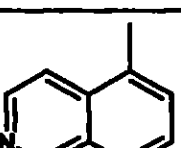
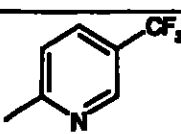
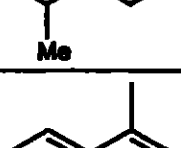
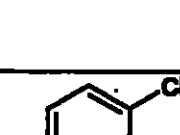
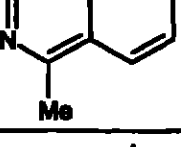
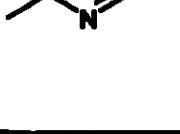
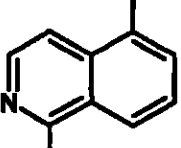
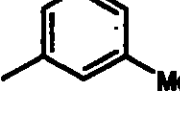
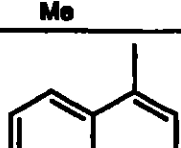
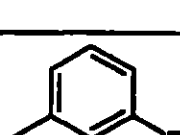
24

9		R	1	1		440, 442
10		R	1	1		477
11		R	1	1		385, 387
12		R	1	1		407
13		R	1	1		373, 375
14		R	1	1		353
15		R	1	1		389
16		R	1	1		384, 386
17		R	1	1		452, 454

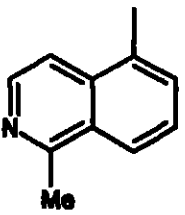
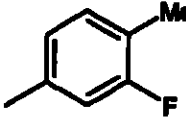
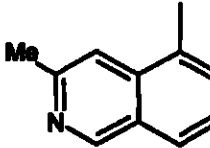
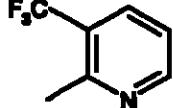
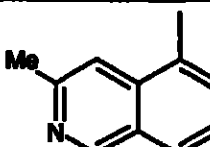
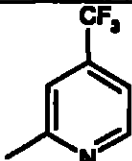
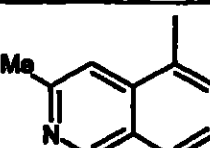
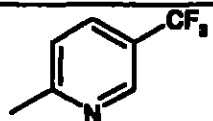
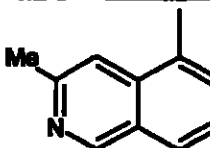
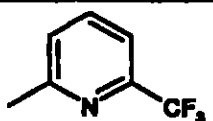
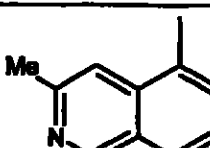
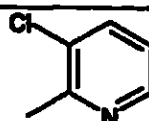
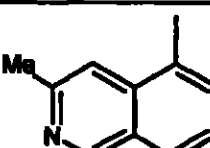
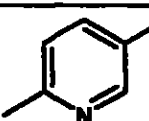
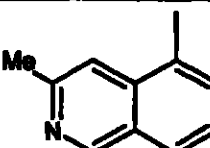
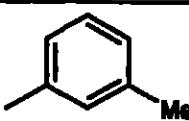
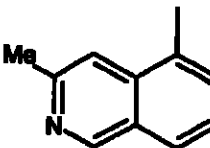
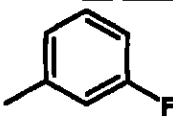
US

18		R	1	1		452, 454
19		R	1	1		420, 422
20		R	1	1		402
21		R	1	1		402
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24		R	1	1		347
25		R	1	1		351

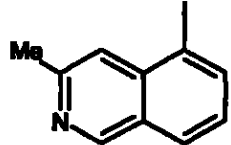
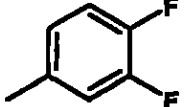
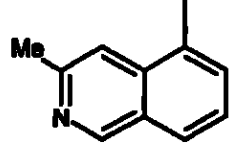
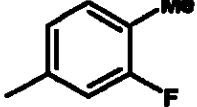
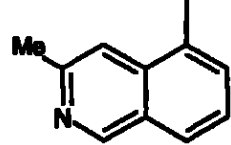
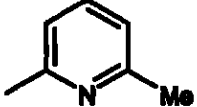
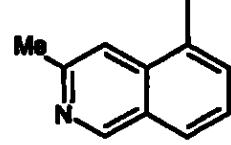
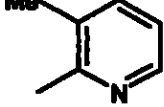
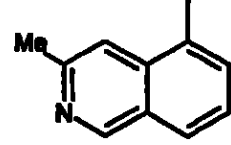
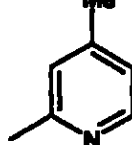
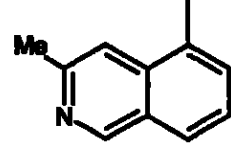
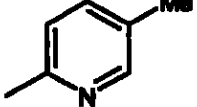
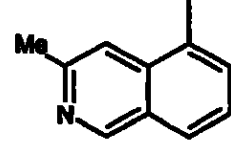
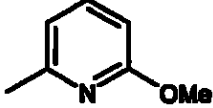
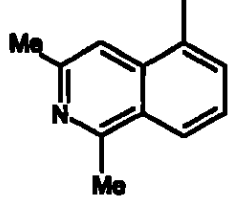
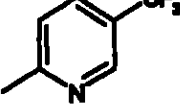
46

26		R	1	1		385
27		R	1	1		389
28		R	1	1		418
29		R	1	1		380, 382
30		R	1	1		381
31		R	1	1		385
32		R	1	1		383

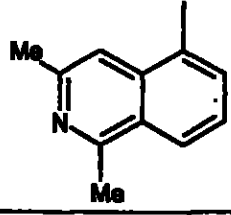
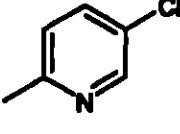
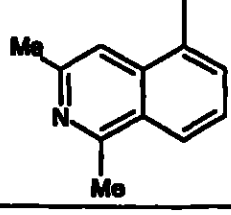
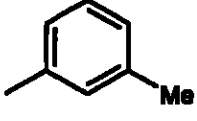
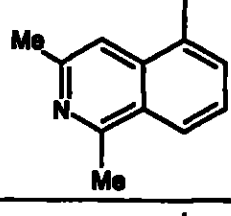
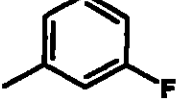
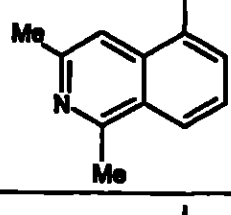
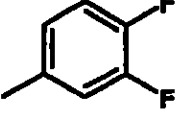
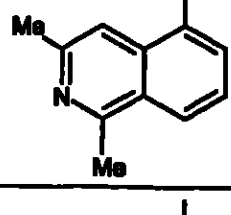
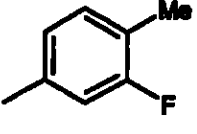
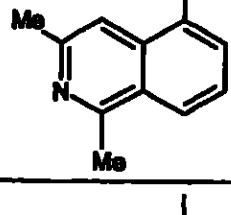
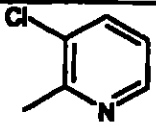
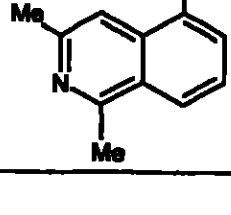
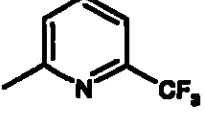
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33		R	1	1		379
34		R	1	1		418
35		R	1	1		418
36		R	1	1		418
37		R	1	1		418
38		R	1	1		381, 383
39		R	1	1		380, 382
40		R	1	1		381
41		R	1	1		385

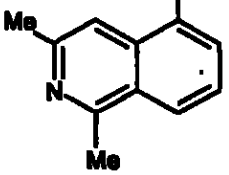
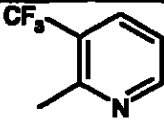
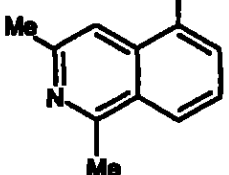
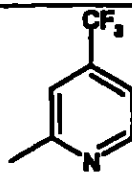
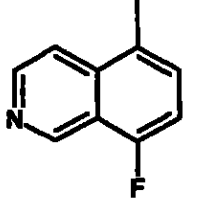
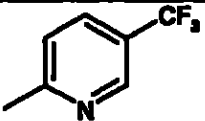
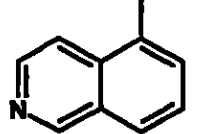
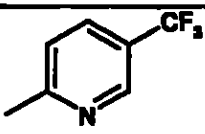
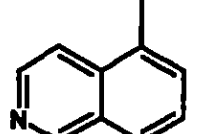
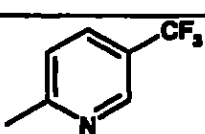
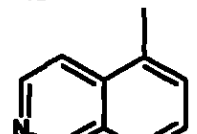
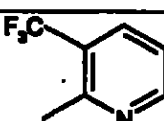
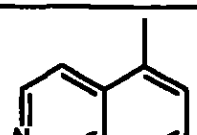
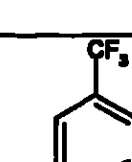
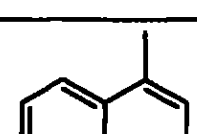
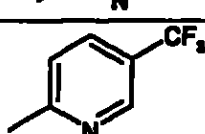
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42		R	1	1		382
43		R	1	1		379
44		R	1	1		382
45		R	1	1		382
46		R	1	1		382
47		R	1	1		382
48		R	1	1		378
49		R	1	1		430

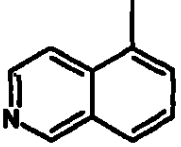
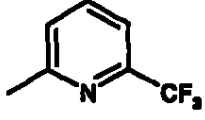
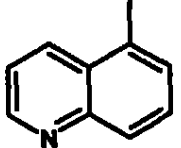
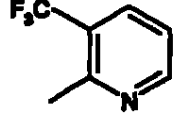
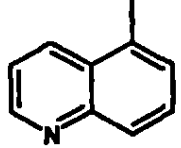
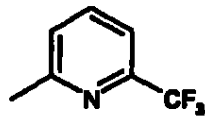
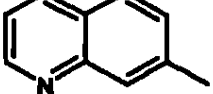
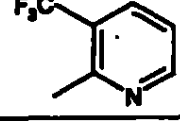
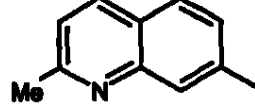
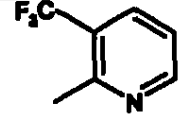
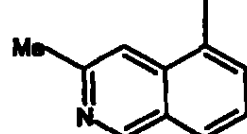
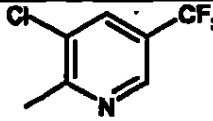
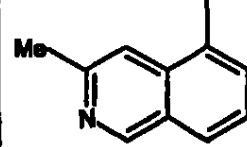
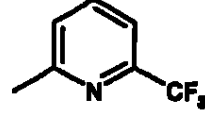
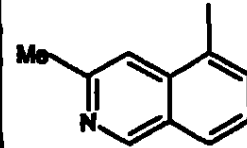
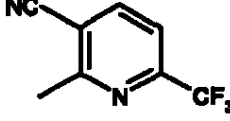
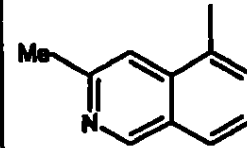
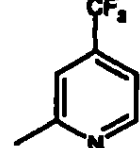
219

80		R	1	1		396, 398
81		R	1	1		375
82		R	1	1		379
83		R	1	1		387
84		R	1	1		393
85		R	1	1		395, 397
88		R	1	1		430

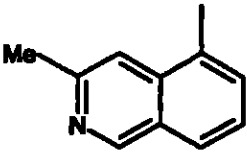
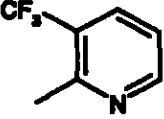
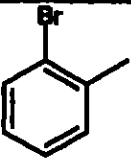
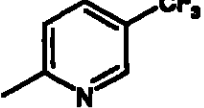
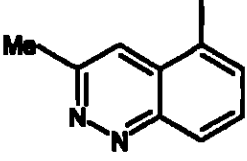
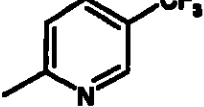
SD

57		R	1	1		430
58		R	1	1		430
59		R	1	1		420
60			1	2		418
61			1	2		418
62		-	2	1		418
63		-	2	1		418
64		-	2	1		418

51

65		-	2	1		416
66		-	2	1		416
67		-	2	1		416
68		-	2	1		416
69		-	2	1		430
70		-	2	1		463, 465
71		-	2	1		430
72		-	2	1		455
74		-	2	1		430

52

75		-	2	1		430
76		S	1	1		429, 431
77		R	1	1		417

SChem = stereochemistry

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Pharmacological Data**(a) In vitro assay**

As referenced above, the compounds of the invention are vanilloid
5 receptor (VR1) antagonists and hence have useful pharmaceutical properties.
Vanilloid receptor (VR1) antagonist activity can be confirmed and demonstrated
for any particular compound by use of conventional methods, for example those
disclosed in standard reference texts such as D. Le Bars, M. Gozarin and S. W.
Cadden, Pharmacological Reviews, 2001, 53(4), 597-652] or such other texts
10 mentioned herein.

The screen used for the compounds of this invention was based upon a
FLIPR based calcium assay, similar to that described by Smart et al. (British
Journal of Pharmacology, 2000, 129, 227-230). Transfected astrocytoma
1321N1 cells, stably expressing human VR1, were seeded into FLIPR plates at
15 25,000 cells/well (96-well plate) and cultured overnight.

The cells were subsequently loaded in medium containing 4 μ M Fluo-3
AM (Molecular Probes) for 2 hours, at room temperature, in the dark. The plates
were then washed 4 times with Tyrode containing 1.5mM calcium, without
probenecid. The cells were pre-incubated with compound or buffer control at
20 room temperature for 30 minutes. Capsaicin (Sigma) was then added to the
cells. Compounds having antagonist activity against the human VR1 were
identified by detecting differences in fluorescence when measured after
capsaicin addition, compared with no compound buffer controls. Thus, for
example, in the buffer control capsaicin addition results in an increase in
25 intracellular calcium concentration resulting in fluorescence. A compound having
antagonist activity blocks the capsaicin binding to the receptor, there is no
signalling and therefore no increase in intracellular calcium levels and
consequently lower fluorescence. pK_b values are generated from the IC₅₀
values using the Cheng-Prusoff equation.

30 All compounds tested by the above methodology had pK_b > 6, preferred
compounds having a pK_b > 7.0.

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(b) FCA-Induced hyperalgesia in the Guinea pig

100µl of 1mg/ml FCA was injected intraplantar into the left paw of 4 groups of 8 male Dunkin Hartley guinea-pigs (batch: 6282434, average weight 340g). 24 hours later compounds were administered orally at 0 (vehicle), 3, 10 5 30mg/kg with vehicle as 1% methylcellulose and dosing volume being 2ml/kg and dosing straight into the stomach. The methylcellulose was added gradually to the compound into the pestle and mortar and ground together.

Behavioural readouts of mechanical hyperalgesia were obtained before FCA administration (naïve reading), after FCA but before drug administration 10 (predose reading) and 1 hour after drug administration. The readout used was paw pressure (Randall-Sellito) and the end point was paw withdrawal. The paw pressure equipment also had one silver disc placed on the point to increase the markings by a factor of 2.

Compounds having a $pK_b > 7.0$ *in vitro*, according to model (a) above, 15 were tested in this model and shown to be active.

20

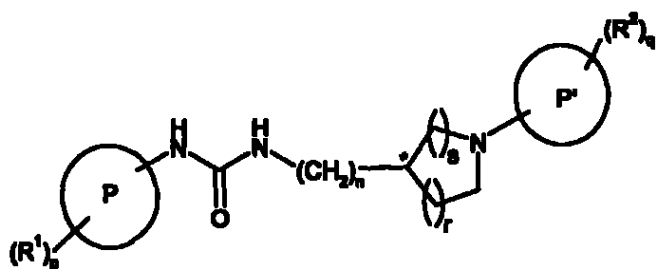
25

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Claims

1. A compound of formula (I),

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(I)

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

P and P' are independently selected from aryl and heteroaryl;

- 10 R¹ and R² are independently selected from -H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO₂, -OH, -OCF₃, -CF₃, -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)_xNR⁴R⁵, -C(O)CF₃, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -C(O)(CH₂)_xOR⁶, -C(O)(CH₂)_xNR⁴R⁵, -C(O)alkoxy, -C(O)NR⁴R⁵, -(CH₂)_xC(O)alkoxy, -
- 15 (CH₂)_xOC(O)R⁶, -(CH₂)_xOR⁶, -(CH₂)_xR⁴R⁵, -(CH₂)_xC(O)NR⁴R⁵, -(CH₂)_xN(R⁴)C(O)R⁶, -(CH₂)_xS(O)₂NR⁴R⁵, -(CH₂)_xN(R⁴)S(O)₂R⁶, -ZAr, -(CH₂)_xS(O)₂R⁶, -(OCH₂)_xS(O)₂R⁶, -N(R⁴)S(O)₂R⁶, -N(R⁴)C(O)R⁶, -(CH₂)_xN(R⁴)S(O)₂R⁶, -(CH₂)_xN(R⁴)C(O)R⁶ or -(CH₂)_xC(O)alkyl;

R⁴ and R⁵ may be the same or different and represent H or alkyl or R⁴ and R⁵

- 20 together with the atoms to which they are attached form a C₃₋₈azacycloalkane, C₃₋₈(2-oxo)azacycloalkane ring or C₃₋₈ polymethylene chain optionally interrupted by heteroatoms such as O or -NR⁷.

Z is O, S or NR⁷;

R⁶ is alkyl or aryl;

- 25 R⁷ is hydrogen, alkyl or aryl;

m is 1 or 2;

n is 0, 1, 2 or 3;

p and q are independently 0, 1, 2, 3 or 4;

5b

r is 1, 2 or 3;

s is 0, 1 or 2; and

x is 0, 1, 2, 3, 4, 5 or 6;

with the proviso that said compound of formula (I) is not a compound selected

5 from:

1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea;

1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea;

N-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

10 *N*-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

N-(4-Fluorophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

N-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

N-(4-Fluorophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

15 *N*-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(1-Naphthyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

20 *N*-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(4-fluoro-3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl)]urea;

N-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

25 *N*-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2,5-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(2,5-Dichlorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

30 *N*-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;

N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;

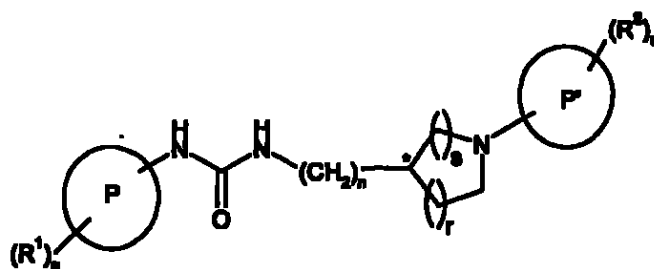
N-(2,5-Dichlorophenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;

57

N-(3-Chloro-2-methylphenyl)-*N'*-[[(*R*)-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl]]urea; and

N-(2,3-Dichlorophenyl)-*N'*-[[(*R*)-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl]]urea.

- 5 2. A compound of formula (I), as claimed in claim 1, or formula (IA),



(IA)

- 10 or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein:
P is phenyl, naphthyl, quinolynyl or isoquinolynyl;
P' is phenyl or pyridyl;
R¹ and R² are independently selected from -H, halo, alkyl, alkoxy, cycloalkyl,
aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO₂, -OH, -OCF₃, -CF₃,
15 -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)_xNR⁴R⁵,
-C(O)CF₃, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -C(O)(CH₂)_xOR⁶, -
C(O)(CH₂)_xNR⁴R⁵, -C(O)alkoxy, -C(O)NR⁴R⁵, -(CH₂)_xC(O)alkoxy, -
(CH₂)_xOC(O)R⁶, -(CH₂)_xOR⁶, -(CH₂)_xR⁴R⁵, -(CH₂)_xC(O)NR⁴R⁵, -
(CH₂)_xN(R⁴)C(O)R⁶, -(CH₂)_xS(O)₂NR⁴R⁵, -(CH₂)_xN(R⁴)S(O)₂R⁶, -ZAr, -
20 (CH₂)_xS(O)₂R⁶, -(OCH₂)_xS(O)₂R⁶, -N(R⁴)S(O)₂R⁶, -N(R⁴)C(O)R⁶, -
(CH₂)_xN(R⁴)S(O)₂R⁶, -(CH₂)_xN(R⁴)C(O)R⁶ or -(CH₂)_xC(O)alkyl;
R⁴ and R⁵ may be the same or different and represent H or alkyl or R⁴ and R⁵
together with the atoms to which they are attached form a C₃₋₈azacycloalkane,
C₃₋₈(2-oxo)azacycloalkane ring or C₃₋₈ polymethylene chain optionally interrupted
25 by heteroatoms such as O or -NR⁷.
Z is O, S or NR⁷;
R⁶ is alkyl or aryl;
R⁷ is hydrogen, alkyl or aryl;

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m is 1 or 2;

n is 0, 1, 2 or 3;

p and q are independently 0, 1, 2, 3 or 4;

r is 1, 2 or 3;

5 s is 0, 1 or 2; and

x is 0, 1, 2, 3, 4, 5 or 6;

with the proviso that the compound of formula (I) is not a compound selected from:

1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea;

10 1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea;

N-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

N-(4-Fluorophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

15 *N*-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea;

N-(4-Fluorophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(4-Fluorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

20 *N*-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(1-Naphthyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((S)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(4-fluoro-3-methylphenyl)pyrrolidin-3-yl)]urea;

25 *N*-(2-Bromophenyl)-*N'*-[*((R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;

N-(2-Bromophenyl)-*N'*-[*((R)*-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl)]urea;

N-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

N-(2,5-Dichlorophenyl)-*N'*-[*((R)*-1-(3-methylphenyl)pyrrolidin-3-yl)]urea;

30 *N*-(2,3-Dichlorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

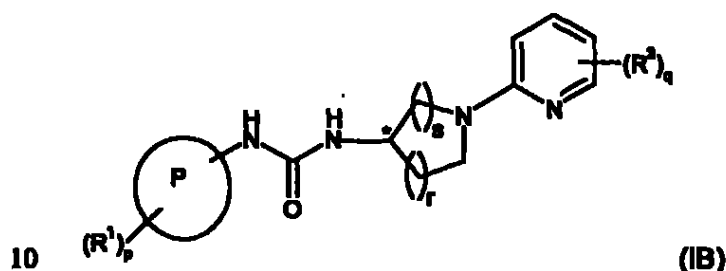
N-(2,5-Dichlorophenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

N-(3-Chloro-2-methylphenyl)-*N'*-[*((R)*-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

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- N*-(3-Chloro-2-methylphenyl)-*N'*-[[(*R*)-1-(3,4-difluorophenyl)pyrrolidin-3-yl]]urea;
N-(2,3-Dichlorophenyl)-*N'*-[[(*R*)-1-(3,4-difluorophenyl)pyrrolidin-3-yl]]urea;
N-(2,5-Dichlorophenyl)-*N'*-[[(*R*)-1-(3,4-difluorophenyl)pyrrolidin-3-yl]]urea;
N-(3-Chloro-2-methylphenyl)-*N'*-[[(*R*)-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl]]urea; and
N-(2,3-Dichlorophenyl)-*N'*-[[(*R*)-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl]]urea.

3. A compound of formula (I), as claimed in claim 1, of formula (IB),



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

P is phenyl, naphthyl, quinoliny or isoquinoliny;

- R¹ and R² are independently selected from -H, halo, alkyl, alkoxy, cycloalkyl,
 15 aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO₂, -OH, -OCF₃, -CF₃,
 -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)_xNR⁴R⁵,
 -C(O)CF₃, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -C(O)(CH₂)_xOR⁶, -
 C(O)(CH₂)_xNR⁴R⁵, -C(O)alkoxy, -C(O)NR⁴R⁵, -(CH₂)_xC(O)alkoxy, -
 (CH₂)_xOC(O)R⁶, -(CH₂)_xOR⁶, -(CH₂)_xR⁴R⁵, -(CH₂)_xC(O)NR⁴R⁵, -
 20 (CH₂)_xN(R⁴)C(O)R⁶, -(CH₂)_xS(O)₂NR⁴R⁵, -(CH₂)_xN(R⁴)S(O)₂R⁶, -ZAr, -
 (CH₂)_xS(O)₂R⁶, -(OCH₂)_xS(O)₂R⁶, -N(R⁴)S(O)₂R⁶, -N(R⁴)C(O)R⁶, -
 (CH₂)_xN(R⁴)S(O)₂R⁶, -(CH₂)_xN(R⁴)C(O)R⁶ or -(CH₂)_xC(O)alkyl;

R⁴ and R⁵ may be the same or different and represent H or alkyl or R⁴ and R⁵ together with the atoms to which they are attached form a C₃₋₈azacycloalkane,

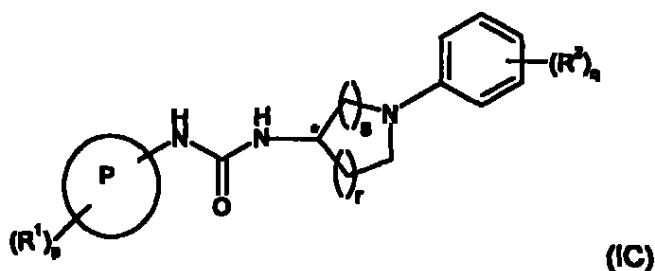
- 25 C₃₋₈(2-oxo)azacycloalkane ring or C₃₋₈ polymethylene chain optionally interrupted by heteroatoms such as O or -NR⁷.

Z is O, S or NR⁷;

R⁶ is alkyl or aryl;

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- R^7 is hydrogen, alkyl or aryl;
 m is 1 or 2;
 n is 0, 1, 2 or 3;
 p and q are independently 0, 1, 2, 3 or 4;
- 5 r is 1, 2 or 3;
 s is 0, 1 or 2; and
 x is 0, 1, 2, 3, 4, 5 or 6;
4. A compound of formula (IB) as claimed in claim 3, wherein:
- 10 R^1 and R^2 are independently selected from halo, hydroxy, alkyl, alkoxy, $-CF_3$, $-NO_2$, $-CN$, $-OCF_3$, amino or mono- or dialkylamino;
 p and q are independently 0, 1 or 2; and
 r and s are independently 1 or 2.
- 15 5. A compound of formula (I), as claimed in claim 1, of formula (IC),

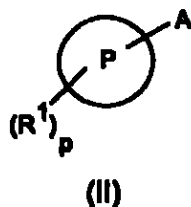


- or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein:
- 20 P is phenyl, naphthyl, quinoliny or isoquinoliny;
 R^1 and R^2 are independently selected from halo, hydroxy, alkyl, alkoxy, $-CF_3$, $-NO_2$, $-CN$, $-OCF_3$, amino or mono- or dialkylamino
 n is 0, 1, 2 or 3;
 p and q are independently 0, 1, 2, 3 or 4;
- 25 r is 1, 2 or 3; and
 s is 0, 1 or 2;
with the proviso that said compound of formula (IB) is not a compound selected from:

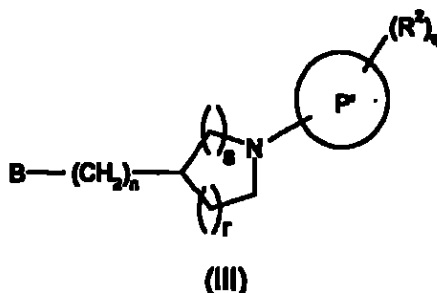
- 61
- 1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea;
 1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea;
N-(4-Fluorophenyl)-*N'*-[*(R)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl]]urea;
N-(2-Bromophenyl)-*N'*-[*(R)*-1-(3-methylphenyl)pyrrolidin-3-yl]]urea;
 5 *N*-(2-Bromophenyl)-*N'*-[*(R)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl]]urea;
N-(4-Fluorophenyl)-*N'*-[*(S)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl]]urea;
N-(2-Bromophenyl)-*N'*-[*(S)*-1-(3-methylphenyl)pyrrolidin-2-ylmethyl]]urea;
N-(4-Fluorophenyl)-*N'*-[*(S)*-1-(3-methylphenyl)pyrrolidin-3-yl]]urea;
N-(2-Bromophenyl)-*N'*-[*(S)*-1-(3-methylphenyl)pyrrolidin-3-yl]]urea;
 10 *N*-(4-Fluorophenyl)-*N'*-[*(R)*-1-(3-methylphenyl)pyrrolidin-3-yl]]urea;
N-(4-Fluorophenyl)-*N'*-[*(R)*-1-(3-fluorophenyl)pyrrolidin-3-yl]]urea;
N-(2-Bromophenyl)-*N'*-[*(R)*-1-(3-fluorophenyl)pyrrolidin-3-yl]]urea;
N-(1-Naphthyl)-*N'*-[*(R)*-1-(3-methylphenyl)pyrrolidin-3-yl]]urea;
N-(2,3-Dichlorophenyl)-*N'*-[*(R)*-1-(3-methylphenyl)pyrrolidin-3-yl]]urea;
 15 *N*-(2-Bromophenyl)-*N'*-[*(S)*-1-(3-fluorophenyl)pyrrolidin-3-yl]]urea;
N-(2-Bromophenyl)-*N'*-[*(R)*-1-(4-fluoro-3-methylphenyl)pyrrolidin-3-yl]]urea;
N-(2-Bromophenyl)-*N'*-[*(R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl]]urea;
N-(2-Bromophenyl)-*N'*-[*(R)*-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl]]urea;
N-(3-Chloro-2-methylphenyl)-*N'*-[*(R)*-1-(3-methylphenyl)pyrrolidin-3-yl]]urea;
 20 *N*-(2,3-Dichlorophenyl)-*N'*-[*(R)*-1-(3-methylphenyl)pyrrolidin-3-yl]]urea;
N-(2,5-Dichlorophenyl)-*N'*-[*(R)*-1-(3-methylphenyl)pyrrolidin-3-yl]]urea;
N-(2,3-Dichlorophenyl)-*N'*-[*(R)*-1-(3-fluorophenyl)pyrrolidin-3-yl]]urea;
N-(2,5-Dichlorophenyl)-*N'*-[*(R)*-1-(3-fluorophenyl)pyrrolidin-3-yl]]urea;
N-(3-Chloro-2-methylphenyl)-*N'*-[*(R)*-1-(3-fluorophenyl)pyrrolidin-3-yl]]urea;
 25 *N*-(3-Chloro-2-methylphenyl)-*N'*-[*(R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl]]urea;
N-(2,3-Dichlorophenyl)-*N'*-[*(R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl]]urea;
N-(2,5-Dichlorophenyl)-*N'*-[*(R)*-1-(3,4-difluorophenyl)pyrrolidin-3-yl]]urea;
N-(3-Chloro-2-methylphenyl)-*N'*-[*(R)*-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl]]urea; and
 30 *N*-(2,3-Dichlorophenyl)-*N'*-[*(R)*-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl]]urea.

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6. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in claim 1, which process comprises coupling a compound of formula (II):



10 In which R¹, P and p are as defined in formula (I) with a compound of formula (III):



- 15 In which P¹, R², n, q, r and s are as defined in formula (I) and A and B contain appropriate functional groups which are capable of reacting together to form the urea moiety;
and thereafter, as necessary, carrying out one or more of the following reactions:
(i) converting one compound of formula (I) into another compound of formula (I);
(ii) removing any protecting group;
20 (iii) preparing a salt or a solvate of the compound so formed.

7. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for use as an active therapeutic substance.

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8. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for use in the treatment and/or prophylaxis of the Disorders of the Invention.
- 5 9. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for use in the treatment and/or prophylaxis of pain.
- 10 10. A method for the treatment and/or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, in mammals including humans, which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.
- 15 11. A method according to claim 11, wherein said disorders are the Disorders of the Invention.
- 20 12. The use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial.
- 25 13. A use according to claim 13 wherein said disorders are the Disorders of the Invention.
- 30 14. A pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, and a pharmaceutically acceptable carrier or excipient therefor.

COMPUESTOS NOVEDOSOS

MEMORIA DESCRIPTIVA

5 Esta invención se refiere a compuestos novedosos, especialmente derivados de urea, que tienen actividad farmacológica, a procedimientos para su preparación, a composiciones que los contienen y a su uso en medicina, especialmente en el tratamiento de varios trastornos.

 Los vainilloides son una clase de compuestos naturales y
10 sintéticos que se caracterizan por la presencia de un grupo vainillilo (4-hidroxi-3-metoxibencilo) o un grupo funcional equivalente. El receptor de vainilloide (VR-1), cuya función es modulada por dichos compuestos, ha sido estudiado ampliamente y ha sido revisado extensamente por Szallasi y Blumberg (*The American Society for Pharmacology and Experimental Therapeutics*, 1999,
15 Vol. 51, No. 2.).

 Se conoce una amplia variedad de compuestos vainilloides de estructuras diferentes, por ejemplo los que se revelan en las solicitudes de patente europea Nos. EP 0 347 000 y EP 0 401 903, la solicitud de patente del Reino Unido No. GB 2226313, y la solicitud de patente internacional No. WO
20 92/09285. Ejemplos particularmente notables de compuestos vainilloides o moduladores del receptor vainilloide son la capsaicina o *trans*-8-metil-N-vainillil-6-nonenoamida, que se aísla de la planta de pimiento, capsazepina (*Tetrahedron*, 53, 1997, 4791), y olvanil o -N-(4-hidroxi-3-

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metoxibencil)oleamida (*J. Med. Chem.*, 36, 1993, 2595).

Las patentes de E.U.A. Nos. US 3,424,760 y US 3,424,761 describen una serie de 3-ureidopirrolidinas, de las que se afirma exhiben actividades analgésicas, en el sistema nervioso central y sicofarmacológicas.

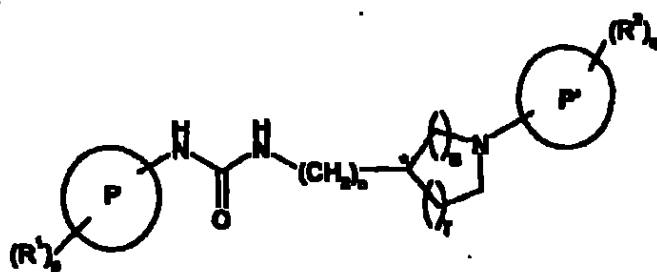
5 Específicamente, estas patentes revelan los compuestos 1-(1-fenil-3-pirrolidinil)-3-fenil-urea y 1-(1-fenil-3-pirrolidinil)-3-(4-metoxifenil)urea, respectivamente.

Las solicitudes de patente internacional Nos. WO 02/08221, WO 02/16317, WO 02/16318 y WO 02/16319, revelan algunos antagonistas del
10 receptor vainilloide y su uso en el tratamiento de enfermedades asociadas con la actividad del receptor vainilloide.

La solicitud de patente internacional copendiente No. PCT/EP02/04802 revela una serie de derivados de urea y su uso en el tratamiento de enfermedades asociadas con la actividad del receptor
15 vainilloide.

De conformidad con un primer aspecto de la presente invención, se provee un compuesto de fórmula (I):

20



(I)

o una sal o solvato farmacéuticamente aceptable del mismo, en

donde:

P y P' se seleccionan independientemente de arilo y heteroarilo;

R¹ y R² se seleccionan independientemente de -H, halógeno,

- 5 alquilo, alcoxí, cicloalquilo, aralquilo, aralcoxí, cicloalquilalquilo, cicloalquilalcoxí, -CN, -NO₂, -OH, -OCF₃, -CF₃, -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)_xNR⁴R⁵, -C(O)CF₃, -C(O)alquilo, -C(O)cicloalquilo, -C(O)aralquilo, -C(O)Ar, -C(O)(CH₂)_xOR⁶, -C(O)(CH₂)_xNR⁴R⁵, -C(O)alcoxí, -C(O)NR⁴R⁵, -(CH₂)_xC(O)alcoxí, -
- 10 (CH₂)_xOC(O)R⁶, -(CH₂)_xOR⁶, -(CH₂)_xR⁴R⁵, -(CH₂)_xC(O)NR⁴R⁵, -(CH₂)_xN(R⁴)C(O)R⁶, -(CH₂)_xS(O)₂NR⁴R⁵, -(CH₂)_xN(R⁴)S(O)₂R⁶, -ZAr, -(CH₂)_xS(O)₂R⁶, -(OCH₂)_xS(O)₂R⁶, -N(R⁴)S(O)₂R⁶, -N(R⁴)C(O)R⁶, -(CH₂)_xN(R⁴)S(O)₂R⁶, -(CH₂)_xN(R⁴)C(O)R⁶ o -(CH₂)_xC(O)alquilo;

- R⁴ y R⁵ pueden ser los mismos o diferentes y representan H o
- 15 alquilo, o R⁴ y R⁵ junto con los átomos a los que están unidos forman un anillo de azacicloalcano de C₃₋₈, (2-oxo)azacicloalcano de C₃₋₈, o una cadena de polimetileno de C₃₋₈ interrumpida opcionalmente por heteroátomos tales como O o -NR⁷.

Z es O, S o NR⁷;

- 20 R⁶ es alquilo o arilo;

R⁷ es hidrógeno, alquilo o arilo;

m es 1 o 2;

n es 0, 1, 2 o 3;

p y q son independientemente 0, 1, 2, 3 o 4;

r es 1, 2 o 3;

s es 0, 1 o 2; y

x es 0, 1, 2, 3, 4, 5 o 6;

- 5 con la condición de que dicho compuesto de fórmula (I) no sea un compuesto seleccionado de:

1-(1-fenil-3-pirrolidinil)-3-fenilurea;

1-(1-fenil-3-pirrolidinil)-3-(4-metoxifenil)urea;

N-(4-fluorofenil)-*N'*-[*((R)*-1-((3-metilfenil)pirrolidin-2-ilmetil))]urea;

10 *N*-(2-bromofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il))]urea;

N-(2-bromofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-2-ilmetil))]urea;

N-(4-fluorofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-2-ilmetil))]urea;

N-(2-bromofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-2-ilmetil))]urea;

N-(4-fluorofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-3-il))]urea;

15 *N*-(2-bromofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-3-il))]urea;

N-(4-fluorofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il))]urea;

N-(4-fluorofenil)-*N'*-[*((R)*-1-(3-fluorofenil)pirrolidin-3-il))]urea;

N-(2-bromofenil)-*N'*-[*((R)*-1-(3-fluorofenil)pirrolidin-3-il))]urea;

N-(1-naftil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il))]urea;

20 *N*-(2,3-diclorofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il))]urea;

N-(2-bromofenil)-*N'*-[*((S)*-1-(3-fluorofenil)pirrolidin-3-il))]urea;

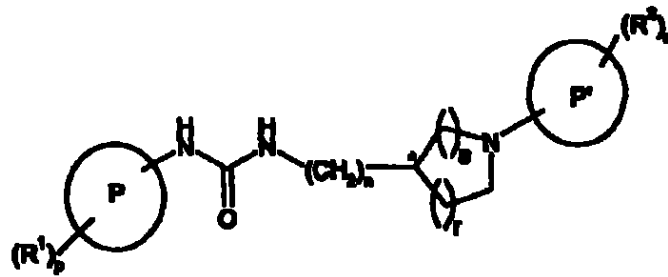
N-(2-bromofenil)-*N'*-[*((R)*-1-(4-fluoro-3-metilfenil)pirrolidin-3-il))-

urea;

- N*-(2-bromofenil)-*N'*-[*((R)*-1-(3,4-difluorofenil)pirrolidin-3-il)]urea;
N-(2-bromofenil)-*N'*-[*((R)*-1-(3-fluoro-4-metilfenil)pirrolidin-3-il)]-
 urea;
- 5 *N*-(3-cloro-2-metilfenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
N-(2,3-diclorofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
N-(2,5-diclorofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
N-(2,3-diclorofenil)-*N'*-[*((R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;
N-(2,5-diclorofenil)-*N'*-[*((R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;
N-(3-cloro-2-metilfenil)-*N'*-[*((R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;
 10 *N*-(3-cloro-2-metilfenil)-*N'*-[*((R)*-1-(3,4-difluorofenil)pirrolidin-3-il)]-
 urea;
- N*-(2,3-diclorofenil)-*N'*-[*((R)*-1-(3,4-difluorofenil)pirrolidin-3-il)]urea;
N-(2,5-diclorofenil)-*N'*-[*((R)*-1-(3,4-difluorofenil)pirrolidin-3-il)]urea;
N-(3-cloro-2-metilfenil)-*N'*-[*((R)*-1-(3-fluoro-4-metilfenil)pirrolidin-3-
 15 il)]urea; y
- N*-(2,3-diclorofenil)-*N'*-[*((R)*-1-(3-fluoro-4-metilfenil)pirrolidin-3-il)]-
 urea.

Convenientemente, P y P' se seleccionan independientemente de fenilo y heteroarilo.

- 20 En un aspecto preferido de la presente invención, se provee un subgrupo de compuestos de fórmula (I), los de la fórmula (IA):



5

(IA)

o una sal o solvato farmacéuticamente aceptable de los mismos,
en donde:

P es fenilo, naftilo, quinolinilo o isoquinolinilo;

P' es fenilo o piridilo;

- 10 R¹ y R² se seleccionan independientemente de -H, halógeno, alquilo, alcoxi, cicloalquilo, aralquilo, aralcoxi, cicloalquilalquilo, cicloalquilalcoxi, -CN, -NO₂, -OH, -OCF₃, -CF₃, -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)_xNR⁴R⁵, -C(O)CF₃, -C(O)alquilo, -C(O)cicloalquilo, -C(O)aralquilo, -C(O)Ar, -C(O)(CH₂)_xOR⁶, -
- 15 C(O)(CH₂)_xNR⁴R⁵, -C(O)alcoxi, -C(O)NR⁴R⁵, -(CH₂)_xC(O)alcoxi, -(CH₂)_xOC(O)R⁶, -(CH₂)_xOR⁶, -(CH₂)_xR⁴R⁵, -(CH₂)_xC(O)NR⁴R⁵, -(CH₂)_xN(R⁴)C(O)R⁶, -(CH₂)_xS(O)₂NR⁴R⁵, -(CH₂)_xN(R⁴)S(O)₂R⁶, -ZAr, -(CH₂)_xS(O)₂R⁶, -(OCH₂)_xS(O)₂R⁶, -N(R⁴)S(O)₂R⁶, -N(R⁴)C(O)R⁶, -(CH₂)_xN(R⁴)S(O)₂R⁶, -(CH₂)_xN(R⁴)C(O)R⁶ o -(CH₂)_xC(O)alquilo;

- 20 R⁴ y R⁵ pueden ser los mismos o diferentes y representan H o alquilo, o R⁴ y R⁵ junto con los átomos a los que están unidos, forman un anillo de azacicloalcano de C₃₋₈, (2-oxo)azacicloalcano de C₃₋₈, o una cadena de polimetileno de C₅₋₈ interrumpida opcionalmente por heteroátomos como O, o -

20

NR⁷.

Z es O, S o NR⁷;

R⁶ es alquilo o arilo;

R⁷ es hidrógeno, alquilo o arilo;

5

m es 1 o 2;

n es 0, 1, 2 o 3;

p y q son independientemente 0, 1, 2, 3 o 4;

r es 1, 2 o 3;

s es 0, 1 o 2; y

10

x es 0, 1, 2, 3, 4, 5 o 6;

con la condición de que dicho compuesto de fórmula (IA) no sea un compuesto seleccionado de:

1-(1-fenil-3-pirrolidinil)-3-fenilurea;

1-(1-fenil-3-pirrolidinil)-3-(4-metoxifenil)urea;

15

N-(4-fluorofenil)-*N'*-[*((R)*-1-((3-metilfenil)pirrolidin-2-ilmetil)]urea;

N-(2-bromofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;

N-(2-bromofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea;

N-(4-fluorofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea;

N-(2-bromofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea;

20

N-(4-fluorofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-3-il)]urea;

N-(2-bromofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-3-il)]urea;

N-(4-fluorofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;

N-(4-fluorofenil)-*N'*-[*((R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;

- N*-(2-bromofenil)-*N'*-[*[(R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;
N-(1-naftil)-*N'*-[*[(R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
N-(2,3-diclorofenil)-*N'*-[*[(R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
N-(2-bromofenil)-*N'*-[*[(S)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;
5 *N*-(2-bromofenil)-*N'*-[*[(R)*-1-(4-fluoro-3-metilfenil)pirrolidin-3-il)]-
urea;
N-(2-bromofenil)-*N'*-[*[(R)*-1-(3,4-difluorofenil)pirrolidin-3-il)]urea;
N-(2-bromofenil)-*N'*-[*[(R)*-1-(3-fluoro-4-metilfenil)pirrolidin-3-il)]-
urea;
10 *N*-(3-cloro-2-metilfenil)-*N'*-[*[(R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
N-(2,3-diclorofenil)-*N'*-[*[(R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
N-(2,5-diclorofenil)-*N'*-[*[(R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
N-(2,3-diclorofenil)-*N'*-[*[(R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;
N-(2,5-diclorofenil)-*N'*-[*[(R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;
15 *N*-(3-cloro-2-metilfenil)-*N'*-[*[(R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;
N-(3-cloro-2-metilfenil)-*N'*-[*[(R)*-1-(3,4-difluorofenil)pirrolidin-3-il)]-
urea;
N-(2,3-diclorofenil)-*N'*-[*[(R)*-1-(3,4-difluorofenil)pirrolidin-3-il)]urea;
N-(2,5-diclorofenil)-*N'*-[*[(R)*-1-(3,4-difluorofenil)pirrolidin-3-il)]urea;
20 *N*-(3-cloro-2-metilfenil)-*N'*-[*[(R)*-1-(3-fluoro-4-metilfenil)pirrolidin-3-il)]urea; y
N-(2,3-diclorofenil)-*N'*-[*[(R)*-1-(3-fluoro-4-metilfenil)pirrolidin-3-il)]-
urea.

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Convenientemente, P es fenilo, quinolinilo o isoquinolinilo. Más convenientemente, P es fenilo, 5-quinolinilo, 7-quinolinilo o 5-isoquinolinilo. De preferencia, P es fenilo o 5-isoquinolinilo.

Convenientemente, P' es fenilo. Convenientemente, P' es
5 piridilo.

Convenientemente, R¹ es halógeno, -CF₃ o alquilo. Preferiblemente, R¹ es flúor, cloro, bromo, -CF₃, metilo o *ter*-butilo.

Cuando p es 2 o 3, los grupos R¹ pueden ser iguales o diferentes.

10 Convenientemente, p es 1 o 2. De preferencia, p es 1.

Convenientemente, m es 1.

Convenientemente, n es 0 o 1. De preferencia, n es 0.

Convenientemente, R² es halógeno, alquilo, alcoxi, -CN o -CF₃. Preferiblemente, R² es flúor, cloro, bromo, metilo, OMe o CF₃.

15 Convenientemente, q es 1 o 2. De preferencia, q es 1.

Convenientemente, x es 1, 2 o 3.

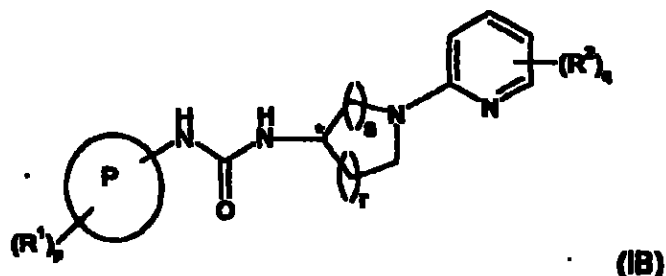
Cuando q es 2 o 3, los grupos R² pueden ser iguales o diferentes.

Cuando q es 2, los ejemplos particularmente preferidos de R²
20 son 3,4-difluoro, 3-fluoro-4-metilo, 3-metil-4-fluoro, 3-cloro-5-trifluorometilo, 3-ciano-5-trifluorometilo y 3-ciano-6-trifluorometilo.

Convenientemente, r y s tienen valores tales que definen un anillo de 4-7 miembros. De preferencia, r y s tienen valores tales que definen

un anillo de 5 o 6 miembros. Muy preferiblemente, r y s tienen valores tales que definen un anillo de 5 miembros.

De acuerdo con un aspecto preferido adicional de la presente invención, se provee un subgrupo de compuestos de fórmula (I), los de
5 fórmula (IB):



10

o una sal o solvato farmacéuticamente aceptable de los mismos, en donde:

P es fenilo, naftilo, quinolinilo o isoquinolinilo;

R¹ y R² se seleccionan independientemente de -H, halógeno,
15 alquilo, alcoxi, cicloalquilo, aralquilo, aralcoxi, cicloalquilalquilo, cicloalquilalcoxi, -CN, -NO₂, -OH, -OCF₃, -CF₃, -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)_xNR⁴R⁵, -C(O)CF₃, -C(O)alquilo, -C(O)cicloalquilo, -C(O)aralquilo, -C(O)Ar, -C(O)(CH₂)_xOR⁶, -C(O)(CH₂)_xNR⁴R⁵, -C(O)alcoxi, -C(O)NR⁴R⁵, -(CH₂)_xC(O)alcoxi, -
20 (CH₂)_xOC(O)R⁶, -(CH₂)_xOR⁶, -(CH₂)_xR⁴R⁵, -(CH₂)_xC(O)NR⁴R⁵, -(CH₂)_xN(R⁴)C(O)R⁶, -(CH₂)_xS(O)₂NR⁴R⁵, -(CH₂)_xN(R⁴)S(O)₂R⁶, -ZAr, -(CH₂)_xS(O)₂R⁶, -(OCH₂)_xS(O)₂R⁶, -N(R⁴)S(O)₂R⁶, -N(R⁴)C(O)R⁶, -(CH₂)_xN(R⁴)S(O)₂R⁶, -(CH₂)_xN(R⁴)C(O)R⁶ o -(CH₂)_xC(O)alquilo;

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R^4 y R^5 pueden ser los mismos o diferentes y representan H o alquilo, o R^4 y R^5 junto con los átomos a los que están unidos, forman un anillo de azacicloalcano de C_{3-8} , (2-oxo)azacicloalcano de C_{3-8} , o una cadena de polimetileno de C_{5-8} interrumpida opcionalmente por heteroátomos como O, o -

5 NR^7 .

Z es O, S o NR^7 ;

R^8 es alquilo o arilo;

R^7 es hidrógeno, alquilo o arilo;

m es 1 o 2;

10 n es 0, 1, 2 o 3;

p y q son independientemente 0, 1, 2, 3 o 4;

r es 1, 2 o 3;

s es 0, 1 o 2; y

x es 0, 1, 2, 3, 4, 5 o 6.

15 Convenientemente, R^1 es halógeno, hidroxí, alquilo, alcoxi, $-CF_3$, $-NO_2$, $-CN$, $-OCF_3$, amino o mono- o dialquilamino. Preferiblemente, R^1 es halógeno, $-CF_3$ o alquilo. Más preferiblemente, R^1 es bromo, cloro, flúor, $-CF_3$, metilo o *ter*-butilo;

20 Convenientemente, R^1 es halógeno, hidroxí, alquilo, alcoxi, $-CF_3$, $-NO_2$, $-CN$, $-OCF_3$, amino o mono- o dialquilamino. Preferiblemente, R^2 es halógeno, alquilo, alcoxi, $-CN$, o $-CF_3$. De preferencia, R^2 es bromo, cloro, flúor, metilo, $-OMe$ o $-CF_3$;

Convenientemente, p y q son independientemente 0, 1 o 2; y

AS

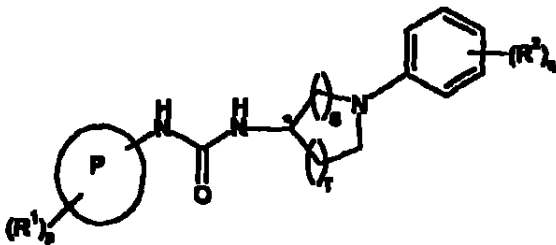
Convenientemente, r y s son independientemente 1 o 2.

Convenientemente, x es 1, 2 o 3.

Compuestos de fórmula (IB) de interés particular de acuerdo con la presente invención son los ejemplos números 1-23, 28, 29, 34-39, 44-50 y 55-76 (presentados más adelante en el cuadro 1), o sales o solvatos farmacéuticamente aceptables de los mismos.

De acuerdo con un aspecto adicional de la presente invención, se provee un subgrupo de compuestos de fórmula (I), los de fórmula (IC):

10



(IC)

o una sal o solvato farmacéuticamente aceptable de los mismos,

15 en donde:

P es fenilo, naftilo, quinolinilo o isoquinolinilo;

R¹ y R² se seleccionan independientemente de halógeno, hidroxilo, alquilo, alcoxi, -CF₃, -NO₂, -CN, -OCF₃, amino, o mono- o dialquilamino;

20

n es 0, 1, 2 o 3;

p y q son independientemente 0, 1, 2, 3 o 4;

r es 1, 2 o 3; y

s es 0, 1 o 2;

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con la condición de que dicho compuesto de fórmula (I) no sea un compuesto seleccionado de:

- 1-(1-fenil-3-pirrolidinil)-3-fenilurea;
- 1-(1-fenil-3-pirrolidinil)-3-(4-metoxifenil)urea;
- 5 *N*-(4-fluorofenil)-*N'*-[*((R)*-1-((3-metilfenil)pirrolidin-2-ilmetil)]urea;
- N*-(2-bromofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
- N*-(2-bromofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea;
- N*-(4-fluorofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea;
- N*-(2-bromofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea;
- 10 *N*-(4-fluorofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
- N*-(2-bromofenil)-*N'*-[*((S)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
- N*-(4-fluorofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
- N*-(4-fluorofenil)-*N'*-[*((R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;
- N*-(2-bromofenil)-*N'*-[*((R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;
- 15 *N*-(1-naftil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
- N*-(2,3-diclorofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;
- N*-(2-bromofenil)-*N'*-[*((S)*-1-(3-fluorofenil)pirrolidin-3-il)]urea;
- N*-(2-bromofenil)-*N'*-[*((R)*-1-(4-fluoro-3-metilfenil)pirrolidin-3-il)]-
- urea;
- 20 *N*-(2-bromofenil)-*N'*-[*((R)*-1-(3,4-difluorofenil)pirrolidin-3-il)]urea;
- N*-(2-bromofenil)-*N'*-[*((R)*-1-(3-fluoro-4-metilfenil)pirrolidin-3-il)]-
- urea;
- N*-(3-cloro-2-metilfenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea;

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- N*-(2,3-diclorofenil)-*N'*-[(((*R*)-1-(3-metilfenil)pirrolidin-3-il)]urea;
N-(2,5-diclorofenil)-*N'*-[(((*R*)-1-(3-metilfenil)pirrolidin-3-il)]urea;
N-(2,3-diclorofenil)-*N'*-[(((*R*)-1-(3-fluorofenil)pirrolidin-3-il)]urea;
N-(2,5-diclorofenil)-*N'*-[(((*R*)-1-(3-fluorofenil)pirrolidin-3-il)]urea;
5 *N*-(3-cloro-2-metilfenil)-*N'*-[(((*R*)-1-(3-fluorofenil)pirrolidin-3-il)]urea;
N-(3-cloro-2-metilfenil)-*N'*-[(((*R*)-1-(3,4-difluorofenil)pirrolidin-3-il)]-
urea;

N-(2,3-diclorofenil)-*N'*-[(((*R*)-1-(3,4-difluorofenil)pirrolidin-3-il)]urea;
N-(2,5-diclorofenil)-*N'*-[(((*R*)-1-(3,4-difluorofenil)pirrolidin-3-il)]urea;
10 *N*-(3-cloro-2-metilfenil)-*N'*-[(((*R*)-1-(3-fluoro-4-metilfenil)pirrolidin-3-
il)]urea; y

N-(2,3-diclorofenil)-*N'*-[(((*R*)-1-(3-fluoro-4-metilfenil)pirrolidin-3-il)]-
urea.
- Convenientemente, *P* es fenilo, quinolinilo o isoquinolinilo.
- 15 Convenientemente, *R*¹ es alquilo. De preferencia, *R*¹ es metilo.
- Convenientemente, *R*² es halógeno o alquilo.
- Convenientemente, *R*² es flúor o metilo.
- Convenientemente, *p* y *q* son independientemente 0, 1 o 2.
- Convenientemente, *r* y *s* son independientemente 1 o 2.
- 20 Los compuestos de fórmula (IC) de interés particular de acuerdo con la presente invención son los ejemplos números 24-27, 30-33, 40-43 y 51-54 (que se ilustran más adelante en el cuadro 1), o sales o solvatos farmacéuticamente aceptables de los mismos.

Algunos de los átomos de carbono de fórmula (I) son átomos de carbono quirales, como el átomo de carbono marcado con "*", y por lo tanto, los compuestos de fórmula (I) pueden existir como estereoisómeros. La invención se extiende a todos los isómeros ópticos tales como las formas estereoisoméricas de los compuestos de fórmula (I), incluyendo enantiómeros y mezclas de los mismos, tales como racematos. Las diferentes formas estereoisoméricas se pueden separar o resolver entre sí mediante los métodos convencionales, o cualquier isómero dado se puede obtener mediante síntesis estereoespecíficas o asimétricas convencionales.

10 Los compuestos preferidos de fórmula (I) tienen el carbono C* en la configuración R.

Algunos compuestos de la presente pueden existir en varias formas tautoméricas y se entiende que la invención abarca todas estas formas tautoméricas.

15 Como se indicó arriba, los compuestos de fórmula (I) pueden formar sales, especialmente sales farmacéuticamente aceptables. Las sales farmacéuticamente aceptables son las que se usan convencionalmente en la técnica e incluyen las que se describen en *J. Pharm. Sci.*, 1977, 66, 1-19, tales como las sales de adición de ácido.

20 Las sales farmacéuticamente aceptables adecuadas incluyen sales de adición de ácido.

Las sales de adición de ácido farmacéuticamente aceptables incluyen sales con ácidos inorgánicos tales como por ejemplo ácido

clorhídrico, ácido bromhídrico, ácido ortofosfórico o ácido sulfúrico, o con ácidos orgánicos tales como por ejemplo ácido metanosulfónico, ácido toluenosulfónico, ácido acético, ácido propiónico, ácido láctico, ácido cítrico, ácido fumárico, ácido málico, ácido succínico, ácido salicílico, ácido maleico, 5 ácido glicerofosfórico o ácido acetilsalicílico.

Las sales o solvatos de los compuestos de fórmula (I) que no son farmacéuticamente aceptables pueden ser útiles como intermediarios en la preparación de las sales o solvatos farmacéuticamente aceptables de los compuestos de fórmula (I), o de los mismos compuestos de fórmula (I), y 10 como tales son parte de otro aspecto de la presente invención.

Los compuestos de fórmula (I) se pueden preparar en forma cristalina o no cristalina, y si están en forma cristalina opcionalmente pueden estar hidratados o solvatados. Esta invención incluye dentro de su alcance hidratos estequiométricos y también compuestos que contienen cantidades 15 variables de agua.

Los solvatos adecuados incluyen solvatos farmacéuticamente aceptables, tales como hidratos.

Los solvatos incluyen solvatos estequiométricos y solvatos no estequiométricos.

20 Como se usa aquí, el término "alquilo", como un grupo o como parte de un grupo, se refiere a un radical hidrocarburo alifático saturado de cadena recta o ramificada que contiene de 1 a 12 átomos de carbono, convenientemente de 1 a 6 átomos de carbono. Estos grupos alquilo incluyen

80

en particular metilo ("Me"), etilo ("Et"), n-propilo ("Prⁿ"), *iso*-propilo ("Prⁱ"), n-butilo ("Buⁿ"), *sec*-butilo ("Bu^s"), *ter*-butilo ("Bu^t"), pentilo y hexilo. Cuando sea apropiado, dichos grupos alquilo pueden estar sustituidos con uno o más grupos seleccionados de halógeno (tal como flúor, cloro, bromo), -CN, -CF₃, -
 5 OH, -OCF₃, alquenilo de C₂₋₆, alquinilo de C₃₋₆, alcoxi de C₁₋₆, arilo y dialquil(C₁₋₆)amino.

Como se usa aquí, el término "alcoxi", como un grupo o como parte de un grupo, se refiere a un radical de éter alquilico en donde el término "alquilo" es como se define arriba. Tales grupos alcoxi incluyen en particular
 10 metoxi, etoxi, n-propoxi, *iso*-propoxi, n-butoxi, *iso*-butoxi, *sec*-butoxi y *ter*-butoxi. Cuando sea apropiado, estos grupos alcoxi pueden estar sustituidos con uno o más grupos seleccionados de halógeno (tal como flúor, cloro, bromo), -CN, -CF₃, -OH, -OCF₃, alquilo de C₁₋₆, alquenilo de C₂₋₆, alquinilo de C₃₋₆, arilo y dialquil(C₁₋₆)amino.

15 Como se usa aquí, el término "arilo", como un grupo o como parte de un grupo, se refiere a un radical aromático carbocíclico ("Ar"). Convenientemente, tales grupos arilo son grupos monocíclicos de 5-6 miembros, o grupos bicíclicos fusionados de 8-10 miembros, especialmente fenilo ("Ph"), bifenilo y naftilo, particularmente naftilo y fenilo.

20 Como se usa aquí, el término "heteroarilo", como un grupo o como parte de un grupo, se refiere a un anillo aromático heterocíclico monocíclico estable de 5-7 miembros, o un anillo aromático heterocíclico bicíclico estable de 7-10 miembros, que consiste de átomos de carbono y de 1

a 4, convenientemente de 1 a 2 heteroátomos seleccionados independientemente del grupo que consiste de N, O y S. Se prefiere que el número total de átomos de S y O en el heterociclo aromático no sea mayor de 1. Ejemplos de grupos heteroarilo adecuados incluyen, sin limitación,

5 acridinilo, azocinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzisoxazolilo, benzisotiazolilo, benzoimidazolilo, carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 2H,6H-1,5,2-ditiazinilo, dihidrobenzofuranilo, furanilo, furazanilo, imidazolilo, 1H-indazolilo, indolinilo,

10 indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolilo, isoquinolinilo, isotiazolilo, isoxazolilo, naftiridinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, oxazolilo, pirimidinilo, ftalazinilo, pteridinilo, purinilo, pirazinilo, pirazolilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, pirrolilo, quinazolinilo, quinolinilo,

15 quinoxalinilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiazolilo, tienilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, triazinilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo.

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

20

El término "naftilo" se usa aquí para denotar, a menos que se indique de otra manera, los grupos tanto 1-naftilo como 2-naftilo.

La presente invención también provee un procedimiento para la preparación de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, dicho procedimiento comprende acoplar un compuesto de fórmula (II):

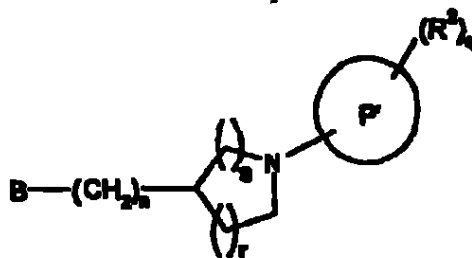
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(II)

en la cual R^1 , P y p son como se define en la fórmula (I), con un compuesto de fórmula (III):

10



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(III)

en la cual P' , R^2 , n, q, r y s son como se define en la fórmula (I), y A y B contienen grupos funcionales apropiados que son capaces de reaccionar juntos para formar la porción urea;

y después, según sea necesario, llevar a cabo una o más de las siguientes reacciones:

20

(i) convertir un compuesto de fórmula (I) en otro compuesto de fórmula (I);

(ii) remover cualquier grupo protector;

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(iii) preparar una sal o solvato del compuesto así formado.

Ejemplos adecuados de grupos A y B apropiados incluyen:

(a) A es -N=C=O y B es NH_2 ; o A es NH_2 y B es N=C=O , o

(b) A es NH_2 y B es NH_2 junto con un agente formador de urea
5 apropiado.

En el procedimiento (a), la reacción se lleva a cabo en un
solvente inerte tal como diclorometano o acetonitrilo.

En el procedimiento (b), el agente formador de urea puede ser
carbonildiimidazol, o fosgeno, o trifosgeno, y se puede llevar a cabo en un
10 solvente orgánico inerte como éter dietílico, tetrahidrofurano, o diclorometano,
a temperatura ambiente o a temperatura elevada, en presencia de una base
como trietilamina o piridina.

Un método de síntesis alternativo de los compuestos de urea
asimétricos de fórmula (I) es a partir de un carbonato de diarilo, por medio del
15 carbamato correspondiente. Dicho método lo describen Freer y otros
(*Synthetic Communications*, 26 (2), 331-349, 1996). Será apreciado por los
expertos que dicho método se puede adaptar fácilmente para la preparación
de los compuestos de fórmula (I).

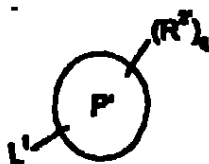
Será apreciado por los expertos que puede ser necesario
20 proteger ciertos sustituyentes reactivos durante algunos de los procedimientos
arriba mencionados. Se pueden usar técnicas estándares de protección y
desprotección, como las que describe Greene T. W. en "Protective groups in
organic synthesis", New York, Wiley (1981). Por ejemplo, las aminas

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primarias se pueden proteger como derivados ftalimida, bencilo, benciloxycarbonilo o tritilo. Los grupos de ácido carboxílico se pueden proteger como ésteres. Los grupos aldehído o cetona se pueden proteger como acetales, cetales, tioacetales o tiocetales. La desprotección de dichos grupos se logra usando procedimientos convencionales muy conocidos en la técnica.

Un compuesto de fórmula (III) se puede preparar por reacción de un compuesto de fórmula (IV):

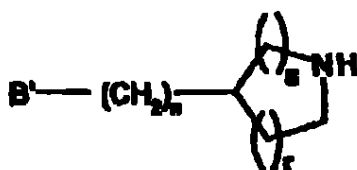
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(IV)

en donde P' es como se define para la fórmula (I) y R² es R² como se define arriba, o una forma protegida del mismo, L¹ es un grupo saliente y q es como se define arriba, con un compuesto de fórmula (V):

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(V)

en donde B' es B como se define arriba, o una forma protegida del mismo, y n, r y s son como se define arriba.

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Convenientemente, L¹ es halógeno, tal como cloro.

Convenientemente, el compuesto de fórmula (V) está en una forma activada, por ejemplo en una forma iónica. Dichas formas activadas se preparan usando la metodología convencional de reacción de acoplamiento, por ejemplo haciendo reaccionar los compuestos (IV) y (V) en presencia de un carbonato alcalino tal como carbonato de potasio, en un solvente aprótico como dimetilformamida, usando condiciones de reacción apropiadas para el método particular elegido, por ejemplo a una temperatura elevada tal como 100 °C.

Los compuestos de las fórmulas (IV) y (V) están disponibles comercialmente o se preparan mediante procedimientos conocidos, como los que se describen en *Heterocycles*, 1984, 22(1), 117, y *J. Chem. Soc., Perkin* 1, 1988, 4, 921, para compuestos de fórmula (IV); y *J. Med. Chem.*, 1992, 35(10), 1764, para compuestos de fórmula (V), o con métodos análogos a estos métodos descritos.

Las sales farmacéuticamente aceptables se pueden preparar convencionalmente por reacción con el ácido o derivado de ácido apropiado.

Los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables tienen actividad antagónica al receptor vainilloide (VR1) y se considera que son de uso potencial para el tratamiento o profilaxis de algunos trastornos, o para el tratamiento del dolor asociado con dichos trastornos, tal como dolor, dolor crónico, dolor neuropático, dolor posquirúrgico, dolor posterior a artritis reumatoide, dolor osteoartrítico, dolor de espalda, dolor

visceral, dolor de cáncer, algesia, neuralgia, dolor dental, dolor de cabeza, migraña, neuropatías, síndrome de túnel carpiano, neuropatía diabética, neuropatía relacionada con VIH, neuralgia postherpética, fibromialgia, neuritis, clática, lesión de nervio, isquemia, neurodegeneración, ataque cerebral, dolor posterior a ataque cerebral, esclerosis múltiple, enfermedades respiratorias, asma, tos, COPD, broncoconstricción, trastornos inflamatorios, esofagitis, acedia, metaplasia de Barrett, disfagia, trastorno de reflujo gastroesofágico (GERD), úlcera estomacal y duodenal, dispepsia funcional, síndrome de intestino irritable, síndrome de intestino inflamatorio, colitis, enfermedad de Crohn, hipersensibilidad pélvica, dolor pélvico, dolor menstrual, cólico renal, incontinencia urinaria, cistitis, quemaduras, comezón, soriasis, prurito, vómito (en adelante referidos como "los trastornos de la invención").

Por consiguiente, la invención también provee un compuesto de fórmula (I), o una sal o solvato farmacéuticamente aceptable del mismo, para usar como una sustancia terapéutica activa, en particular en el tratamiento o profilaxis de los trastornos de la invención.

En particular, la invención provee un compuesto de fórmula (I), o una sal o solvato farmacéuticamente aceptable del mismo, para usar en el tratamiento o profilaxis del dolor.

La invención provee además un método para el tratamiento o profilaxis de trastornos en los cuales es benéfico el antagonismo al receptor vainilloide (VR1), en particular los trastornos de la invención, en mamíferos incluyendo seres humanos, que comprende administrar a un mamífero en

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necesidad de dicho tratamiento o profilaxis una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I) o una sal o solvato farmacéuticamente aceptable del mismo.

5 La invención provee el uso de un compuesto de fórmula (I), o una sal o solvato farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para el tratamiento o profilaxis de trastornos en los cuales es benéfico un antagonismo al receptor vainilloide (VR1), particularmente los trastornos de la invención.

10 Para usar los compuestos de la invención en terapia, normalmente serán formulados en una composición farmacéutica de acuerdo con la práctica farmacéutica estándar. De esta manera, la presente invención también provee una composición farmacéutica que comprende un compuesto de fórmula (I), o una sal o solvato farmacéuticamente aceptable del mismo, y un vehículo o excipiente farmacéuticamente aceptable.

15 Una composición farmacéutica de la invención, que se puede preparar por mezcla, convenientemente a temperatura ambiente y presión atmosférica, usualmente se adapta para su administración oral, parenteral, rectal o intravesical en la vejiga y, como tal, puede estar en la forma de tabletas, cápsulas, preparaciones líquidas orales, polvos, gránulos, pastillas, 20 polvos reconstituibles, soluciones inyectables o infundibles, suspensiones o supositorios. Generalmente se prefieren las composiciones administrables oralmente.

Las tabletas y cápsulas para administración oral pueden estar en

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forma de dosis unitaria y pueden contener excipientes convencionales tales como agentes aglutinantes, rellenos, lubricantes de tableteado, desintegrantes y agentes humectantes aceptables. Las tabletas se pueden recubrir de acuerdo con los métodos bien conocidos en la práctica farmacéutica normal.

- 5 Las preparaciones líquidas orales pueden estar, por ejemplo, en forma de suspensiones acuosas u oleosas, soluciones, emulsiones, jarabes o elixires, o pueden estar en forma de un producto seco para su reconstitución con agua u otro vehículo adecuado antes de usar. Dichas preparaciones líquidas pueden contener aditivos convencionales tales como agentes de
- 10 suspensión, agentes emulsionantes, vehículos no acuosos (que pueden incluir agentes comestibles), conservadores y, si se desea, saborizantes o colorantes convencionales.

- Para administración parenteral, las formas de dosis unitarias fluidas se preparan utilizando un compuesto de la invención o una sal
- 15 farmacéuticamente aceptable del mismo, y un vehículo estéril. El compuesto, dependiendo del vehículo y la concentración usada, se puede suspender o disolver en el vehículo. Para preparar las soluciones, el compuesto se puede disolver para su inyección, y se esteriliza por filtración antes de envasar y sellar en una ampolleta o frasco adecuado. Convenientemente se disuelven
- 20 en el vehículo auxiliares tales como un anestésico local, conservadores y agentes amortiguadores. Para mejorar la estabilidad, la composición se puede congelar después de envasarla en el frasco y el agua se puede remover al vacío. Las suspensiones parenterales se preparan

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sustancialmente de la misma forma, excepto que el compuesto se suspende en el vehículo en lugar de ser disuelto, y la esterilización no se puede realizar por filtración. El compuesto se puede esterilizar por exposición a óxido de etileno antes de suspenderlo en un vehículo estéril. Ventajosamente se incluye en la composición un agente tensioactivo o agente de mojado para facilitar la distribución uniforme del compuesto.

La composición puede contener de 0.1% a 99% en peso, de preferencia de 10% a 60% en peso del material activo, dependiendo del método de administración.

La dosis del compuesto usado en el tratamiento de los trastornos anteriormente mencionados varía de la forma usual con la seriedad de los trastornos, el peso del paciente y otros factores similares. Para administración sistémica en el tratamiento de dolor es útil una dosificación de 0.01 mg a 100 mg por kilogramo de peso corporal. Sin embargo, como una guía general adecuada, las dosis unitarias pueden ser de 0.05 mg a 1000 mg, mas convenientemente de 0.05 mg a 20 mg, de 20 mg a 250 mg, o de 0.1 mg a 500.0 mg, por ejemplo de 0.2 mg a 5 mg, y de 0.1 mg a 250 mg; y dichas dosis unitarias se pueden administrar mas de una vez al día, por ejemplo dos o tres veces al día, de tal manera que la dosis diaria total está en la escala de aproximadamente 0.5 mg a 1000 mg; y dicha terapia se puede extender durante varias semanas o meses.

No se indican efectos toxicológicos inaceptables con los compuestos de la invención cuando se administran de acuerdo con la

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invención.

Todas las publicaciones citadas en esta especificación, incluyendo sin limitación las patentes y las solicitudes de patente, se incorporan aquí como referencia como si se indicara específica e individualmente que cada publicación individual está incorporada como referencia en la presente.

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

10

Abreviaciones

BINAP- 2,2'-bis(difenilfosfino)-1,1'-binaftilo

CLAR- Cromatografía de líquidos de alto rendimiento

MgSO₄- Sulfato de magnesio

TFA- Acido trifluoroacético

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DCM- Diclorometano

Descripción 1

Ester *ter*-butílico del ácido [(*R*)-1-(5-trifluorometilpiridin-2-il)-pírolidin-3-il]-carbámico (D1)

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A una solución de 2-cloro-5-trifluorometilpiridina (7.3 g, 0.04 mol) y 3*R*-(+)-3-(*ter*-butiloxycarbonilamino)pírolidina (7.5 g, 0.04 mol) en dimetilformamida seca (100 ml), se le agregó carbonato de potasio en polvo (6.6 g, 0.05 mol), y la reacción se calentó a 100 °C durante 7 horas, y después

se enfrió. El solvente se eliminó a presión reducida y el residuo se dividió entre acetato de etilo y agua. La fase orgánica se separó, se secó (MgSO_4) y se filtró. La remoción del solvente a presión reducida dio un sólido. La cromatografía sobre gel de sílice eluyendo con acetato de etilo y DCM (elución por gradiente, 20 % máximo) produjo el compuesto del título como un sólido blanco.

Descripción 2

(R)-1-(5-Trifluorometilpiridin-2-il)-pirrolidin-3-ilamina (D2)

10 Una solución de D1 (11.5 g, 0.04 mol) en DCM (80 ml) se enfrió (baño de hielo) y se le agregó ácido trifluoroacético (exceso, 50 ml). La reacción se calentó a temperatura ambiente, se agitó 3 horas y se dividió entre acetato de etilo y solución acuosa de hidróxido de sodio. La fase orgánica se separó, se secó (MgSO_4) y se filtró. La remoción del solvente a presión reducida dio el producto crudo como un aceite amarillo. La destilación de bulbo a bulbo bajo presión reducida produjo inicialmente el compuesto del título como un aceite, que cristalizó al reposar.

Descripción 3

1,3-Dimetil-5-nitroisquinolina (D3)

20 Se enfrió 1,3-dimetilisoquinolina [(*Chem. Lett.*, 1983; p. 791), 2.39 g, 15.20 mM] en ácido sulfúrico concentrado (15 ml), a $<4^\circ\text{C}$. Se le agregó a gotas una solución de nitrato de potasio (1.69 g, 16.72 mM) en ácido

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sulfúrico concentrado, manteniendo la temperatura por debajo de 4 °C. Después de completar la adición, la solución se agitó a esta temperatura durante 2 horas mas y después se calentó a temperatura ambiente durante 1 hora. La mezcla de reacción se vació en agua de hielo y la solución se
5 basificó con hidróxido de sodio y se extrajo con DCM. El extracto se lavó con salmuera, se secó y se concentró hasta quedar un sólido amarillo. La purificación por cromatografía en gel de sílice produjo el compuesto del título como un sólido cristalino amarillo.

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Descripción 45-Amino-1,3-dimetilisoquinolina (D4)

Una solución de D3 (2.01 g, 9.94 mM) y paladio al 10% sobre carbón (1g) en metanol, se hidrogenó a presión atmosférica durante 1 hora. El catalizador se separó por filtración y el filtrado se concentró a presión
15 reducida para producir el compuesto del título como un sólido blanquecino.

Descripción 53-Metil-5-nitroisoquinolina (D5)

Una solución de 3-metilisoquinolina (5.4 g, 0.038 mol) en ácido
20 sulfúrico concentrado (30 ml), se agregó cuidadosamente a una solución de nitrato de potasio (4.25 g, 1.1 eq) en ácido sulfúrico concentrado (23 ml), manteniendo al mismo tiempo la temperatura por debajo de 4 °C (baño de hielo). La agitación se continuó 2 horas y después la temperatura se elevó a

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temperatura ambiente. La reacción se agitó 3 horas mas y después se vació en una suspensión de hielo y agua (500 ml). La neutralización usando carbonato de potasio sólido produjo un sólido amarillo que se filtró y se lavó con agua. El producto crudo se disolvió en etanol (200 ml), se filtró y se
5 concentró a presión reducida para producir el compuesto de título como un sólido amarillo.

Descripción 6

5-Amino-3-metilisoquinolina (D6)

10 El compuesto del título se preparó a partir de D5 usando el procedimiento indicado en la descripción 4.

Descripción 7

N-(2,2-Dimetoxietil)-(1-fenil)etilamina (D7)

15 Una solución de α -metilbencilamina (8.37 g, 0.07 mol) y dimetilacetal de bromoacetaldehído (11.67 g, 0.07 mol) en acetonitrilo (150 ml) conteniendo carbonato de potasio (12.39 g, 0.09 mol), se calentó a reflujo durante 2 días y después se enfrió. El sólido se separó por filtración y el filtrado se concentró a presión reducida para dejar un aceite. La
20 cromatografía sobre gel de sílice eluyendo con acetato de etilo produjo el compuesto del título como un aceite.

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Descripción 8**1-Metilisoquinolina (D8)**

A una solución fría de ácido clorosulfónico (16 ml, -10 °C), se le agregó cuidadosamente D7 (5 g, 0.024 mol) durante un período de 2 horas.

- 5 La reacción se dejó calentar a temperatura ambiente y la agitación se continuó durante 3 días. Después, la reacción se vació en una suspensión de hielo y agua (500 ml), se basificó usando carbonato de potasio sólido, seguido por extracción usando DCM. La fase orgánica se separó, se secó sobre MgSO_4 , se filtró y se concentró a presión reducida para dejar un aceite. La
- 10 cromatografía sobre gel de sílice eluyendo con acetato de etilo produjo el compuesto del título como un aceite amarillo.

Descripción 9**1-Metil-5-nitroisoquinolina (D9)**

- 15 Una solución de D8 (1 g, 7 mmol) en ácido sulfúrico (2.5 ml) se enfrió (<4 °C) y se le agregó ácido nítrico concentrado (1 ml) durante 10 minutos. La reacción se agitó 30 minutos y después se calentó 2 horas a 60 °C. Después de enfriar, la mezcla de reacción se vació en una suspensión de agua y hielo (100 ml) y se basificó usando carbonato de potasio sólido,
- 20 seguido por extracción usando DCM. La fase orgánica se separó, se secó sobre MgSO_4 , se filtró y se concentró bajo presión reducida para producir el compuesto del título como un sólido blanco.

AS

Descripción 10

5-Amino-1-metilisoquinolina (D10)

El compuesto del título se preparó a partir de (D9) usando el procedimiento indicado en la descripción 4.

5

Descripción 11

Ester *ter*-butilico del ácido ((*R*)-1-(3-metilfenil)pirrolidin-3-il)carbámico (D11)

Una suspensión de BINAP (1.25 g, 2 mmol), acetato de paladio
10 (0.3 g, 1.3 mmol), carbonato de cesio (6.6 g, 0.02 mol), 3-bromotolueno (4.6 g, 0.027 mol) y (3*R*)-(+)-3-(*ter*-butiloxycarbonilamino)pirrolidina (2.5 g, 0.013 mol) en 1,4-dioxano (anhidro, 50 ml), se calentó a reflujo bajo una atmósfera de argón durante 18 horas. Después de enfriar, el solvente se removió bajo presión reducida y el residuo se dividió entre DCM y agua. La fase orgánica
15 se separó, se secó sobre MgSO₄, se filtró y se concentró a presión reducida para dejar un aceite. La cromatografía sobre gel de sílice eluyendo con acetato de etilo y hexano (elución por gradiente, máximo 4%), produjo el compuesto del título como un sólido blanquecino.

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Descripción 12

(*R*)-1-(3-Metilfenil)pirrolidin-3-ilamina (D12)

Una solución de D11 (2.07 g, 7.5 mmol) en TFA (1.2 ml) y DCM (20 ml), se agitó a temperatura ambiente durante 18 horas. El solvente se

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eliminó a presión reducida y el residuo se dividió entre DCM y solución acuosa de carbonato ácido de sodio. La fase orgánica se separó, se secó sobre MgSO₄, se filtró y se concentró a presión reducida para producir el compuesto del título como un aceite.

5

Descripción 13

Ester *ter*-butílico del ácido (R)-1-(3-fluorofenil)pirrolidin-3-il)carbámico (D13)

El compuesto del título se preparó a partir de (3*R*)-(+)-3-(*ter*-butyloxycarbonilamino)pirrolidina y 1-bromo-3-fluorobenceno usando el procedimiento indicado en la descripción 11.

10

Descripción 14

(R)-1-(3-Fluorofenil)pirrolidin-3-ilamina (D14)

El compuesto del título se preparó a partir de D13 usando el procedimiento indicado en la descripción 12.

15

Descripción 15

Ester *ter*-butílico del ácido (R)-1-(3,4-difluorofenil)pirrolidin-3-carbámico (D15)

20

El compuesto del título se preparó a partir de (3*R*)-(+)-3-(*ter*-butoxicarbonilamino)pirrolidina y 4-bromo-1,2-difluorobenceno usando el procedimiento indicado en la descripción 11.

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Descripción 16**(R)-1-(3,4-Difluorofenil)-pirrolidin-3-ilamina (D16)**

El compuesto del título se preparó a partir de D15 usando el procedimiento indicado en la descripción 12.

5

Descripción 17**Ester *ter*-butílico del ácido (R)-1-(3-fluoro-4-metilfenil)pirrolidin-3-carbámico (D17)**

El compuesto del título se preparó a partir de (3R)-(+)-3-(*ter*-butoxicarbonilamino)pirrolidina y 4-bromo-2-fluorotolueno, usando el procedimiento indicado en la descripción 11.

10

Descripción 18**(R)-1-(3-Fluoro-4-metilfenil)-pirrolidin-3-il-amina (D18)**

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El compuesto del título se preparó a partir de D17 usando el procedimiento indicado en la descripción 12.

Descripción 19**(2,2-Dietoxietil)-(2-fluorobenciliden)amina (D19)**

20

Se agregó 2-fluorobenzaldehído (7.45 g) a dietilacetal de aminoacetaldehído (9.16 g), y la reacción se calentó a 3 horas a 100 °C. Después de enfriar, la mezcla se transfirió a un embudo de separación y se dividió entre éter dietílico y agua. La capa de éter se separó, se secó sobre

sulfato de magnesio, se filtró y se concentró a presión reducida para dejar un aceite. La destilación a 0.6-0.8 mm recogiendo la fracción que hierve a 102-106 °C, produjo el compuesto del título como un aceite incoloro.

5 Descripción 20

8-Fluoroisoquinolina (D20)

Una solución de pentóxido de fósforo (18 g) en ácido sulfúrico concentrado (5 ml), se calentó a 160 °C y se trató cuidadosamente con una solución de D19 (11.5 g) en ácido sulfúrico concentrado (75 ml) durante un
10 período de 5 minutos. Después de calentar 25 minutos, la reacción se enfrió y se vació en una suspensión de agua y hielo (1 l). La basificación con hidróxido de sodio sólido hasta pH 10 se siguió por extracción de acetato de etilo. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida para dar el producto crudo. La cromatografía
15 sobre gel de sílice eluyendo con acetato de etilo y hexano (gradiente, máximo 10%), dio el producto como un sólido cristalino de color amarillo claro.

Descripción 21

8-Fluoro-5-nitroisoquinolina (D21)

20 Una solución de D20 (0.278 g) en ácido sulfúrico concentrado (2 ml) se enfrió a 0 °C. Se le agregó en porciones nitrato de potasio (0.21 g), manteniendo al mismo tiempo la temperatura por abajo de 0 °C. Después de completar la adición, la solución se agitó a 0 °C durante 1.5 horas mas y

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después se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se vació en una suspensión de agua y hielo, se basificó con hidróxido de sodio y se extrajo con acetato de etilo. La solución de acetato de etilo se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida para dejar el producto crudo. La purificación por cromatografía de gel de sílice eluyendo con acetato de etilo produjo el compuesto del título como un sólido cristalino amarillo.

Descripción 22

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5-Amino-8-fluoroisoquinolina (D22)

Una solución de D21 (0.283 g) en etanol (2 ml) se trató con ácido clorhídrico concentrado (2 ml). La mezcla de reacción se enfrió en un baño de hielo y se le agregó en porciones durante 10 minutos una solución de cloruro de estaño (II) dihidratado (1.45 g) en etanol (2 ml). Después de 20 minutos mas, la mezcla de reacción se basificó con hidróxido de sodio y se extrajo con DCM. La solución de DCM se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida para dejar el producto crudo. La cromatografía sobre gel de sílice eluyendo con acetato de etilo dio el compuesto del título como un sólido de color crema.

100

Descripción 23

Ester *ter*-butilico del ácido (1-bencil-piperidin-4-il)-carbámico

(D23)

A una solución de 1-bencil-4-aminopiperidina (30 g, 0.16 mol) en
5 DCM (200 ml), se le agregó gota a gota una solución de dicarbonato de di-*ter*-
butilo (1.1 eq., 37.9 g) en DCM (100 ml) durante un período de 2 horas. La
reacción se agitó a temperatura ambiente durante 18 horas y después el
solvente se eliminó a presión reducida para producir el compuesto del título
como un sólido blanco.

10

Descripción 24

Ester *ter*-butilico del ácido piperidin-4-il-carbámico (D24)

Una solución de D23 (10 g, 3.4 mmol) en metanol (150 ml) se
hidrogenó a 3.5 kg/cm² en un hidrogenador de Parr usando catalizador de
15 paladio al 10 % sobre carbón (800 mg) durante 18 horas. El catalizador se
separó por filtración y el filtrado se concentró a presión reducida para producir
el compuesto del título como un sólido blanco.

Descripción 25

20 **Ester *ter*-butilico del ácido 1-[(5-trifluorometilpiridin-2-il)piperidin-
4-il]amino]-carbámico (D25)**

El compuesto del título se preparó a partir de D24 y 2-cloro-5-
trifluorometilpiridina usando el procedimiento indicado en la descripción 1.

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Descripción 26**1-(5-Trifluorometilpiridin-2-il)-piperidin-4-ilamina (D26)**

El compuesto del título se preparó a partir de D25 usando el procedimiento que se indica en la descripción 2.

5

Descripción 27**Ester *ter*-butílico del ácido 3-(3'-isoquinolin-5-il-ureldo)-piperidin-1-carboxílico (D27)**

A una suspensión de ácido 1-(*ter*-butoxicarbonil)-3-piperidincarboxílico (1 g, 4.4 mmol) en tolueno (10 ml) y trietilamina (0.68 ml), se le agregó difenilfosforilazida (1.1 eq., 1.33 g). La reacción se calentó a reflujo 1 hora y después se enfrió. Se le agregó 5-aminoisoquinolina (629 mg, 4.4 mmol) y la reacción se agitó a temperatura ambiente durante 56 horas. El solvente se eliminó a presión reducida y el residuo se sometió a cromatografía sobre gel de sílice eluyendo con hexano-acetato de etilo (elución por gradiente, máximo 50%) para producir el compuesto del título como una espuma.

20

Descripción 28**N-(Isoquinolin-5-il)-N'-(piperidin-3-il)-urea (D28)**

El compuesto del título se preparó a partir de D27 usando el procedimiento indicado en la descripción 2.

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Descripción 29

Ester *ter*-butílico del ácido [(*R*)-1-(3-trifluorometilpiridin-2-il)-pirrolidin-3-il]-carbámico (D29)

El compuesto del título se preparó a partir de 2-cloro-3-trifluorometilpiridina y 3*R*-(+)-3-(*ter*-butiloxicarbonilamino)pirrolidina usando el procedimiento indicado en la descripción 1.

Descripción 30

(*R*)-1-(3-Trifluorometilpiridin-2-il)-pirrolidin-3-ilamina (D30)

El compuesto del título se preparó a partir de D29 usando el procedimiento indicado en la descripción 2.

Descripción 31

Ester *ter*-butílico del ácido [(*R*)-1-(4-trifluorometilpiridin-2-il)-pirrolidin-3-il]-carbámico (D31)

El compuesto del título se preparó a partir de 2-cloro-4-trifluorometilpiridina y 3*R*-(+)-3-(*ter*-butiloxicarbonilamino)pirrolidina usando el procedimiento indicado en la descripción 1.

Descripción 32

(*R*)-1-(4-Trifluorometilpiridin-2-il)-pirrolidin-3-ilamina (D32)

El compuesto del título se preparó a partir de D31 usando el procedimiento indicado en la descripción 2.

Descripción 33

Ester *ter*-butilico del ácido [(*R*)-1-(6-trifluorometilpiridin-2-il)-pirrolidin-3-il]-carbámico (D33)

El compuesto del título se preparó a partir de 2-cloro-6-trifluorometilpiridina y 3*R*-(+)-3-(*ter*-butiloxycarbonilamino)pirrolidina usando el procedimiento indicado en la descripción 1.

Descripción 34

(*R*)-1-(6-Trifluorometilpiridin-2-il)-pirrolidin-3-ilamina (D34)

El compuesto del título se preparó a partir de D33 usando el procedimiento indicado en la descripción 2.

Descripción 35

Ester *ter*-butilico del ácido [(*R*)-1-(3-cloropiridin-2-il)-pirrolidin-3-il]-carbámico (D35)

El compuesto del título se preparó a partir de 2,3-dicloropiridina y 3*R*-(+)-3-(*ter*-butiloxycarbonilamino)pirrolidina usando el procedimiento indicado en la descripción 1.

20

Descripción 36

(*R*)-1-(3-Cloropiridin-2-il)-pirrolidin-3-ilamina (D36)

El compuesto del título se preparó a partir de D35 usando el procedimiento indicado en la descripción 2.

Descripción 37

Ester *ter*-butilico del ácido [(*R*)-1-(5-cloropiridin-2-il)-pirrolidin-3-il]-carbámico (D37)

El compuesto del título se preparó a partir de 2,5-dicloropiridina y
 5 **3*R*-(+)-3-(*ter*-butiloxycarbonilamino)pirrolidina** usando el procedimiento
 indicado en la descripción 1.

Descripción 38

(*R*)-1-(5-Cloropiridin-2-il)-pirrolidin-3-ilamina (D38)

10 El compuesto del título se preparó a partir de D37 usando el
 procedimiento indicado en la descripción 2.

Descripción 39

Ester *ter*-butilico del ácido [(*R*)-1-(5-bromopiridin-2-il)-pirrolidin-3-il]-carbámico (D39)

15 El compuesto del título se preparó a partir de 2-cloro-5-
 bromopiridina y **3*R*-(+)-3-(*ter*-butiloxycarbonilamino)pirrolidina** usando el
 procedimiento indicado en la descripción 1.

20 **Descripción 40**

(*R*)-1-(5-Bromopiridin-2-il)-pirrolidin-3-ilamina (D40)

El compuesto del título se preparó a partir de D39 usando el
 procedimiento indicado en la descripción 2.

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Descripción 41

Ester *ter*-butilico del ácido [(*R*)-1-(6-metilpiridin-2-il)-pirrolidin-3-il]-carbámico (D41)

El compuesto del título se preparó a partir de 2-cloro-6-metilpiridina y 3*R*-(+)-3-(*ter*-butiloxycarbonilamino)pirrolidina usando el procedimiento indicado en la descripción 1.

Descripción 42

(*R*)-1-(6-Metilpiridin-2-il)-pirrolidin-3-ilamina (D42)

El compuesto del título se preparó a partir de D41 usando el procedimiento indicado en la descripción 2

Descripción 43

Ester *ter*-butilico del ácido 1-[(3-trifluorometilpiridin-2-il)piperidin-4-il]amino]-carbámico (D43)

El compuesto del título se preparó a partir de D24 y 2-cloro-3-trifluorometilpiridina usando el procedimiento indicado en la descripción 1.

Descripción 44

1-(3-Trifluorometilpiridin-2-il)-piperidin-4-ilamina (D44)

El compuesto del título se preparó a partir de D43 usando el procedimiento indicado en la descripción 2.

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Descripción 45

Ester ter-butilico del ácido 1-(((6-trifluorometilpiridin-2-il)piperidin-4-il)amino)-carbámico (D45)

El compuesto del título se preparó a partir de D24 y 2-cloro-6-trifluorometilpiridina usando el procedimiento indicado en la descripción 1.

Descripción 46

1-(6-Trifluorometilpiridin-2-il)-piperidin-4-ilamina (D46)

El compuesto del título se preparó a partir de D45 usando el procedimiento indicado en la descripción 2.

Descripción 47

Ester ter-butilico del ácido 1-(((4-trifluorometilpiridin-2-il)piperidin-4-il)amino)-carbámico (D47)

El compuesto del título se preparó a partir de D24 y 2-cloro-4-trifluorometilpiridina usando el procedimiento indicado en la descripción 1.

Descripción 48

1-(4-Trifluorometilpiridin-2-il)-piperidin-4-ilamina (D48)

El compuesto del título se preparó a partir de D47 usando el procedimiento indicado en la descripción 2.

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Descripción 49

Ester *ter*-butilico del ácido 1-(((3-cloro-5-trifluorometilpiridin-2-il)-piperidin-4-il)amino)-carbámico (D49)

El compuesto del título se preparó a partir de D24 y 2,3-dicloro-5-trifluorometilpiridina usando el procedimiento indicado en la descripción 1.

Descripción 50

1-(3-Cloro-5-trifluorometilpiridin-2-il)-piperidin-4-ilamina (D50)

El compuesto del título se preparó a partir de D49 usando el procedimiento indicado en la descripción 2.

Las siguientes aminas se prepararon usando métodos similares a los descritos anteriormente.

(*R*)-1-(3-Metilpiridin-2-il)-pirrolidin-3-ilamina (D51).

(*R*)-1-(4-Metilpiridin-2-il)-pirrolidin-3-ilamina (D52).

15 (*R*)-1-(5-Metilpiridin-2-il)-pirrolidin-3-ilamina (D53).

(*R*)-1-(6-Metoxipiridin-2-il)-pirrolidin-3-ilamina (D54).

1-(3-Ciano-5-trifluorometilpiridin-2-il)-piperidin-4-ilamina (D55).

La (*3R*)-(+)-3-(*ter*-butiloxycarbonilamino)pirrolidina, 5-amino-isoquinolina, 1-aminoisoquinolina, 5-aminoquinolina y 7-aminoquinolina, están disponibles comercialmente de TCI (Japón), Aldrich Chemical Company y Specs y BioSpecs B. V., respectivamente. El tricarbonato de di-*ter*-butilo se preparó de acuerdo con el procedimiento descrito en la literatura (*Org. Synth.*, 1978, 57, p. 45). La 2-metil-7-aminoquinolina se preparó de acuerdo con el

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procedimiento descrito en la literatura (*J. Med. Chem.*, 1977, 20 (11), p. 1528).

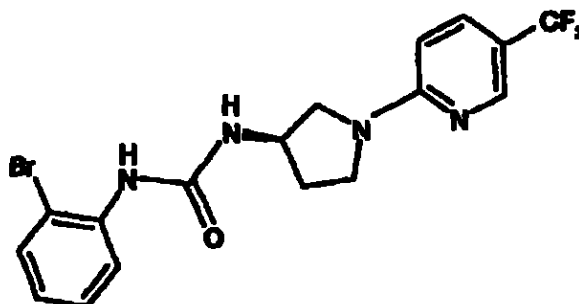
Ejemplo 1

N-(2-Bromofenil)-N'-[((R)-1-(5-trifluorometil-2-piridil)pirrolidin-3-il)]urea

5

(E1)

10



Una solución de isocianato de 2-bromofenilo (Aldrich Chemical Company) (27.4 ml, 0.222 mol) en éter dietílico seco (65 ml), se agregó gota a gota durante 0.5 horas a una solución eficazmente agitada de D2 (51.4 g, 0.222 mol) en éter dietílico seco (0.8 l) bajo argón a temperatura ambiente.

15 Después de agitar 18 horas, se separó por filtración un precipitado blanco y se lavó con éter dietílico seco (2 x 150 ml). El sólido se trituró para dejar un polvo fino y después se volvió a agitar con éter dietílico (470 ml) durante 4 horas a temperatura ambiente. El producto insoluble se separó por filtración, se lavó con éter dietílico (100 ml) y se secó a 50 °C/vacío/24 horas, para

20 producir el compuesto del título como un sólido blanco.

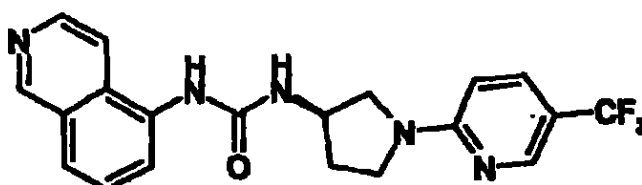
¹H RMN (d₆-DMSO, 400 MHz) δ 1.94-1.98 (1H, m), 2.19-2.28 (1H, m), 3.31-3.41 (1H, m), 3.56 (2H, br, 2), 3.67-3.71 (1H, m), 4.34-4.36 (1H, m), 6.62 (1H, d, J 9.0Hz), 6.89 (1H, t, J 7.8Hz), 7.28 (1H, t, 8.5Hz), 7.47 (1H,

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d, J 6.7Hz), 7.55 (1H, dd, J 8.0, 1.4Hz), 7.76-7.79 (2H, m), 8.12 (1H, dd, J 8.3, 1.4Hz), 8.41 (1H, s). MH^+ 429,431.

EJEMPLO 2

5 N-(isoquinol-5-yl)-N'-(((R)-1-(5-trifluorometil-2-piridil)pirrolidin-3-yl))urea (E2)



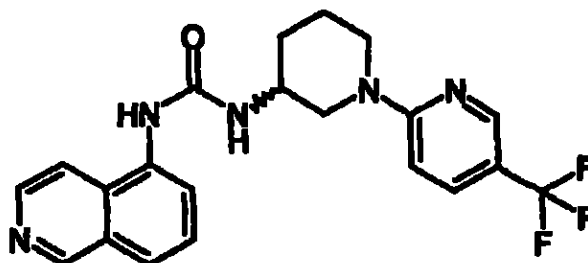
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A una solución de tricarbonato de di-ter-butilo (0.681 g, 2.595 mmol), en DCM seco (1 ml), se le agregó una solución de D2 (0.5 g, 2.162 mmol) en DCM seco (1 ml) en una porción. Después de la efervescencia inicial, la solución se agitó a temperatura ambiente durante 0.3 horas. Se le
15 agregó una solución de 5-aminoisoquinolina (0.312 g, 2.162 mmol) en DCM seco (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El precipitado resultante se removió por centrifugación, y el sólido se lavó con éter y se secó para dar el compuesto del título como un sólido blanco.

20 1H RMN (d_6 -DMSO, 250 MHz) δ 9.26 (1H, s), 8.57 (1H, s), 8.52 (1H, d), 8.41 (1 H, s), 8.31 (1 H, d), 7.88 (1 H, d), 7.78 (1H, dd), 7.70 (1H, d), 7.60 (1H, t), 6.99 (1H, d), 6.64 (1H, d), 4.41 (1H, m), 3.73 (1H, dd), 3.59 (2H, m), 3.42 (1H, m), 2.28 (1H, m) y 2.02 (1H, m). MH^+ 402.

EJEMPLO 3**(±)-N-(isoquinol-5-yl)-N'-[(1-(5-trifluorometil-2-piridil)piiperidin-3il)]urea****(E3)**

5



Una mezcla de D28 (0.2 g, 0.74 mmol), 2-cloro-5-
 10 trifluorometilpiridina (3 eq., 0.4 g) en dimetilformamida (10 ml) y carbonato de
 potasio finamente pulverizado (3 eq. 0.31 g), se calentó 18 horas a 90 °C y
 después se enfrió. El solvente se eliminó a presión reducida y el residuo se
 dividió entre acetato de etilo y agua. La fase orgánica se separó, se secó
 (MgSO₄) y se filtró. La eliminación del solvente a presión reducida dio el
 15 producto del título. Este se sometió a cromatografía en gel de sílice eluyendo
 con acetato de etilo para dar el compuesto del título como un sólido
 blanquecino que se convirtió a una sal clorhidrato. MH⁺ (base libre) 416.

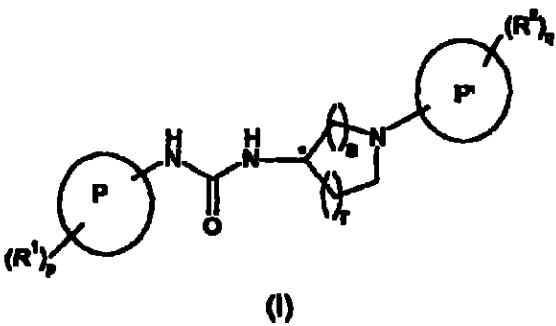
Los dos enantiómeros (E3A y E3B) se separaron por CLAR
 usando una columna Chiralpak AD (250 mm x 19 mm d.i.), y eluyendo con n-
 20 hexano:etanol (80:20 v/v), a una velocidad de flujo de 1 ml/min, con detección
 UV a 215 nm.

Los ejemplos presentados en el cuadro 1 se prepararon de
 acuerdo con los procedimientos aquí descritos y son similares a los de E1-E3.

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Cuadro 1

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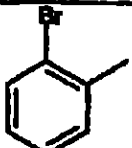
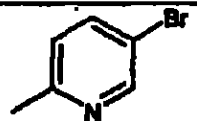
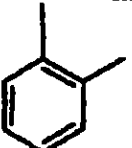
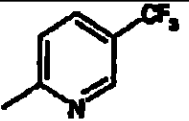
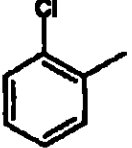
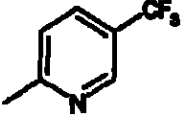
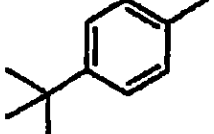
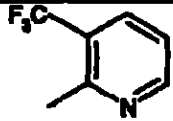
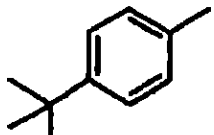
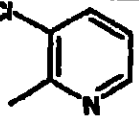
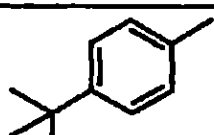
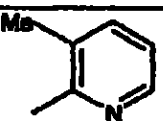
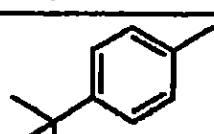
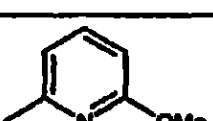
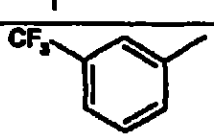
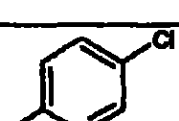
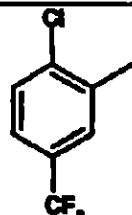
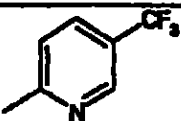
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Ej.		Estereo- química	s	r		MH+
4		R	1	1		429, 431
5		R	1	1		429, 431
6		R	1	1		429, 431
7		R	1	1		398, 398
8		R	1	1		398, 398

Cuadro 1 (Continuación)

9		R	1	1		440, 442
10		R	1	1		477
11		R	1	1		385, 387
12		R	1	1		407
13		R	1	1		373, 375
14		R	1	1		353
15		R	1	1		389
16		R	1	1		384, 386
17		R	1	1		452, 454

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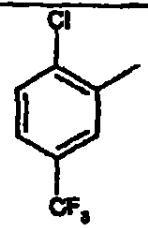
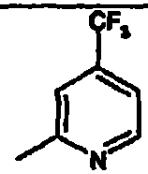
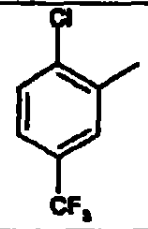
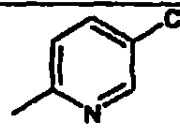
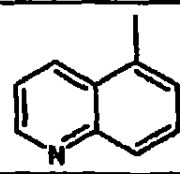
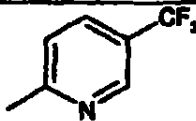
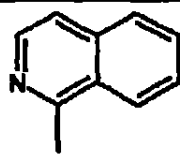
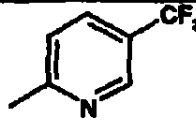
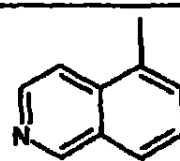
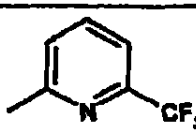
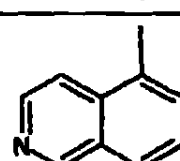
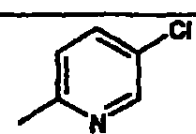
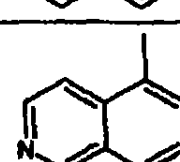
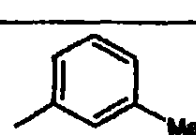
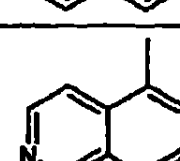
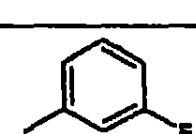
Cuadro 1 (Continuación)

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18		R	1	1		452, 464
19		R	1	1		420, 422
20		R	1	1		402
21		R	1	1		402
22		R	1	1		402
23		R	1	1		366, 370
24		R	1	1		347
25		R	1	1		351

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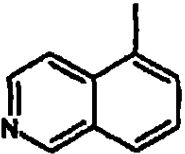
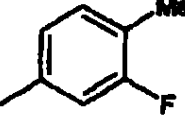
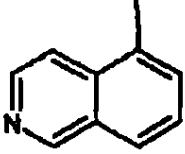
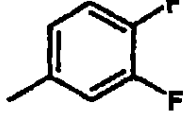
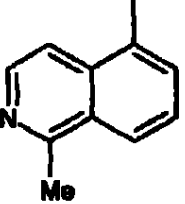
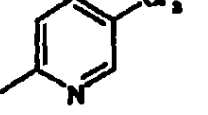
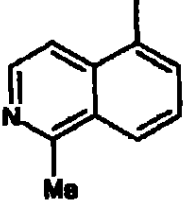
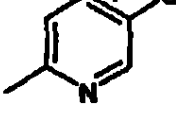
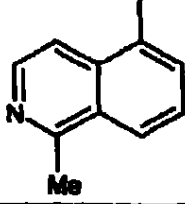
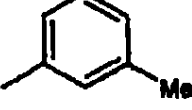
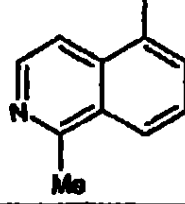
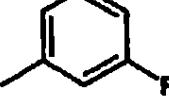
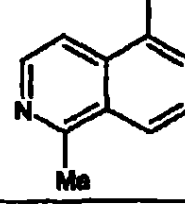
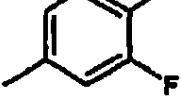
Cuadro 1 (Continuación)

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26		R	1	1		365
27		R	1	1		366
28		R	1	1		418
29		R	1	1		380, 382
30		R	1	1		381
31		R	1	1		386
32		R	1	1		383

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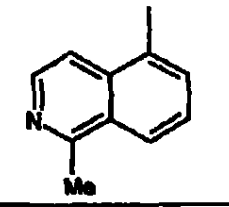
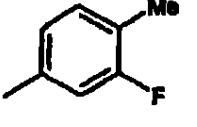
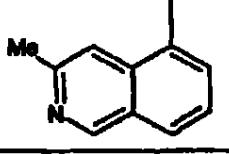
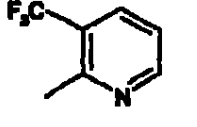
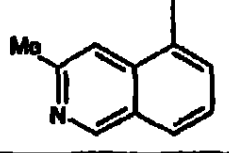
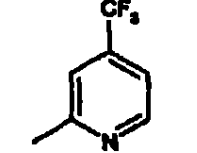
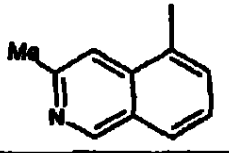
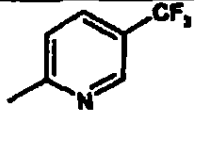
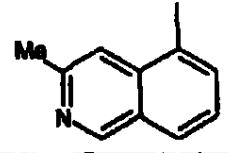
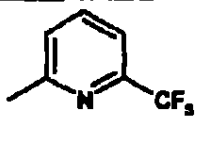
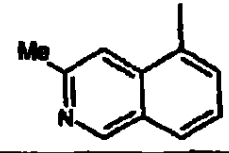
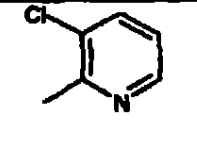
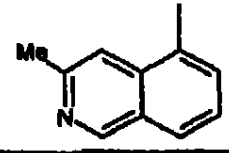
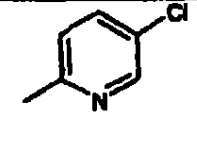
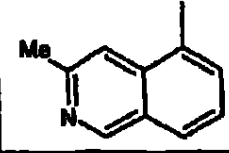
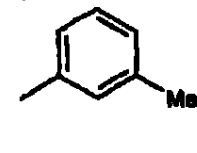
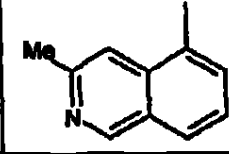
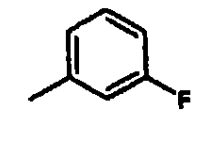
Cuadro 1 (Continuación)

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33		R	1	1		379
34		R	1	1		416
35		R	1	1		416
36		R	1	1		416
37		R	1	1		416
38		R	1	1		381, 383
39		R	1	1		380, 382
40		R	1	1		381
41		R	1	1		385

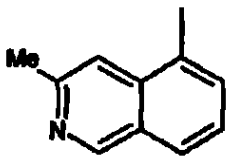
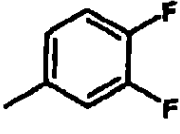
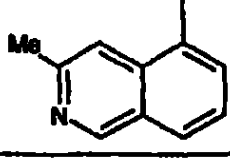
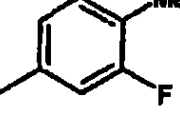
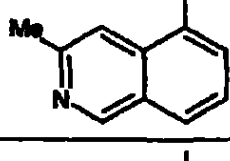
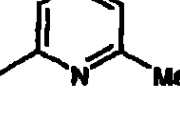
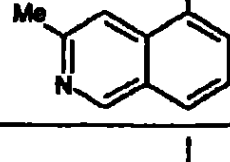
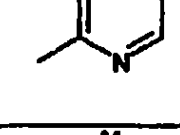
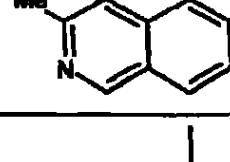
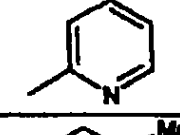
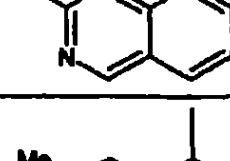
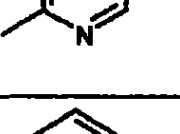
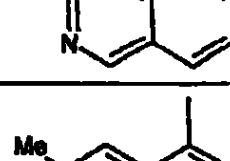
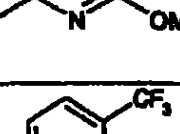
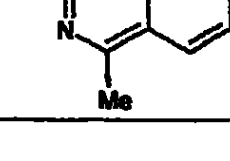
Cuadro 1 (Continuación)

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42		R	1	1		382
43		R	1	1		379
44		R	1	1		382
45		R	1	1		382
46		R	1	1		382
47		R	1	1		382
48		R	1	1		378
49		R	1	1		430

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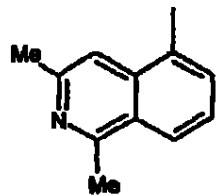
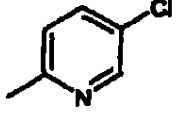
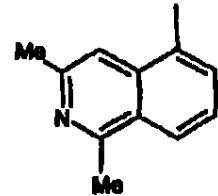
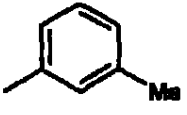
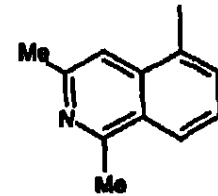
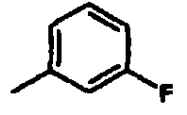
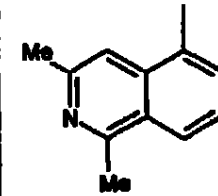
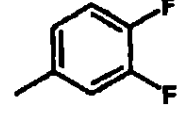
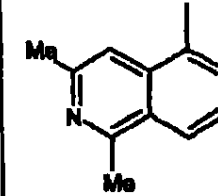
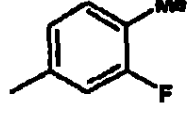
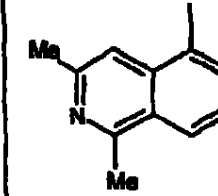
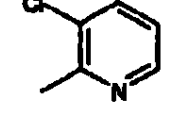
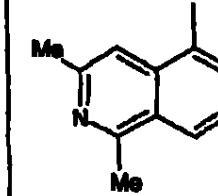
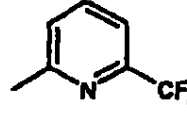
Cuadro 1 (Continuación)

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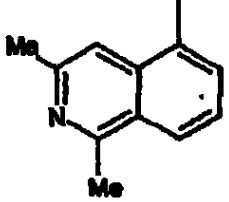
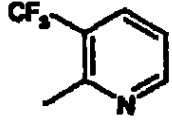
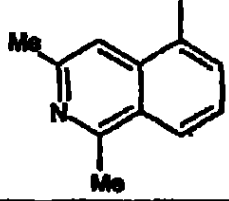
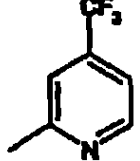
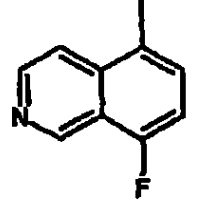
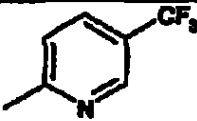
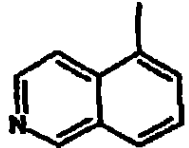
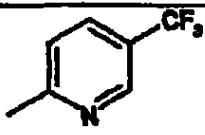
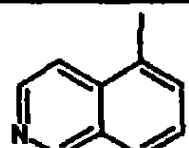
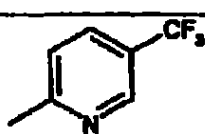
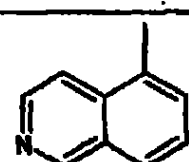
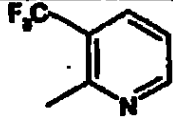
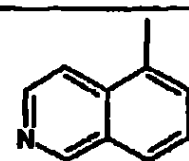
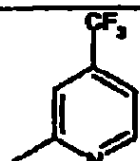
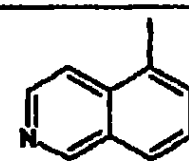
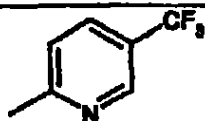
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50		R	1	1		386, 388
51		R	1	1		375
52		R	1	1		379
53		R	1	1		387
54		R	1	1		383
55		R	1	1		385, 387
56		R	1	1		430

Cuadro 1 (Continuación)

57		R	1	1		430
58		R	1	1		430
59		R	1	1		420
60			1	2		416
61			1	2		416
62		-	2	1		416
63		-	2	1		416
64		-	2	1		416

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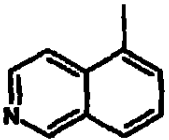
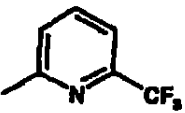
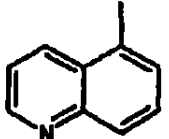
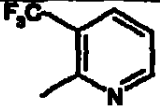
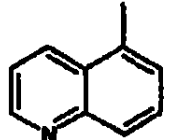
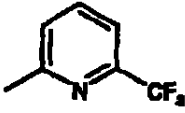
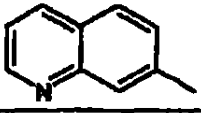
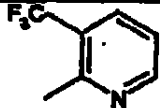
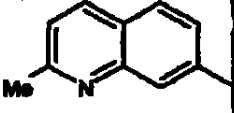
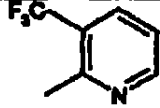
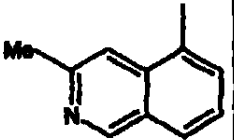
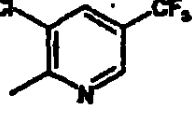
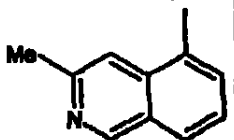
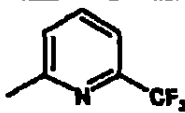
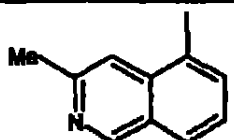
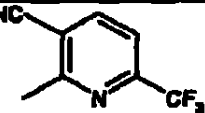
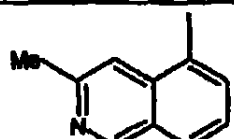
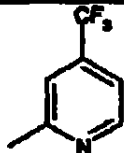
Cuadro 1 (Continuación)

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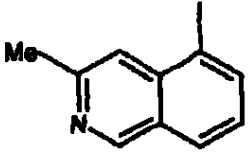
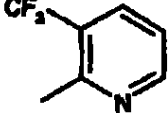
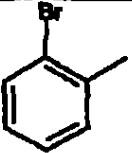
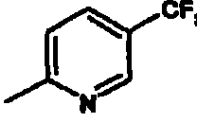
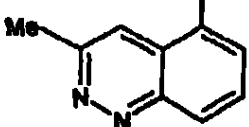
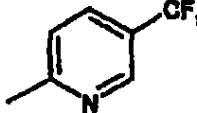
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65		-	2	1		416
66		-	2	1		416
67		-	2	1		416
68		-	2	1		416
69		-	2	1		430
70		-	2	1		483, 485
71		-	2	1		430
72		-	2	1		495
74		-	2	1		430

120

Cuadro 1 (Continuación)

75		-	2	1		430
76		8	1	1		429, 431
77		R	1	1		417

Datos Farmacológicos

a) Prueba *in vitro*

Como se indicó arriba, los compuestos de la invención son antagonistas del receptor vainilloide (VR1), y por lo tanto tienen propiedades farmacéuticas útiles. La actividad antagónica al receptor vainilloide (VR1) se puede confirmar y demostrar para cualquier compuesto particular usando los métodos convencionales, por ejemplo los que se describen en los textos de referencia estándares tales como D. Le Bars, M. Gozarin y S. W. Cadden, *Pharmacological Reviews*, 2001, 53(4), 597-652, u otros textos similares mencionados en la presente.

La selección usada de los compuestos de esta invención se basa en una prueba de calcio basada en FLIPR, similar a la descrita por Smart y otros (*British Journal of Pharmacology*, 2000, 129, 227-230). Células de astrocitoma transfectadas 1321N1, que expresan establemente VR1 humano, se sembraron en placas FLIPR a 25,000 células/cavidad (placa de 96 cavidades), y se cultivaron durante la noche.

Después, las células se cargaron en un medio que contenía 4 μ M de Fluo-3-AM (Molecular Probes) durante 2 horas a temperatura ambiente en la oscuridad. Después, las placas se lavaron 4 veces con Tyrode conteniendo calcio 1.5 mM sin probenecid. Las células se incubaron previamente con compuesto o amortiguador de control a temperatura ambiente durante 30 minutos. Después se agregó capsaicina (Sigma) a las células. Los compuestos que tenían actividad antagónica contra el VR1 humano se identificaron detectando las diferencias de fluorescencia medida después de la adición de capsaicina, en comparación con controles de amortiguador sin compuesto. De esta manera, por ejemplo, en el amortiguador de control la adición de capsaicina da como resultado un aumento de la concentración intracelular de calcio, resultando fluorescencia. Un compuesto que tiene actividad antagónica bloquea la unión de capsaicina con el receptor, no hay señalización y por lo tanto no hay aumento del nivel intracelular de calcio, y consecuentemente la fluorescencia es mas baja. Se generaron valores pK_b a partir de los valores de CI₅₀ usando la ecuación de Cheng-Prusoff.

Todos los compuestos probados con el método anterior tenían

una $pK_b > 6$, y los compuestos preferidos tenían una $pK_b > 7.0$.

b) Hiperalgnesia Inducida por FCA en conejillos de Indias

Se inyectaron 100 μ l de FCA 1 mg/ml por vía intraplantar en la pata izquierda en 4 grupos de 8 conejillos de Indias machos Dunkin Hartley (lote: 6282434, peso promedio 340 g). Veinticuatro horas después los compuestos se administraron oralmente a 0 (vehículo), 3, 10, 30 mg/kg con vehículo de metilcelulosa 1%, y siendo el volumen de dosificación de 2 ml/kg y dosificando directamente en el estómago. La metilcelulosa se agregó gradualmente al compuesto en el mortero y se molieron juntos.

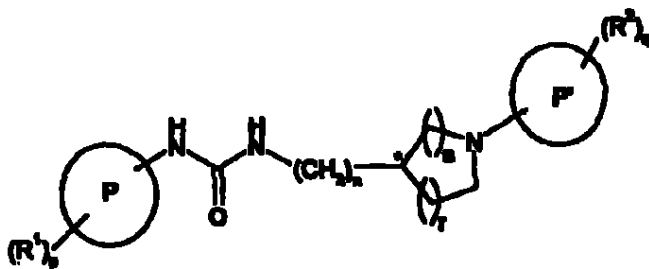
Se obtuvieron lecturas de conducta de hiperalgnesia mecánica antes de la administración de FCA (lectura de animal intacto), después de administrar FCA pero antes de la administración de fármaco (lectura de predosificación), y una hora después de la administración del fármaco. La lectura usada fue la presión de la pata (Randall-Sellito) y el punto final fue el retiro de la pata. El equipo de presión de la pata también tenía un disco de plata colocado en el punto para aumentar la marcación en un factor de 2.

Los compuestos que tenían una $pK_b > 7.0$ *in vitro* de acuerdo con el modelo (a) anterior, se probaron en este modelo y mostraron ser activos.

NOVEDAD DE LA INVENCION**REIVINDICACIONES**

5

1.- Un compuesto de fórmula (I):



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(I)

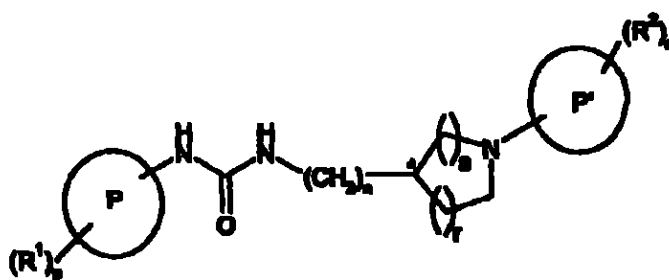
o una sal o solvato farmacéuticamente aceptable del mismo, en donde: P y P' se seleccionan independientemente de arilo y heteroarilo; R¹ y R² se seleccionan independientemente de -H, halógeno, alquilo, alcoxi, cicloalquilo, aralquilo, aralcoxi, cicloalquilalquilo, cicloalquilalcoxi, -CN, -NO₂, -OH, -OCF₃, -CF₃, -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)_xNR⁴R⁵, -C(O)CF₃, -C(O)alquilo, -C(O)cicloalquilo, -C(O)aralquilo, -C(O)Ar, -C(O)(CH₂)_xOR⁶, -C(O)(CH₂)_xNR⁴R⁵, -C(O)alcoxi, -C(O)NR⁴R⁵, -C(O)(CH₂)_xC(O)alcoxi, -(CH₂)_xOC(O)R⁶, -(CH₂)_xOR⁶, -(CH₂)_xR⁴R⁵, -(CH₂)_xC(O)NR⁴R⁵, -(CH₂)_xN(R⁴)C(O)R⁶, -(CH₂)_xS(O)₂NR⁴R⁵, -(CH₂)_xN(R⁴)S(O)₂R⁶, -ZAr, -(CH₂)_xS(O)₂R⁶, -(OCH₂)_xS(O)₂R⁶, -N(R⁴)S(O)₂R⁶, -N(R⁴)C(O)R⁶, -(CH₂)_xN(R⁴)S(O)₂R⁶, -(CH₂)_xN(R⁴)C(O)R⁶ o -(CH₂)_xC(O)alquilo; R⁴ y R⁵ pueden ser los mismos o diferentes y representan

H o alquilo, o R⁴ y R⁶ junto con los átomos a los que están unidos forman un anillo de azacicloalcano de C₃₋₆, (2-oxo)azacicloalcano de C₃₋₆, o una cadena de polimetileno de C₅₋₈ interrumpida opcionalmente por heteroátomos tales como O, o -NR⁷; Z es O, S o NR⁷; R⁸ es alquilo o arilo; R⁷ es hidrógeno, alquilo o arilo; m es 1 o 2; n es 0, 1, 2 o 3; p y q son independientemente 0, 1, 2, 3 o 4; r es 1, 2 o 3; s es 0, 1 o 2; y x es 0, 1, 2, 3, 4, 5 o 6; con la condición de que dicho compuesto de fórmula (I) no sea un compuesto seleccionado de:

1-(1-fenil-3-pirrolidinil)-3-fenilurea; 1-(1-fenil-3-pirrolidinil)-3-(4-metoxifenil)urea; N-(4-fluorofenil)-N'-[(R)-1-((3-metilfenil)pirrolidin-2-ilmetil)]urea; N-(2-bromofenil)-N'-[[(R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[[(R)-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea; N-(4-fluorofenil)-N'-[[(S)-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea; N-(2-bromofenil)-N'-[[(S)-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea; N-(4-fluorofenil)-N'-[[(S)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[[(S)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(4-fluorofenil)-N'-[[(R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(4-fluorofenil)-N'-[[(R)-1-(3-fluorofenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[[(R)-1-(3-fluorofenil)pirrolidin-3-il)]urea; N-(1-naftil)-N'-[[(R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2,3-diclorofenil)-N'-[[(R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[[(S)-1-(3-fluorofenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[[(R)-1-(4-fluoro-3-metilfenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[[(R)-1-(3,4-difluorofenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[[(R)-1-(3-fluoro-4-metilfenil)pirrolidin-3-il)]urea; N-(3-cloro-2-metilfenil)-N'-[[(R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2,3-diclorofenil)-N'-[[(R)-1-(3-metilfenil)pirrolidin-3-

il))urea; *N*-(2,5-diclorofenil)-*N'*-[(((*R*)-1-(3-metilfenil)pirrolidin-3-il))urea; *N*-(2,3-diclorofenil)-*N'*-[(((*R*)-1-(3-fluorofenil)pirrolidin-3-il))urea; *N*-(2,5-diclorofenil)-*N'*-[(((*R*)-1-(3-fluorofenil)pirrolidin-3-il))urea; *N*-(3-cloro-2-metilfenil)-*N'*-[(((*R*)-1-(3-fluorofenil)pirrolidin-3-il))urea; *N*-(3-cloro-2-metilfenil)-*N'*-[(((*R*)-1-(3,4-difluorofenil)pirrolidin-3-il))urea; *N*-(2,3-diclorofenil)-*N'*-[(((*R*)-1-(3,4-difluorofenil)pirrolidin-3-il))urea; *N*-(2,5-diclorofenil)-*N'*-[(((*R*)-1-(3,4-difluorofenil)pirrolidin-3-il))urea; *N*-(3-cloro-2-metilfenil)-*N'*-[(((*R*)-1-(3-fluoro-4-metilfenil)pirrolidin-3-il))urea; y *N*-(2,3-diclorofenil)-*N'*-[(((*R*)-1-(3-fluoro-4-metilfenil)pirrolidin-3-il))urea.

2.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque es de la fórmula (IA):



(IA)

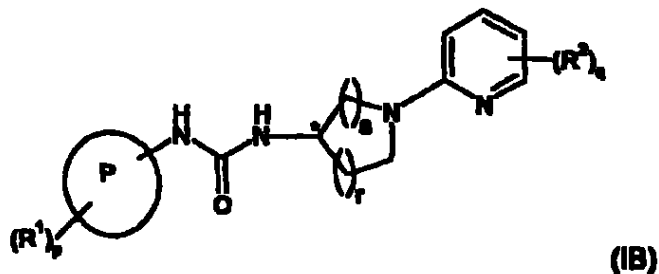
o una sal o solvato farmacéuticamente aceptable del mismo, en donde: P es fenilo, naftilo, quinolinilo o isoquinolinilo; P' es fenilo o piridilo; R¹ y R² se seleccionan independientemente de -H, halógeno, alquilo, alcoxi, cicloalquilo, aralquilo, aralcoxi, cicloalquilalquilo, cicloalquilalcoxi, -CN, -NO₂, -OH, -OCF₃, -CF₃, -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)_xNR⁴R⁵, -C(O)CF₃, -C(O)alquilo, -C(O)cicloalquilo, -C(O)aralquilo, -C(O)Ar, -C(O)(CH₂)_xOR⁶, -C(O)(CH₂)_xNR⁴R⁵, -C(O)alcoxi, -C(O)NR⁴R⁵, -

$(CH_2)_x C(O) \text{alcoxi}$, $-(CH_2)_x OC(O)R^6$, $-(CH_2)_x OR^6$, $-(CH_2)_x R^4 R^5$,
 $(CH_2)_x C(O)NR^4 R^5$, $-(CH_2)_x N(R^4)C(O)R^6$, $-(CH_2)_x S(O)_2 NR^4 R^5$,
 $(CH_2)_x N(R^4)S(O)_2 R^6$, $-ZAr$, $-(CH_2)_x S(O)_2 R^6$, $-(OCH_2)_x S(O)_2 R^6$, $-N(R^4)S(O)_2 R^6$,
 $-N(R^4)C(O)R^6$, $-(CH_2)_x N(R^4)S(O)_2 R^6$, $-(CH_2)_x N(R^4)C(O)R^6$ o

- 5 $(CH_2)_x C(O) \text{alquilo}$; R^4 y R^5 pueden ser los mismos o diferentes y representan H o alquilo, o R^4 y R^5 junto con los átomos a los que están unidos, forman un anillo de azacicloalcano de C_{3-8} , (2-oxo)azacicloalcano de C_{3-8} , o una cadena de polimetileno de C_{3-8} interrumpida opcionalmente por heteroátomos como O, o $-NR^7$; Z es O, S o NR^7 ; R^6 es alquilo o arilo; R^7 es hidrógeno, alquilo o arilo;
 10 m es 1 o 2; n es 0, 1, 2 o 3; p y q son independientemente 0, 1, 2, 3 o 4; r es 1, 2 o 3; s es 0, 1 o 2; y x es 0, 1, 2, 3, 4, 5 o 6; con la condición de que dicho compuesto de fórmula (I) no sea un compuesto seleccionado de: 1-(1-fenil-3-pirrolidinil)-3-fenilurea; 1-(1-fenil-3-pirrolidinil)-3-(4-metoxifenil)urea; N-(4-fluorofenil)-N'-[(R)-1-((3-metilfenil)pirrolidin-2-ilmetil)]urea; N-(2-bromofenil)-N'-
 15 [((R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[((R)-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea; N-(4-fluorofenil)-N'-[((S)-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea; N-(2-bromofenil)-N'-[((S)-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea; N-(4-fluorofenil)-N'-[((S)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[((S)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(4-fluorofenil)-N'-[((R)-1-(3-metilfenil)pirrolidin-3-il)]urea;
 20 1-(3-metilfenil)pirrolidin-3-il)]urea; N-(4-fluorofenil)-N'-[((R)-1-(3-fluorofenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[((R)-1-(3-fluorofenil)pirrolidin-3-il)]urea; N-(1-naftil)-N'-[((R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2,3-diclorofenil)-N'-[((R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-

[((S)-1-(3-fluorofenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[((R)-1-(4-fluoro-3-
 metilfenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[((R)-1-(3,4-difluorofenil)-
 pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[((R)-1-(3-fluoro-4-metilfenil)pirrolidin-
 3-il)]urea; N-(3-cloro-2-metilfenil)-N'-[((R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-
 5 (2,3-diclorofenil)-N'-[((R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2,5-diclorofenil)-
 N'-[((R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2,3-diclorofenil)-N'-[((R)-1-(3-
 fluorofenil)pirrolidin-3-il)]urea; N-(2,5-diclorofenil)-N'-[((R)-1-(3-fluorofenil)-
 pirrolidin-3-il)]urea; N-(3-cloro-2-metilfenil)-N'-[((R)-1-(3-fluorofenil)pirrolidin-3-
 il)]urea; N-(3-cloro-2-metilfenil)-N'-[((R)-1-(3,4-difluorofenil)pirrolidin-3-il)]urea;
 10 N-(2,3-diclorofenil)-N'-[((R)-1-(3,4-difluoro-fenil)pirrolidin-3-il)]urea; N-(2,5-
 diclorofenil)-N'-[((R)-1-(3,4-difluorofenil)-pirrolidin-3-il)]urea; N-(3-cloro-2-
 metilfenil)-N'-[((R)-1-(3-fluoro-4-metilfenil)-pirrolidin-3-il)]urea; y N-(2,3-
 diclorofenil)-N'-[((R)-1-(3-fluoro-4-metilfenil)-pirrolidin-3-il)]urea.

3.- El compuesto de fórmula (I) de conformidad con la
 15 reivindicación 1, caracterizado además porque es de la fórmula (IB):



20

o una sal o solvato farmacéuticamente aceptable del mismo, en donde: P es
 fenilo, naftilo, quinolinilo o isoquinolinilo; R¹ y R² se seleccionan
 independientemente de -H, halógeno, alquilo, alcoxi, cicloalquilo, aralquilo,

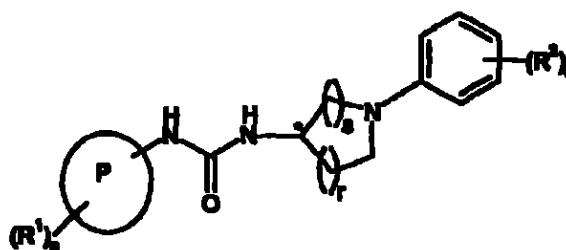
- aralcoxi, cicloalquilalquilo, cicloalquilalcoxi, -CN, -NO₂, -OH, -OCF₃, -CF₃, -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, -O(CH₂)_xNR⁴R⁵, -C(O)CF₃, -C(O)alquilo, -C(O)cicloalquilo, -C(O)aralquilo, -C(O)Ar, -C(O)(CH₂)_xOR⁶, -C(O)(CH₂)_xNR⁴R⁵, -C(O)alcoxi, -C(O)NR⁴R⁵, -
- 5 (CH₂)_xC(O)alcoxi, -(CH₂)_xOC(O)R⁶, -(CH₂)_xOR⁶, -(CH₂)_xR⁴R⁵, -(CH₂)_xC(O)NR⁴R⁵, -(CH₂)_xN(R⁴)C(O)R⁶, -(CH₂)_xS(O)₂NR⁴R⁵, -(CH₂)_xN(R⁴)S(O)₂R⁶, -ZAr, -(CH₂)_xS(O)₂R⁶, -(OCH₂)_xS(O)₂R⁶, -N(R⁴)S(O)₂R⁶, -N(R⁴)C(O)R⁶, -(CH₂)_xN(R⁴)S(O)₂R⁶, -(CH₂)_xN(R⁴)C(O)R⁶ o -(CH₂)_xC(O)alquilo; R⁴ y R⁵ pueden ser los mismos o diferentes y representan
- 10 H o alquilo, o R⁴ y R⁵ junto con los átomos a los que están unidos, forman un anillo de azacicloalcano de C₃₋₈, (2-oxo)azacicloalcano de C₃₋₈, o una cadena de polimetileno de C₅₋₈ interrumpida opcionalmente por heteroátomos como O, o -NR⁷; Z es O, S o NR⁷; R⁶ es alquilo o arilo; R⁷ es hidrógeno, alquilo o arilo; m es 1 o 2; n es 0, 1, 2 o 3; p y q son independientemente 0, 1, 2, 3 o 4; r es
- 15 1, 2 o 3; s es 0, 1 o 2; y x es 0, 1, 2, 3, 4, 5 o 6.

4.- El compuesto de fórmula (IB) de conformidad con la reivindicación 3, caracterizado además porque: R¹ y R² se seleccionan independientemente de halógeno, hidroxilo, alcoxi, -CF₃, -NO₂, -CN, -OCF₃, amino, o mono- o dialquilamino; p y q son independientemente 0, 1 o 2; y r y s son independientemente 1 o 2.

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5.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque es de la fórmula (IC):

12d



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(IC)

o una sal o solvato farmacéuticamente aceptable del mismo, en donde: P es fenilo, naftilo, quinolinilo o isoquinolinilo; R¹ y R² se seleccionan independientemente de halógeno, hidroxilo, alquilo, alcoxi, -CF₃, -NO₂, -CN, -OCF₃, amino, o mono- o dialquilamino; n es 0, 1, 2 o 3; p y q son

10 Independientemente 0, 1, 2, 3 o 4; r es 1, 2 o 3; y s es 0, 1 o 2; con la condición de que dicho compuesto de fórmula (IB) no sea un compuesto seleccionado de: 1-(1-fenil-3-pirrolidinil)-3-fenilurea; 1-(1-fenil-3-pirrolidinil)-3-(4-metoxifenil)urea; N-(4-fluorofenil)-N'-[(R)-1-((3-metilfenil)pirrolidin-2-ilmetil)]-urea; N-(2-bromofenil)-N'-[((R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2-

15 bromofenil)-N'-[((R)-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea; N-(4-fluorofenil)-N'-[((S)-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea; N-(2-bromofenil)-N'-[((S)-1-(3-metilfenil)pirrolidin-2-ilmetil)]urea; N-(4-fluorofenil)-N'-[((S)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[((S)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(4-fluorofenil)-N'-[((R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(4-

20 fluorofenil)-N'-[((R)-1-(3-fluorofenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[((R)-1-(3-fluorofenil)pirrolidin-3-il)]urea; N-(1-naftil)-N'-[((R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2,3-diclorofenil)-N'-[((R)-1-(3-metilfenil)pirrolidin-3-il)]urea; N-(2-bromofenil)-N'-[((S)-1-(3-fluorofenil)pirrolidin-3-il)]urea; N-(2-

(30)

bromofenil)-*N'*-[*((R)*-1-(4-fluoro-3-metilfenil)pirrolidin-3-il)]urea; *N*-(2-bromofenil)-*N'*-[*((R)*-1-(3,4-difluorofenil)pirrolidin-3-il)]urea; *N*-(2-bromofenil)-*N'*-[*((R)*-1-(3-fluoro-4-metilfenil)pirrolidin-3-il)]urea; *N*-(3-cloro-2-metilfenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea; *N*-(2,3-diclorofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea; *N*-(2,5-diclorofenil)-*N'*-[*((R)*-1-(3-metilfenil)pirrolidin-3-il)]urea; *N*-(2,3-diclorofenil)-*N'*-[*((R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea; *N*-(2,5-diclorofenil)-*N'*-[*((R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea; *N*-(3-cloro-2-metilfenil)-*N'*-[*((R)*-1-(3-fluorofenil)pirrolidin-3-il)]urea; *N*-(3-cloro-2-metilfenil)-*N'*-[*((R)*-1-(3,4-difluorofenil)pirrolidin-3-il)]urea; *N*-(2,3-diclorofenil)-*N'*-[*((R)*-1-(3,4-difluoro-fenil)pirrolidin-3-il)]urea; *N*-(2,5-diclorofenil)-*N'*-[*((R)*-1-(3,4-difluorofenil)-pirrolidin-3-il)]urea; *N*-(3-cloro-2-metilfenil)-*N'*-[*((R)*-1-(3-fluoro-4-metilfenil)-pirrolidin-3-il)]urea; y *N*-(2,3-diclorofenil)-*N'*-[*((R)*-1-(3-fluoro-4-metilfenil)-pirrolidin-3-il)]urea.

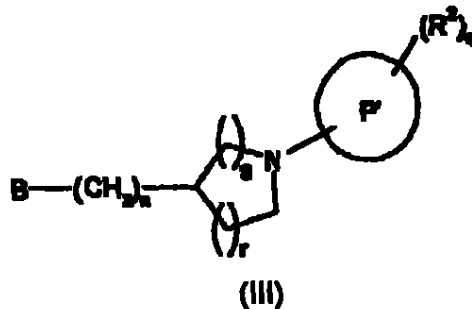
6.- Un procedimiento para la preparación de un compuesto de fórmula (I) como el que se reclama en la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, que comprende acoplar un compuesto de fórmula (II):



(II)

en la cual R^1 , P y p son como se define para la fórmula (I), con un compuesto de fórmula (III):

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en la cual P' , R^2 , n, q, r y s son como se define para la fórmula (I), y A y B contienen grupos funcionales apropiados que son capaces de reaccionar juntos para formar la porción urea; y posteriormente, conforme sea necesario, llevar a cabo una o más de las siguientes reacciones: (i) convertir un compuesto de fórmula (I) en otro compuesto de fórmula (I); (ii) remover cualquier grupo protector; (iii) preparar una sal o un solvato del compuesto así formado.

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7.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, o una sal o solvato farmacéuticamente aceptable del mismo, caracterizado además porque se usa como una sustancia terapéutica activa.

8.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, o una sal o solvato farmacéuticamente aceptable del mismo, caracterizado además porque se usa en el tratamiento o profilaxis de los trastornos de la invención.

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9.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, o una sal o solvato farmacéuticamente aceptable del mismo,

caracterizado además porque se usa en el tratamiento o profilaxis del dolor.

10.- Un método para el tratamiento o profilaxis de trastornos en los cuales es benéfico el antagonismo al receptor vainilloide (VR1) en mamíferos incluyendo seres humanos, que comprende administrar a un
5 mamífero en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o una sal o solvato farmacéuticamente aceptable del mismo.

11.- El método que se reclama en la reivindicación 11, en donde dichos trastornos son los trastornos de la invención.

10 12.- El uso de un compuesto de fórmula (I), o una sal o solvato farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para el tratamiento o profilaxis de trastornos en los cuales es benéfico el antagonismo al receptor vainilloide (VR1).

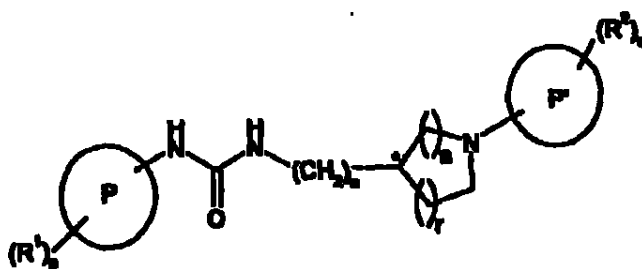
15 13.- El uso que se reclama en la reivindicación 12, en donde dichos trastornos son los trastornos de la invención.

14.- Una composición farmacéutica que comprende un compuesto de fórmula (I) como el que se reclama en la reivindicación 1, o una sal o solvato farmacéuticamente aceptable del mismo, y un vehículo o excipiente farmacéuticamente aceptable.

RESUMEN DE LA INVENCION

Se describen algunos compuestos de fórmula (I),

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(I)

10 o una sal o solvato farmacéuticamente aceptable de los mismos, en donde R¹, R², P, P', n, p, q, r y s son como se define en la especificación; un procedimiento para preparar dichos compuestos; una composición farmacéutica que comprende dichos compuestos; y el uso de dichos compuestos y composición en medicina.

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P04/197F

PATENT COOPERATION TREATY

WIPO International
Corporate IP

18 DEC 2003

Received NFSP

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Giddings, Peter John
GLAXOSMITHKLINE
Corporate Intellectual Property
CN925.1
980 Great West Road
Brentford
Middlesex TW8 9GS
GRANDE BRETAGNE

GlaxoSmithKline
Corporate IP
Received BRENTFORD
17 DEC 2003

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

ATTY: ☒ OK: ☒ DATE OF MAILING (day/month/year): 15.12.2003
--

Applicant's or agent's file reference: LLKP32894A	IMPORTANT NOTIFICATION
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International application No. PCT/GB02/04208	International filing date (day/month/year) 13.09.2002	Priority date (day/month/year) 13.09.2001
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Applicant SMITHKLINE BEECHAM P.L.C. et al
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1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

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

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

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

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

Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5618 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tlx 31 851 epo nl Fax +31 70 340 - 3018	Authorized Officer Janzing, M Tel. +31 70 340-4140 
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135 x 17

PATENT CO OPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LLKP32894A		FOR FURTHER ACTION - See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA18)	
International application No. PCT/GB02/04208	International filing date (day/month/year) 13.09.2002	Priority date (day/month/year) 13.09.2001	
International Patent Classification (IPC) or both national classification and IPC C07D207.00			
Applicant SMITHKLINE BEECHAM P.L.C. et al			
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 8 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.			
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☒ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application			
Date of submission of the demand 04.04.2003		Date of completion of this report 15.12.2003	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tlx 31 651 epo nl Fax: +31 70 340 - 3018		Authorized Officer Saltner, I Telephone No. +31 70 340-2388 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB02/04206**

I. Basis of the report

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

Description, Pages

1-47 as originally filed

Claims, Numbers

1-14 as originally filed

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

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

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

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

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

4. The amendments have resulted in the cancellation of:

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

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

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

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB02/04206**

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

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

- ☐ the entire international application,
☒ claims Nos. 10,11 (with respect to industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 10 and 11 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
☐ no international search report has been established for the said claims Nos.

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

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

IV. Lack of unity of invention

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

- ☐ restricted the claims.
☐ paid additional fees.
☐ paid additional fees under protest.
☒ neither restricted nor paid additional fees.

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

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

- ☐ complied with.
☒ not complied with for the following reasons:

see separate sheet

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB02/04206**

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

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1,2,5-14 (all partially) .

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

1. Statement

Novelty (N)	Yes: Claims	5-14
	No: Claims	1,2
Inventive step (IS)	Yes: Claims	
	No: Claims	1,2,5-14
Industrial applicability (IA)	Yes: Claims	1,2,5-9,12-14
	No: Claims	

2. Citations and explanations

see separate sheet

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Re Item III

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

Claims 10 and 11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 10 and 11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV

Lack of unity of invention

The present application lacks unity for the following reasons:

IV.1. According to Rule 13.1 PCT, "The International application shall relate to one invention only OR to a group of inventions so linked as to form a single general inventive concept".

This is further clarified in Rule 13.2 PCT, which details that "the requirement for unity of invention shall only be fulfilled when there is a technical relationship among those inventions involving one or more of the same corresponding special technical features that defines a contribution which each of the claimed inventions, considered as a whole makes over the prior art".

IV.2. For the purpose of unity, a single general inventive concept is required.

It is considered that the problem to be solved by the present application is the provision

1240

of further compounds for the treatment of pain.

The solution is provided by urea compounds according to formula (I) of claim 1.

Thus, the single general concept can be identified as the provision of urea compounds according to the formula (I) of claim 1 for the treatment of pain.

IV.3. The following documents were retrieved during the preliminary search:

**D1: US-A-3 424 760 (WELSTEAD WILLIAM J JR ET AL) 28 January 1969
(1969-01-28) cited in the application**

**D2: US-A-3 424 761 (LUNSFORD CARL D ET AL) 28 January 1969 (1969-01-
28) cited in the application**

D1 discloses (see example 3 as well as column 1, lines 45-54) analgesics of present formula (I) of claim 1 in which $P=P'$ =phenyl, $n=p=q=0$, and $s=r=1$.

D2 discloses (see example 8 as well as column 1, lines 43-51) analgesics of the present formula (I) of claim 1 in which $P=P'$ =phenyl, $R1=4-OMe$, $n=q=0$, and $s=r=1$.

The compounds of D1 and D2 solve the problem, namely the provision of further compounds for the treatment of pain in an identical manner to the present application. Thus, D1 and D2 provide solutions to the problem identified in the above mentioned single general concept. Therefore, the single general concept which could link the different inventions of the present application cannot be considered as inventive and there is a lack of unity.

IV.4. In the light of the above, the following four inventions have been identified:

1.) Compounds according to formula (I) of claim 1 in which $P=aryl$ and $P'=aryl$ as well as their pharmaceutical use and compositions.

2.) Compounds according to formula (I) of claim 1 in which $P=aryl$ and $P'=heteroaryl$ as well as their pharmaceutical use and compositions.

3.) Compounds according to formula (I) of claim 1 in which $P=heteroaryl$ and $P'=aryl$ as well as their pharmaceutical use and compositions.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB02/04206

4.) Compounds according to formula (I) of claim 1 in which P=heteroaryl and P'=heteroaryl as well as their pharmaceutical use and compositions.

Re Item V

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

Since no additional fees were paid, only above mentioned invention 1 will be subject to the following reasoned statement.

Further reference is made to the following documents D3-D5:

D3: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TANIGUCHI, NOBUAKI ET AL: 'Preparation of heterocyclic moiety-containing benzonitrile derivatives as antiandrogen agents' retrieved from STN Database accession no. 136:279475 XP002225002 -& JP 2002 088073 A (YAMANOUCHI PHARMACEUTICAL CO., LTD., JAPAN) 27 March 2002 (2002-03-27)

D4: PAN P-C ET AL: 'Soluble Polymer-Supported Synthesis of Arylpiperazines' TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 39, no. 51, 17 December 1998 (1998-12-17), pages 9505-9508, XP004144238 ISSN: 0040-4039

D5: HELSLEY G C ET AL: 'SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 1-SUBSTITUTED 3-PYRROLIDINYLUREAS' JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 11, no. 5, September 1968 (1968-09), pages 1034-1037, XP001095126 ISSN: 0022-2623

V.1. Novelty:

Document D3 discloses antiandrogenic N-[1-[4,cyano-3-(trifluoromethyl)phenyl]-4-

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB02/04206

piperidiny]-N'-(4-fluorophenyl)-urea and N-[1-[4,cyano-3-(trifluoromethyl)phenyl]-4-piperidiny]methyl]-N'-(4-fluorophenyl)-urea which are covered by the scope of present claim 1.

Document D4 discloses a compound of the present formula (I) in which P' represents 2-NO₂-4-methoxycarbonyl-phenyl, P represents phenyl and n=r=s=1.

Therefore, the subject matter of the present claims 1 and 2 cannot be considered as novel over the prior art (Article 33(2) PCT).

V.2. Inventive Step:

As mentioned under point IV.3., documents D1 and D2 (and also D5), which are considered to represent the most relevant state of the art, disclose analgesics which fall under the scope of the general formula (I) of claim 1 (even if disclaimed in the proviso at the end of claim 1).

The general formula of claim 1 of D2 moreover overlaps with the present formula (I) when, in D2, R1 represents phenyl, R2 hydrogen, and R3 lower-alkylphenyl, lower-alkoxyphenyl, halophenyl, trifluoromethylphenyl, or phenyl.

In view of the explicitly disclosed compounds of D1, D2, and D5 and the overlapping formulae, the attention of the skilled person would have been drawn to this class of urea compounds when investigating possibilities to provide further compounds for the treatment of pain. Thus, the teaching of D1, D2, and D5, would have lead the skilled person to make a selection of compounds from the general formula of D2 and/or to introduce slight structural modifications in compounds known from the prior art.

Hence, the solution proposed in claim 1 and 2 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT).

V.3. Industrial Applicability:

The compounds of the present application are useful for the treatment of pain and therefore the present application is regarded as industrially applicable (Article 33(4) PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference LLK/P32894A	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/GB 02/ 04206	International filing date (day/month/year) 13/09/2002	(Earliest) Priority Date (day/month/year) 13/09/2001
Applicant SMITHKLINE BEECHAM P.L.C.		

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 9 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, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

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

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

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:

UREA-COMPOUNDS ACTIVE AS VANILLOID RECEPTOR ANTAGONISTS FOR THE TREATMENT OF PAIN

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 36.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/04206

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 C07D401/14 C07D401/12 A61K31/4025 A61K31/4709
A61K31/4725 A61P25/00 A61P9/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

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

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

EPO-Internal, WPI Data, PAJ, 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.
X	US 3 424 760 A (WELSTEAD WILLIAM J JR ET AL) 28 January 1969 (1969-01-28) cited in the application column 1, line 45 - line 54 column 4; example 3	1,2,5-9
X	US 3 424 761 A (LUNSFORD CARL D ET AL) 28 January 1969 (1969-01-28) cited in the application page 1, line 43 - line 51 column 5; example 8	1,2,5-9
E	WO 02 090326 A (RAMI HARSHAD KANTILAL; WYMAN PAUL ADRIAN (GB); THOMPSON MERVYN (GB) 14 November 2002 (2002-11-14) claims 1-10 -/-	1,2,5-9

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to 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
- *S* document member of the same patent family

Date of the actual completion of the international search

11 April 2003

Date of mailing of the international search report

27 05 2003

Name and mailing address of the ISA

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Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/04206

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TANIGUCHI, NOBUAKI ET AL: "Preparation of heterocyclic moiety-containing benzonitrile derivatives as antiandrogen agents" retrieved from STN Database accession no. 136:279475 XP002225002 CAS RN: 405907-66-6; 405907-67-7 abstract -& JP 2002 088073 A (YAMANOUCHI PHARMACEUTICAL CO., LTD., JAPAN) 27 March 2002 (2002-03-27) examples 6-1,6-2	1,2,7
X	PAN P-C ET AL: "Soluble Polymer-Supported Synthesis of Arylpiperazines" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 39, no. 51, 17 December 1998 (1998-12-17), pages 9505-9508, XP004144238 ISSN: 0040-4039 example 10C	1,2
X	HELSLEY G C ET AL: "SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 1-SUBSTITUTED 3-PYRROLIDINYLUREAS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 11, no. 5, September 1968 (1968-09), pages 1034-1037, XP001095126 ISSN: 0022-2623 examples 38,40; table III	1,2,7
A	WO 01 28987 A (DU PONT PHARM CO) 26 April 2001 (2001-04-26) examples 15-22 claims 26,27	1,7,8
A	EP 0 790 240 A (TANABE SEIYAKU CO) 20 August 1997 (1997-08-20) example 114; table 13 example 105; table 11 page 79, line 16-22	1,7,8
X	US 4 001 422 A (DANILEWICZ JOHN C ET AL) 4 January 1977 (1977-01-04) abstract; examples 16,19	1,7
	-/-	

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MASTERS, JOHN J. ET AL: "Non-Amidine-Containing 1,2-Dibenzamidobenzene Inhibitors of Human Factor Xa with Potent Anticoagulant and Antithrombotic Activity" JOURNAL OF MEDICINAL CHEMISTRY (2000), 43(11), 2087-2092 , XP002238143 abstract examples 13,15,18,20,22-25	1,2,7
X	WO 99 00128 A (BEIGHT DOUGLAS WADE ;GOODSON THEODORE JUNIOR (US); HERRON DAVID KE) 7 January 1999 (1999-01-07) examples 40B,40C,40D	1,2
X	WO 99 00121 A (BEIGHT DOUGLAS WADE ;GOODSON THEODORE JR (US); HERRON DAVID KENT () 7 January 1999 (1999-01-07) abstract; examples 216,216B,216C,217-222	1,2,7
A	WO 92 19618 A (ABBOTT LAB) 12 November 1992 (1992-11-12) examples 14-16 page 5, line 17 ~ line 20	1,8

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2,5-14 (all partially);

Compounds according to the general formula (I) of claim 1 in which P=aryl and P'=aryl as well as the method for their preparation and their therapeutical use.

2. Claims: 1-4,6-14 (all partially)

Compounds according to the general formula (I) of claim 1 in which P=aryl and P'=heteroaryl as well as the method for their preparation and their therapeutical use.

3. Claims: 1,2,5-14 (all partially)

Compounds according to the general formula (I) of claim 1 in which P=heteroaryl and P'=aryl as well as the method for their preparation and their therapeutical use.

4. Claims: 1-4,6-14 (all partially)

Compounds according to the general formula (I) of claim 1 in which P=heteroaryl and P'=heteroaryl as well as the method for their preparation and their therapeutical use.

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

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 10 and 11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

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

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

see additional sheet

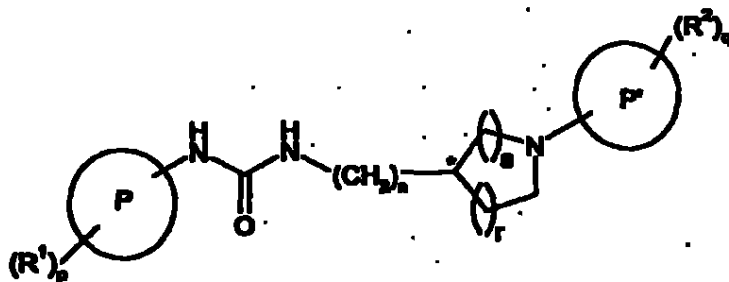
1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐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

Remark on Protest

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

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Certain compounds of formula (I),



(I)

or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein R¹, R², P, P', n, p, q, r and s are as defined in the specification, a process for preparing such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds and composition for the treatment of disorders relating to the vanilloid receptor (VR1) such as pain, migraine, neuropathy, ischaemia, neurodegeneration, stroke, multiple sclerosis, asthma, inflammatory diseases.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 02/04206

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3424760	A	28-01-1969	NONE
US 3424761	A	28-01-1969	GB 1172033 A 26-11-1969
WO 02090326	A	14-11-2002	WO 02090326 A1 14-11-2002
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

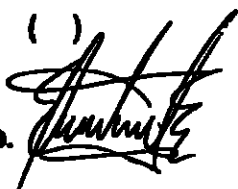
PCT/GB 02/04206

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4001422	A	SE 420921 B	09-11-1981
		SE 7508101 A	26-01-1976
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		IE 920801 A1	04-11-1992
		PT 100443 A	31-08-1993
		WO 9219618 A1	12-11-1992

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN	(/)	()
Indicación de que se solicita la concesión de una patente	(/)	()
Datos de identificación del solicitante o de la persona que se presenta la solicitud.	(/)	()
Descripción de la invención	()	()
Dibujos de ser estos pertinentes.	(/)	()
Comprobante de Pago de las tasas establecidas.		
COMPLETA ()	INCOMPLETA (/)	()
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
Representación gráfica del esquema de trazado	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable.



Fecha

SUPERINDUSTRIA Y COMERCIO

Radicación : 04022033 00000000

Folios 151

Fecha (UMB): 2004-03-11 09:16-41

Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES



2020
Bogotá, D.C.,

Doctor:
Carlos R. Olarte
Apoderado
Smithkline Beecham P.L.C.

Oficio N° 05890

ASUNTO:	Radicación N°	04-22055
	Solicitud internacional	PCT/GB2002/04206
	Fecha Inicio fase nacional	13/04/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 28-k) Decisión 486).

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

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


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

73 ABR 2004

El anterior requerimiento fue notificado por fijación en lista de fecha, _____.