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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 04-022055-A-00000-0000
Fecha: 2004-03-11 09:16:41 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 151

PC

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIVISIÓN DE NUEVAS CREACIONES

04-22055-A

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO PIRROLIDINIL UREAS COMO ANTAGONISTAS DE LOS RECEPTORES VANILÓIDES

SOLICITANTE: SMITHKLINE BEECHAM P.L.C.

DIRECCIÓN: 980 Great West Road, Brentford, Middlesex TW8 9GS. GRAN BRETAÑA

APODERADO: CARLOS R. OLARTE

BOGOTÁ 27 de Diciembre de 2007

P2004/00013A

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PETITORIO

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04-022055-A

Industria y Comercio
SUPERINTENDENCIA

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 04-022055-A-00000-0000
Fecha. 2004-03-11 09:16:41 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 151

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

[X] Patente de Invención [ ] Patente de Modelo de Utilidad
[ ] Capítulo I. [X] 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 APODERADO

Nombre: CARLOS R. OLARTE

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

Teléfono: 6386200 Fax: 6386201

E-Mail: filings@olarteraisbeck.com

IDENTIFICACION

C.C. [X] 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. (ver folio 2)

(7) Clasificación Internacional (51) C07D 401/00 ; A61K 31/40 ; A61P 29/00

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	Septiembre 13, 2001	0122156.3
GB	Diciembre 20, 2001	0130547.3
GB	Diciembre 20, 2001	0130503.6
GB	Diciembre 20, 2001	0130505.1

Comprobante de pago No. 12.959 **Fecha 19-02-04**

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

OLARTERAISBECK
OLARTE RAISBECK FRIERI MOURE & CASTRO LTDA.

2

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S.

Ref: Expediente No. 04-022.055
Solicitud de patente titulada: "PIRROLIDINIL UREAS COMO ANTAGONISTAS DE LOS RECEPTORES VANILÓIDES"
Solicitante: SMITHKLINE BEECHAM P.L.C.

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente:

1. Me permito presentar una **SOLICITUD DIVISIONAL** para la solicitud de patente en referencia.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Solicitud Divisional.

P2004/0000134

OlarteRaisbeck

3

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación.

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD DIVISIONAL
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2004/000013A**

SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] 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: GRAN BRETAÑA

Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE

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

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79782747Bta
TP 74.295

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 (86)**

Solicitud Internacional No. PCT/GB02/04206 Fecha Septiembre 13, 2002

Publicación Internacional No. WO 03/022809 Fecha Marzo 20, 2003

(6) **Título (54)** PIRROLIDINIL UREAS COMO ANTAGONISTAS DE LOS RECEPTORES VANILÓIDES

Clasificación Internacional (51) **C07D 207/00**

Prioridad
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	Septiembre 13, 2001	0122156.3
GB	Diciembre 20, 2001	0130547.3
GB	Diciembre 20, 2001	0130503.6
GB	Diciembre 20, 2001	0130505.1

(9) **Comprobante de pago No.** **07-104.827** **Fecha** **Diciembre 26, 2007**

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver Exp. Nº 04-022.055.
- [x] Documento de cesión del inventor al solicitante o a su causante. Ver expediente No. 04-022.055
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [x] 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.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

4A

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 104,827
FECHA : DICIEMBRE 26 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 04-022055- -00007-0000

Fecha: 2007-12-27 17:13:47 Dep: 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 444 RESPUESTAREQUE Folios: 115

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO POPULAR	050-00110-6	43955480	26/12/2007	4,746,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN		482,000.00
		TOTAL :	$	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

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 Smithlkline Beecham p.l.c. firmado por James Kerr Milligan

APOSTILLA

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

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

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos 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.

Marlen Neira C

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

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

C E R T I F I C O:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada **"SMITHKLINE BEECHAM p.l.c."**, Sociedad legalmente constituída y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **2337959**, con domicilio social en 980 Great West Road, Brentford, Middlesex TW8 9GS, Inglaterra;

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

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

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

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

SCRIVENER NOTARIES

DE PINNA
35 Piccadilly London W1J OLJ
Telephone:+44 (0)20 7208 2900 Facsimile: +44 (0)20 7208 0068 DX No. 48521 Piccadilly 2

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 / a été signé par **James Kerr Milligan**

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

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

5. at London/à Londres

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

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

8. Number/sous No **G229471**

9. Stamp: / timbre:

   10. Signature: **J. Garbrah**

FOREIGN AND COMMONWEALTH OFFICE
LONDON

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

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

OLARTERAISBECK
OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Power of Attorney

The undersigned,

SmithKline Beecham p.l.c.

domiciled in

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

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

Poder

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, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____

Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 March 2003 (20.03.2003)

PCT

(10) International Publication Number
WO 03/022809 A2

(51) International Patent Classification[7]: C07D 207/00

(21) International Application Number: PCT/GB02/04206

(22) International Filing Date:
13 September 2002 (13.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0122156.3	13 September 2001 (13.09.2001)	GB
0130547.3	20 December 2001 (20.12.2001)	GB
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

(75) Inventors/Applicants *(for US only)*: **RAMI, Harshad, Kantilal** [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).

(74) Agent: **GIDDINGS, Peter, John**; GlaxoSmithKline, Coporate Intellectual Property_CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, 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.

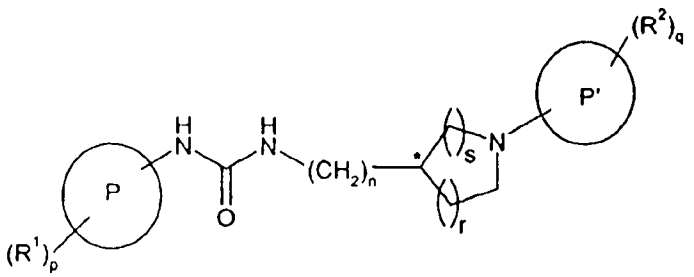
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, 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)

(57) Abstract: Certain compounds of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein R^1, R^2, 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.

WO 03/022809 A2

NOVEL COMPOUNDS

This invention relates to novel compounds, especially urea derivatives, 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 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.).

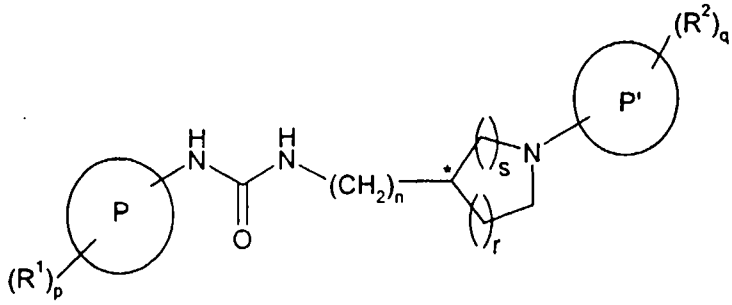
A wide variety of Vanilloid compounds of different structures are known in the art, for example those disclosed in European Patent Application Numbers, EP 0 347 000 and EP 0 401 903, UK Patent Application Number GB 2226313 and International Patent Application, Publication Number WO 92/09285. Particularly notable examples of vanilloid compounds or vanilloid receptor modulators are capsaicin or trans 8-methyl-N-vanillyl-6-nonenamide which is isolated from the pepper plant, capsazepine (*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 system, and pyschopharmacologic 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 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:

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

R^1 and R^2 are independently selected from –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO_2, -OH, -OCF_3, -CF_3, -NR^4R^5, -$S(O)_mR^6$, -$S(O)_2NR^4R^5$, -$OS(O)_2R^6$, -$OS(O)_2CF_3$, -$O(CH_2)_xNR^4R^5$, -$C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -$C(O)(CH_2)_xOR^6$, -$C(O)(CH_2)_xNR^4R^5$, -C(O)alkoxy, -$C(O)NR^4R^5$, -$(CH_2)_xC(O)$alkoxy, -$(CH_2)_xOC(O)R^6$, -$(CH_2)_xOR^6$, -$(CH_2)_xR^4R^5$, -$(CH_2)_xC(O)NR^4R^5$, -$(CH_2)_xN(R^4)C(O)R^6$, -$(CH_2)_xS(O)_2NR^4R^5$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, -$(CH_2)_xS(O)_2R^6$, -$(OCH_2)_xS(O)_2R^6$, -$N(R^4)S(O)_2R^6$, -$N(R^4)C(O)R^6$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -$(CH_2)_xN(R^4)C(O)R^6$ or –$(CH_2)_xC(O)$alkyl;

R^4 and R^5 may be the same or different and represent H or alkyl or R^4 and R^5 together with the atoms to which they are attached form a C_{3-6}azacycloalkane, C_{3-6}(2-oxo)azacycloalkane ring or C_{5-8} polymethylene chain optionally interrupted by heteroatoms such as O or –NR^7.

Z is O, S or NR^7;

R^6 is alkyl or aryl;

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;

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 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;

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;

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;

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;

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;

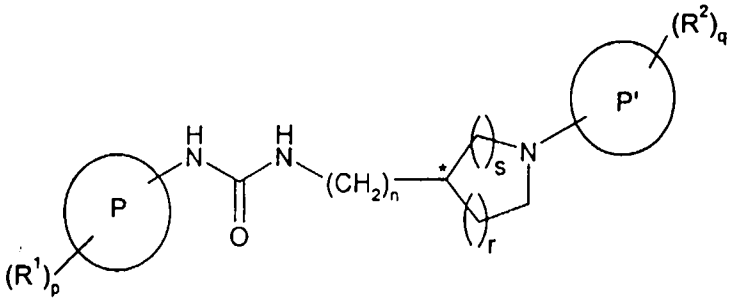
N-(3-Chloro-2-methylphenyl)-*N'*-[((*R*)-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;

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.

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),



(IA)

or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein:
P is phenyl, naphthyl, quinolinyl or isoquinolinyl;
P' is phenyl or pyridyl;
R^1 and R^2 are independently selected from –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO_2, -OH, -OCF_3, -CF_3, -NR^4R^5, -$S(O)_mR^6$, -$S(O)_2NR^4R^5$, -$OS(O)_2R^6$, -$OS(O)_2CF_3$, -$O(CH_2)_xNR^4R^5$, -$C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -$C(O)(CH_2)_xOR^6$, -$C(O)(CH_2)_xNR^4R^5$, -C(O)alkoxy, -$C(O)NR^4R^5$, -$(CH_2)_xC(O)$alkoxy, -$(CH_2)_xOC(O)R^6$, -$(CH_2)_xOR^6$, -$(CH_2)_xR^4R^5$, -$(CH_2)_xC(O)NR^4R^5$, -$(CH_2)_xN(R^4)C(O)R^6$, -$(CH_2)_xS(O)_2NR^4R^5$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, -$(CH_2)_xS(O)_2R^6$, -$(OCH_2)_xS(O)_2R^6$, -$N(R^4)S(O)_2R^6$, -$N(R^4)C(O)R^6$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -$(CH_2)_xN(R^4)C(O)R^6$ or –$(CH_2)_xC(O)$alkyl;
R^4 and R^5 may be the same or different and represent H or alkyl or R^4 and R^5 together with the atoms to which they are attached form a C_{3-6}azacycloalkane,

C_{3-6}(2-oxo)azacycloalkane ring or C_{5-8} polymethylene chain optionally interrupted by heteroatoms such as O or $-NR^7$.

Z is O, S or NR^7;

R^6 is alkyl or aryl;

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;

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 (IA) 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;

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;

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;

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;

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;
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.

Suitably, P is phenyl, quinolinyl or isoquinolinyl. More suitably P is phenyl, 5-quinolinyl, 7-quinolinyl or 5-isoquinolinyl. Preferably, P is phenyl or 5-isoquinolinyl.

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.

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.

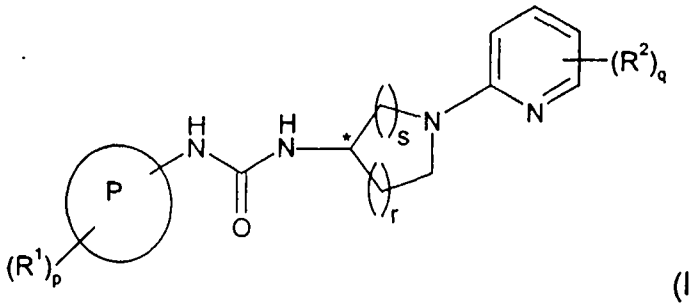
Suitably, x is 1, 2 or 3.

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.

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.

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



(IB)

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

P is phenyl, naphthyl, quinolinyl or isoquinolinyl;

R^1 and R^2 are independently selected from –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO_2, -OH, -OCF_3, -CF_3, -NR^4R^5, -$S(O)_mR^6$, -$S(O)_2NR^4R^5$, -$OS(O)_2R^6$, -$OS(O)_2CF_3$, -$O(CH_2)_xNR^4R^5$, -$C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -$C(O)(CH_2)_xOR^6$, -$C(O)(CH_2)_xNR^4R^5$, -C(O)alkoxy, -$C(O)NR^4R^5$, -$(CH_2)_xC(O)$alkoxy, -$(CH_2)_xOC(O)R^6$, -$(CH_2)_xOR^6$, -$(CH_2)_xR^4R^5$, -$(CH_2)_xC(O)NR^4R^5$, -$(CH_2)_xN(R^4)C(O)R^6$, -$(CH_2)_xS(O)_2NR^4R^5$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, -$(CH_2)_xS(O)_2R^6$, -$(OCH_2)_xS(O)_2R^6$, -$N(R^4)S(O)_2R^6$, -$N(R^4)C(O)R^6$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -$(CH_2)_xN(R^4)C(O)R^6$ or –$(CH_2)_xC(O)$alkyl;

R^4 and R^5 may be the same or different and represent H or alkyl or R^4 and R^5 together with the atoms to which they are attached form a C_{3-6}azacycloalkane, C_{3-6}(2-oxo)azacycloalkane ring or C_{5-8} polymethylene chain optionally interrupted by heteroatoms such as O or –NR^7.

Z is O, S or NR^7;

R^6 is alkyl or aryl;

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;

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^1 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 $-CF_3$;

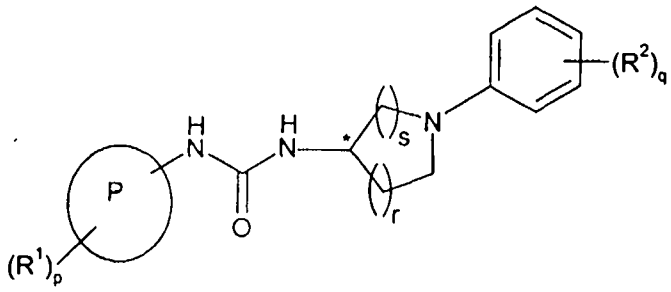
Suitably, p and q are independently 0, 1 or 2; and

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),



(IC)

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

P is phenyl, naphthyl, quinolinyl or isoquinolinyl;

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;

r is 1, 2 or 3; and

s is 0, 1 or 2;

17

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;

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;

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;

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;

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;

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.

Suitably, P is phenyl, quinolinyl or isoquinolinyl.

Suitably, R^1 is alkyl. Preferably R^1 is methyl.

Suitably, R^2 is halo or alkyl. Suitably, R^2 is fluoro or methyl.

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.

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 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.

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 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 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.

19

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.

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 ("Pr^n"), *iso*-propyl ("Pr^i"), n-butyl ("Bu^n"), *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, $-CF_3$, -OH, $-OCF_3$, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} 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, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, aryl and di-C_{1-6} 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.

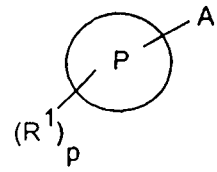
As used herein, the term "heteroaryl" as a group or part of a group refers to a stable 5- 7-membered monocyclic or 7- to 10-membered bicyclic

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-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, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyrrolyl, quinazolinyl, quinolinyl, 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, thienoimidazolyl, 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 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.

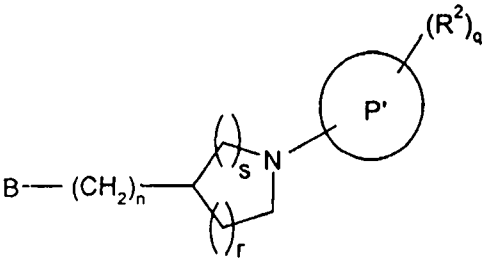
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises coupling a compound of formula (II):



21

(II)

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



(III)

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);

(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.

In process (a) the reaction is carried out in an inert solvent such as dichloromethane or acetonitrile.

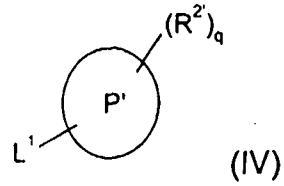
In process (b) the urea forming agent can be carbonyl diimidazole or phosgene or triphosgene, and carried out in an inert organic solvent such as diethyl ether, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

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).

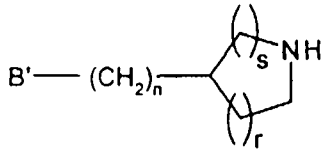
It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above-mentioned procedures. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic synthesis', New York, 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):



(IV)

wherein, P' is as defined in relation to formula (I) and $R^{2'}$ is R^2 as defined above or a protected form thereof, L^1 is a leaving group and q is as defined above, with a compound of formula (V):



(V)

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

Suitably L^1 is a halogen, such as chlorine.

23

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)**, 117and 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, postrheumatoid arthritic pain, osteoarthritic pain, back pain, visceral pain, cancer pain, algesia, 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, gastroeosophageal relux 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

24

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 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 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 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 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 usually adapted for oral, parenteral, rectal administration or intravesical adminstration 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.

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

25

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

26

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 Perfomance Liquid Chromatography
$MgSO_4$ - 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*-butyloxycarbonylamino)pyrrolidine (7.5g, 0.04mol) in dry dimethylformamide (100ml) was added powdered potassium carbonate (6.6g, 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 ($MgSO_4$) and filtered. Removal of solvent under reduced pressure gave a solid.

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

Description 2

(*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 aqueous sodium hydroxide. The organic phase was separated, dried ($MgSO_4$) 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.

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 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, 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)

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

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

Description 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 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 affored a yellow solid which was filtered and washed with water. The crude product was dissolved in ethanol (200ml), filtered and concentrated under reduced pressure to afford the title compound as a yellow solid.

Description 6

5-Amino-3-methylisoquinoline (D6)

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

Description 7

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

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 reduced pressure to leave an oil. Chromatography on silica gel eluting with ethyl acetate afforded the title compound as an oil.

29

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 $MgSO_4$, 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 $MgSO_4$, 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.

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) cesium carbonate (6.6g, 0.02mol), 3-bromotoluene (4.6g, 0.027mol) and (3*R*)-(+)-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 $MgSO_4$, filtered and concentrated under reduced pressure to leave an oil. Chromatography on silica gel eluting with ethyl acetate and hexane (gradient elution, maxium 4%) afforded the title compound as an off-white solid.

Description 12

(*R*)-1-(3-Methylphenyl)pyrrolidin-3-ylamine (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 partitoned between DCM and aqueous sodium hydrogen carbonate. Organic phase was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the title compound as an oil.

Description 13

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

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

Description 14

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

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)

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

Description 16

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

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

Description 17

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

The title compound was prepared from (3*R*)-(+)-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)

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

32

Description 19

(2,2-Diethoxyethyl)-(2-fluorobenzylidene)amine (D19)

2-Fluorobenzaldehyde (7.45g), was added to aminoacetaldehyde diethylacetal (9.16g) and the reaction heated to 100°C for 3h. After cooling, the mixture was transferred to a separating funnel and partitoned 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 compound as a colourless oil.

Description 20

8-Fluoroisoquinoline (D20)

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 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.

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 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

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.

Description 22

5-Amino-8-fluoroisoquinoline (D22)

D21, (0.283g), in ethanol (2ml), was treated with concentrated 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 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)

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 afford the title compound as a white solid.

Description 24

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

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)

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

Description 25

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.

Description 26

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

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)

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 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 affored the title compound as a foam.

Description 28

***N*-(Isoquinolin-5-yl)-*N'*-(piperidin-3-yl)-urea (D28)**

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)

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

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.

Description 31

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

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

36

Description 32

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

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)

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

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.

Description 35

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

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

Description 36

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

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)

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

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

Description 39

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

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

Description 40

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

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)

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

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

Description 43

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

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)

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

39

Description 45

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

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)

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

Description 47

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.

Description 48

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

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)

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

Description 50

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

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

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

(*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).

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

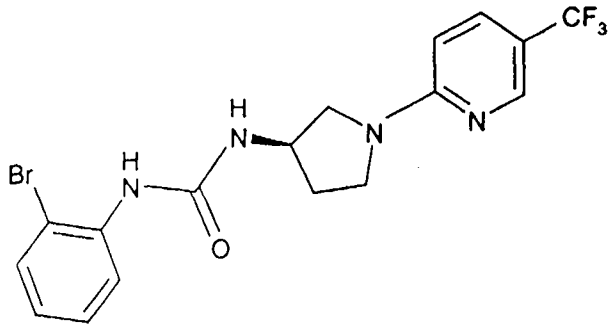
1-(3-Cyano-5-trifluoromethylpyridin-2-yl)-piperidin-4-ylamine (D55).

(3*R*)-(+)-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 BioSpecs B.V. respectively. Di-*tert*-butyl tricarbonate 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 (J Med. Chem., 1977, **20**(11), p.1528).

41

Example 1

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



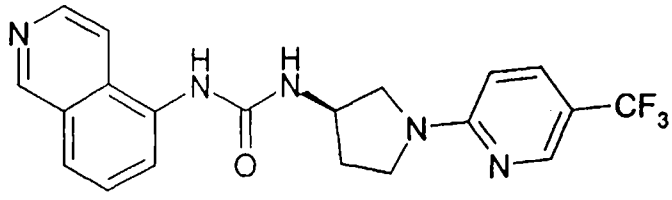
A solution of 2-bromophenyl isocyanate (Aldrich Chemical Company) (27.4ml, 0.222mol) in dry diethyl ether (65ml) was added dropwise over 0.5h to an efficiently stirred solution of D2 (51.4g, 0.222mol) in dry diethyl ether (0.8L) under argon at ambient temperature. After stirring for 18h, a white precipitate 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.

^{1}H NMR (d_6-DMSO, 400MHz) δ 1.94-1.98 (1H, m), 2.19-2.28 (1H, m), 3.31-3.41 (1H, m), 3.56 (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.

42

Example 2

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

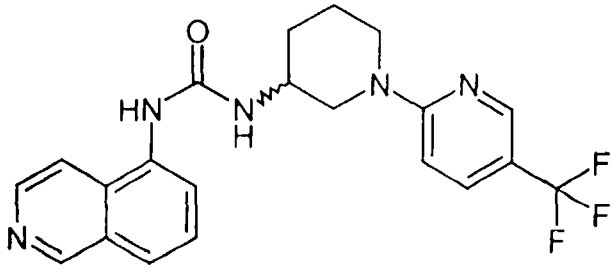


To a solution of di-*tert*-butyl tricarbonate, (0.681g, 2.595mmol), in dry DCM (1ml) was added a solution of D2, (0.5g, 2.162mmol) in in dry DCM (1ml) in one portion. After the initial effervescence, the solution was stirred at room temperature for 0.3h. A solution of 5-aminoisoquinoline, (0.312g, 2.162mmol) 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.

^{1}H NMR (d_6-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*-(Isoquinol-5-yl)-*N'*-[(1-(5-trifluoromethyl-2-pyridyl)piperidin-3-yl)]urea (E3)

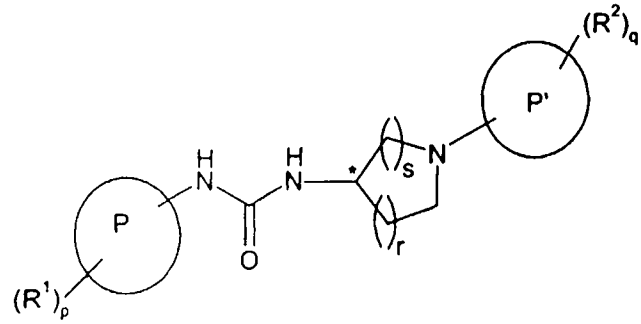


D28 (0.2g, 0.74mmol), 2-chloro-5-trifluoromethylpyridine (3eq., 0.4g) in dimethylformamide (10ml) and finely powdered potassium carbonate (3eq. 0.31g) were heated at 90°C for 18h and cooled. Solvent was removed under reduced pressure and the residue partitoned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$) 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.

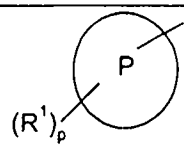
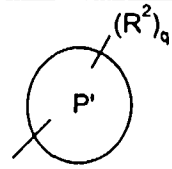
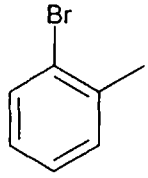
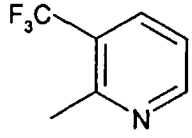
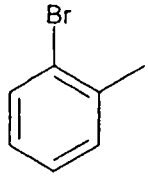
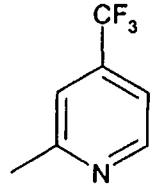
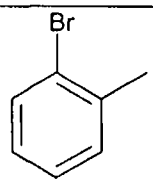
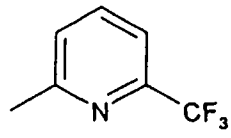
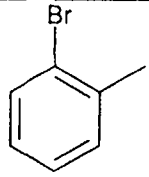
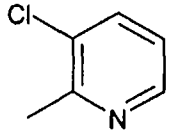
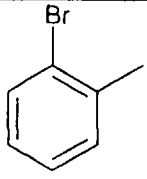
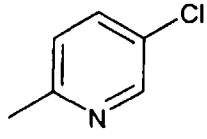
The two enantiomers (E3A and E3B) were separated by HPLC using Chiralpak AD column (250x19mm id), and eluting with n-hexane:ethanol (80:20 v/v) at a flow rate of 1ml/min with UV detection at 215nm.

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

Table 1



(I)

Ex		S'Chem	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		396, 398
8		R	1	1		396, 398

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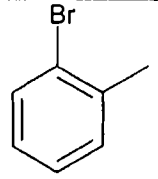
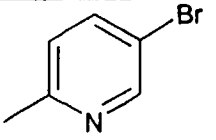
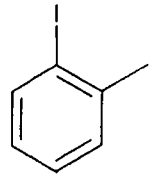
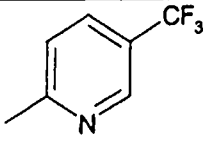
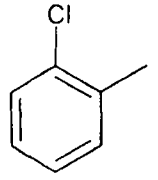
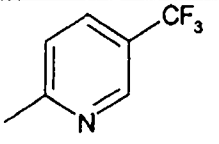
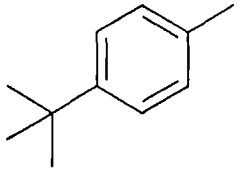
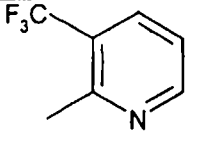
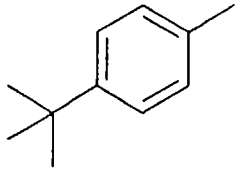
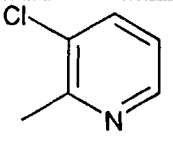
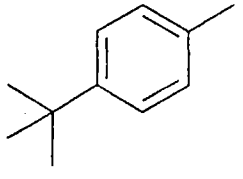
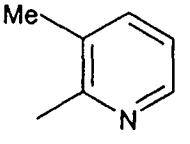
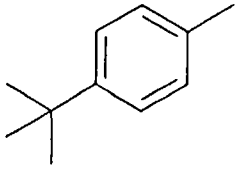
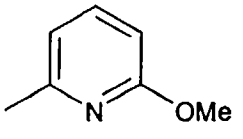
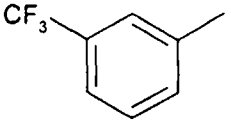
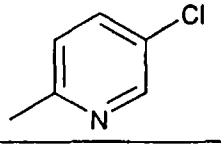
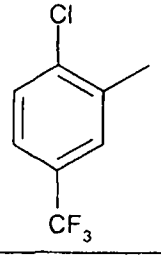
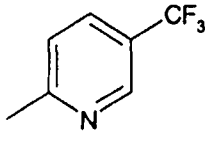
9		R	1	1		440, 442
10		R	1	1		477
11		R	1	1		385, 387
12		R	1	1		407
13		R	1	1		373, 375
14		R	1	1		353
15		R	1	1		369
16		R	1	1		384, 386
17		R	1	1		452, 454

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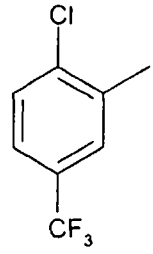
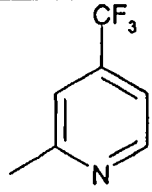
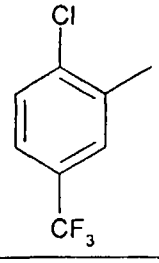
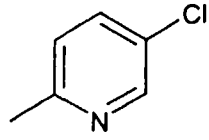
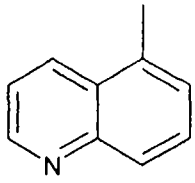
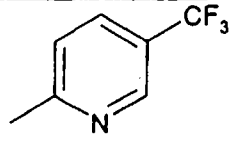
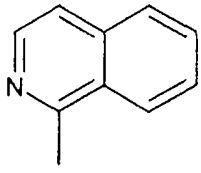
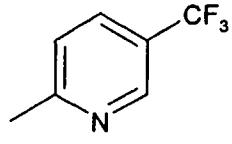
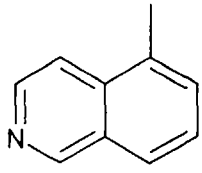
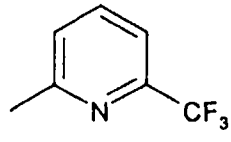
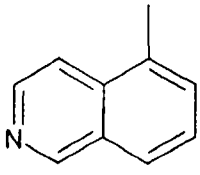
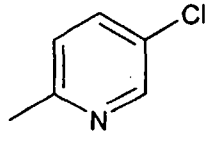
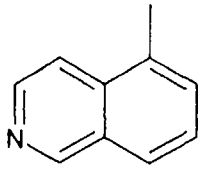
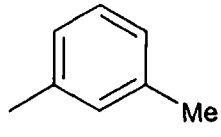
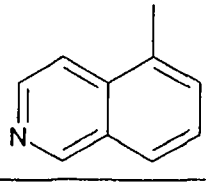
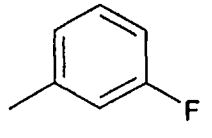
18		R	1	1		452, 454
19		R	1	1		420, 422
20		R	1	1		402
21		R	1	1		402
22		R	1	1		402
23		R	1	1		368, 370
24		R	1	1		347
25		R	1	1		351

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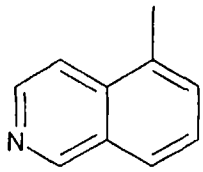
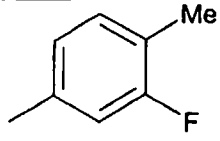
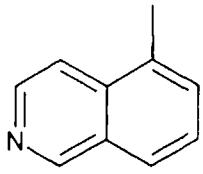
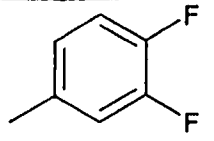
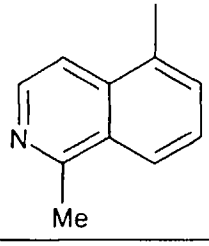
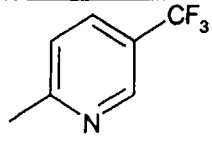
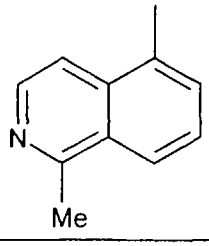
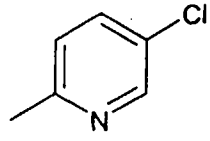
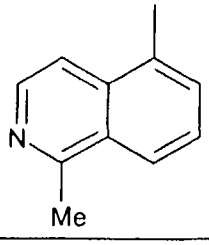
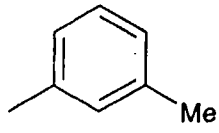
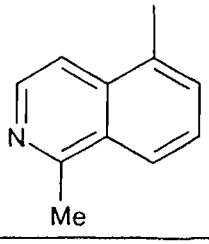
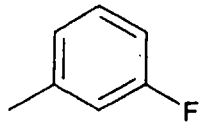
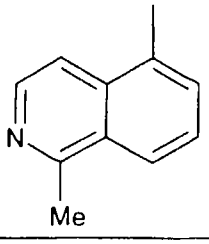
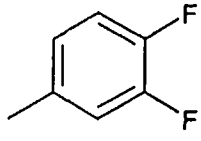
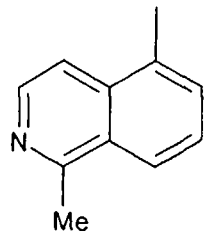
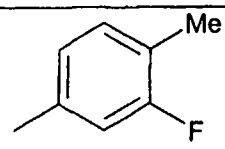
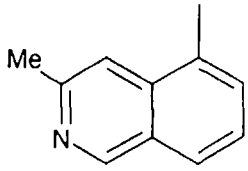
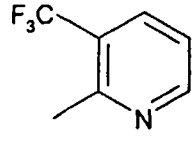
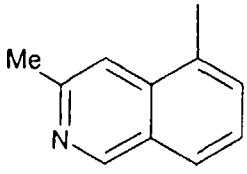
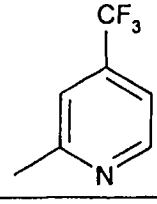
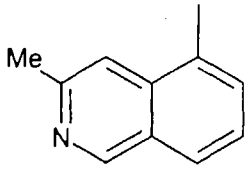
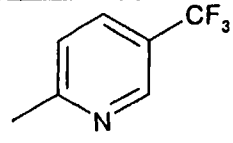
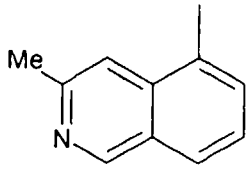
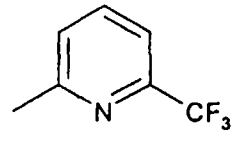
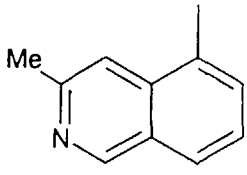
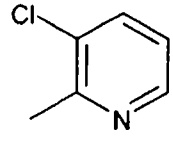
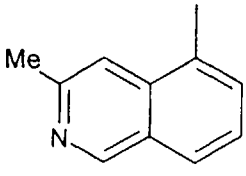
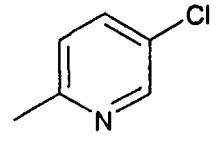
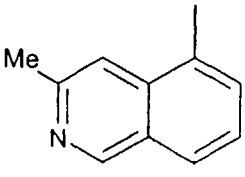
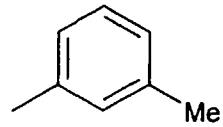
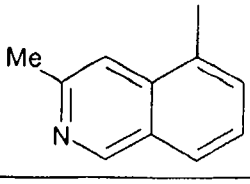
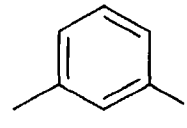
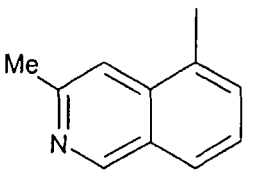
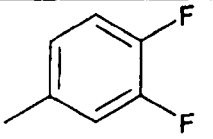
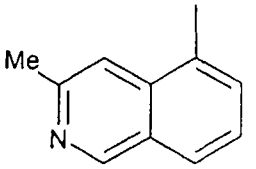
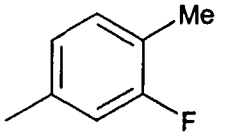
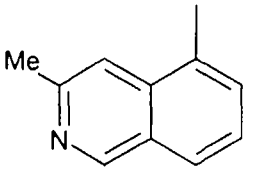
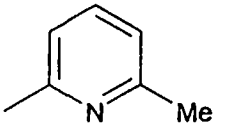
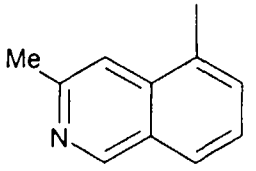
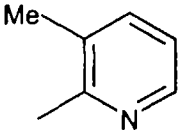
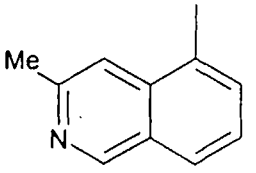
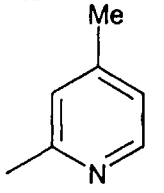
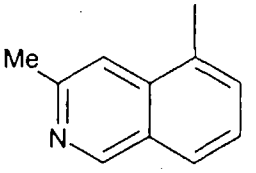
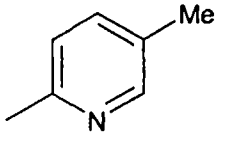
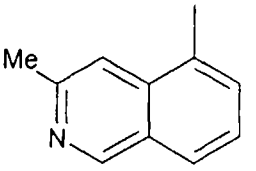
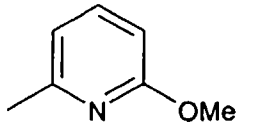
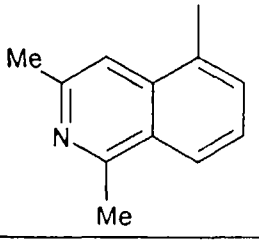
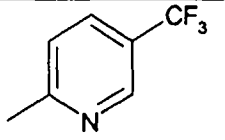
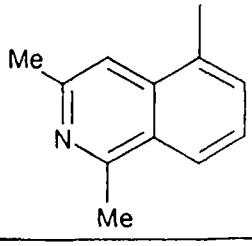
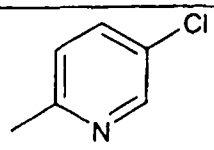
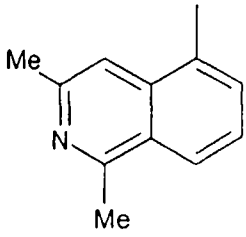
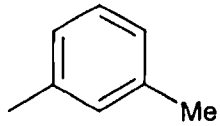
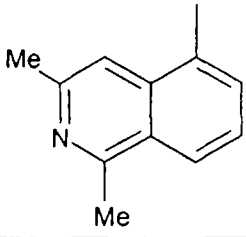
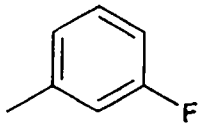
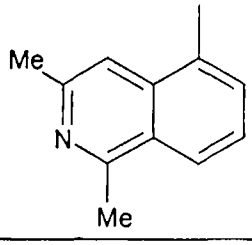
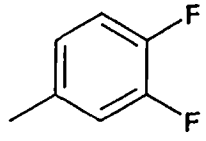
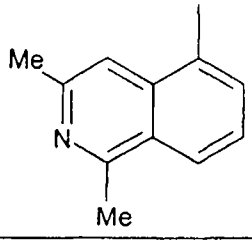
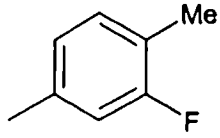
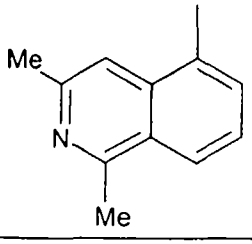
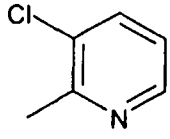
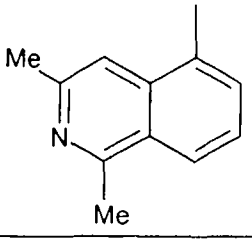
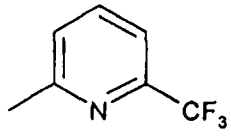
26		R	1	1		365
27		R	1	1		369
28		R	1	1		416
29		R	1	1		380, 382
30		R	1	1		361
31		R	1	1		365
32		R	1	1		383

48

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		361
41		R	1	1		365

49

42		R	1	1		382
43		R	1	1		379
44		R	1	1		362
45		R	1	1		362
46		R	1	1		362
47		R	1	1		362
48		R	1	1		378
49		R	1	1		430

50		R	1	1		396, 398
51		R	1	1		375
52		R	1	1		379
53		R	1	1		397
54		R	1	1		393
55		R	1	1		395, 397
56		R	1	1		430

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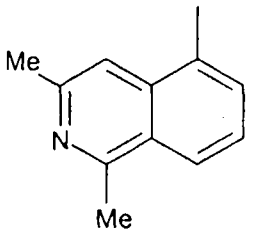
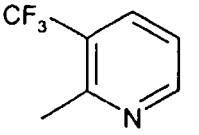
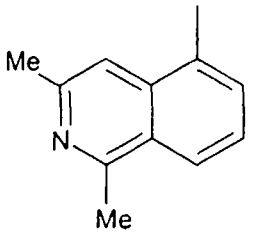
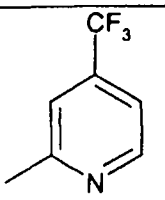
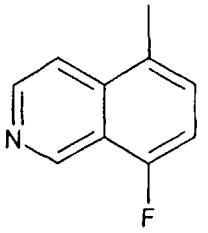
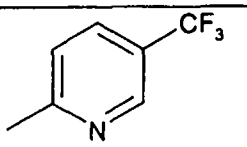
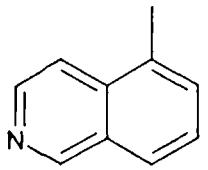
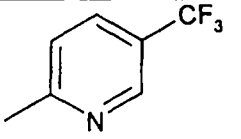
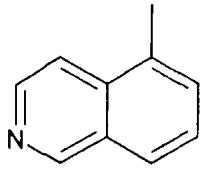
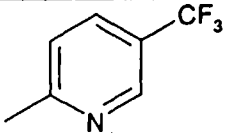
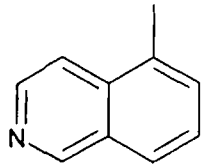
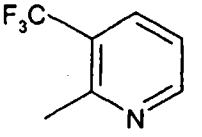
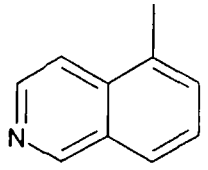
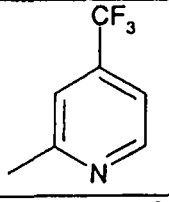
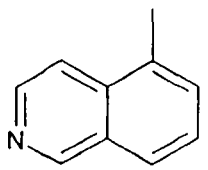
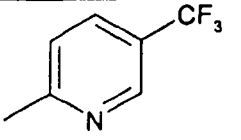
57		R	1	1		430
58		R	1	1		430
59		R	1	1		420
60			1	2		416
61			1	2		416
62		-	2	1		416
63		-	2	1		416
64		-	2	1		416

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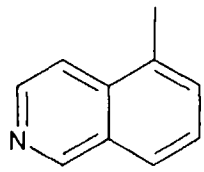
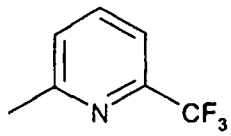
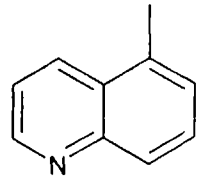
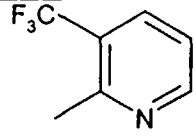
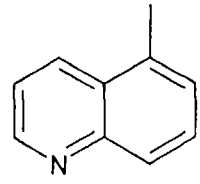
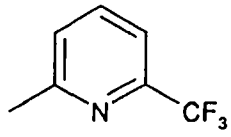
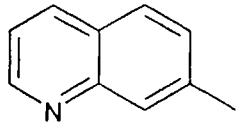
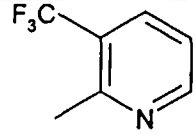
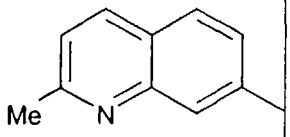
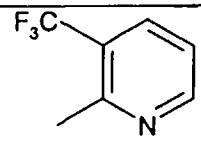
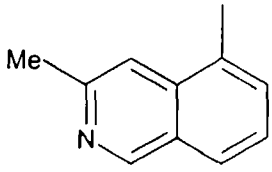
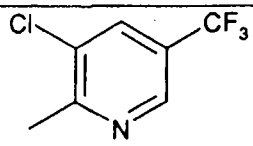
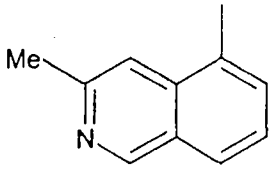
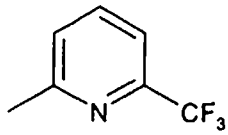
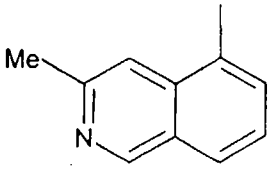
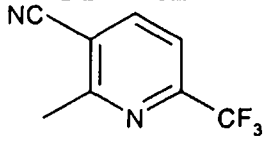
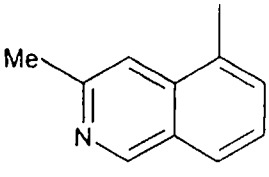
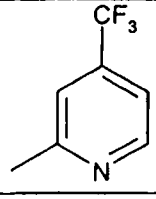
65		-	2	1		416
66		-	2	1		416
67		-	2	1		416
68		-	2	1		416
69		-	2	1		430
70		-	2	1		463, 465
71		-	2	1		430
72		-	2	1		455
74		-	2	1		430

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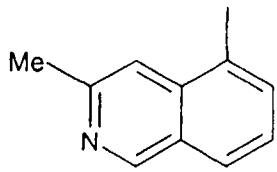
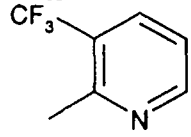
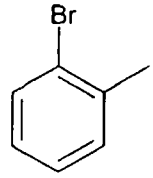
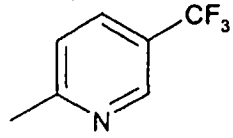
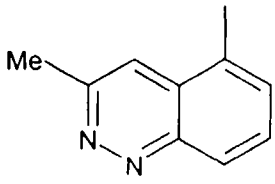
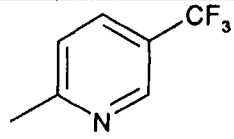
75		-	2	1		430
76		S	1	1		429, 431
77		R	1	1		417

S'Chem = stereochemistry

54

Pharmacological Data

(a) In vitro assay

As referenced above, the compounds of the invention are vanilloid 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 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 25,000cells/well (96-well plate) and cultured overnight.

The cells were subsequently loaded in medium containing 4μM 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 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 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. pKb values are generated from the IC_{50} values using the Cheng-Prusoff equation.

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

55

(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 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.

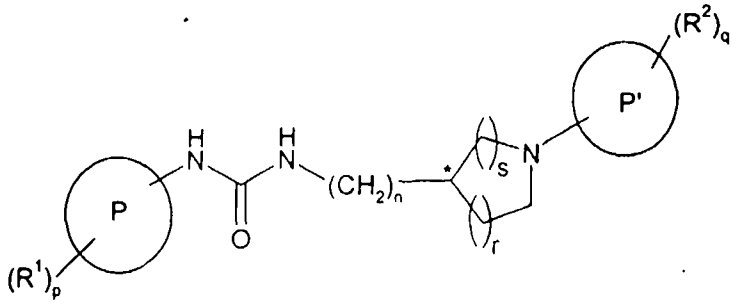
Behavioural readouts of mechanical hyperalgesia were obtained before FCA administration (naïve reading), after FCA but before drug administration (predose reading) and 1 hour after drug administration. The readout used was paw pressure (Randall-Sellito) and the end point was paw withdrawal. The paw pressure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

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

56

Claims

1. A compound of formula (I),



(I)

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

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

R^1 and R^2 are independently selected from –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO_2, -OH, -OCF_3, -CF_3, -NR^4R^5, -$S(O)_mR^6$, -$S(O)_2NR^4R^5$, -$OS(O)_2R^6$, -$OS(O)_2CF_3$, -$O(CH_2)_xNR^4R^5$, -$C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -$C(O)(CH_2)_xOR^6$, -$C(O)(CH_2)_xNR^4R^5$, -C(O)alkoxy, -$C(O)NR^4R^5$, -$(CH_2)_xC(O)$alkoxy, -$(CH_2)_xOC(O)R^6$, -$(CH_2)_xOR^6$, -$(CH_2)_xR^4R^5$, -$(CH_2)_xC(O)NR^4R^5$, -$(CH_2)_xN(R^4)C(O)R^6$, -$(CH_2)_xS(O)_2NR^4R^5$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, -$(CH_2)_xS(O)_2R^6$, -$(OCH_2)_xS(O)_2R^6$, -$N(R^4)S(O)_2R^6$, -$N(R^4)C(O)R^6$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -$(CH_2)_xN(R^4)C(O)R^6$ or –$(CH_2)_xC(O)$alkyl;

R^4 and R^5 may be the same or different and represent H or alkyl or R^4 and R^5 together with the atoms to which they are attached form a C_{3-6}azacycloalkane, C_{3-6}(2-oxo)azacycloalkane ring or C_{5-8} polymethylene chain optionally interrupted by heteroatoms such as O or –NR^7.

Z is O, S or NR^7;

R^6 is alkyl or aryl;

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;

57

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 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;

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;

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;

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;

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;

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;

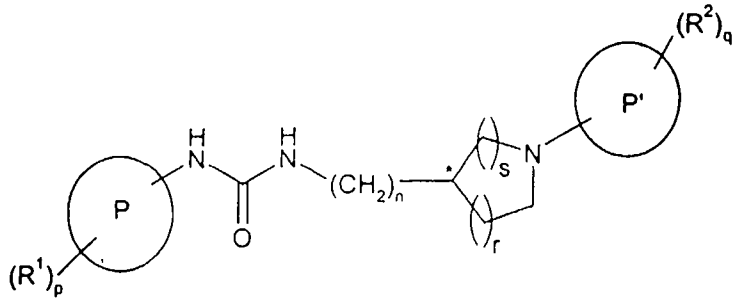
N-(2,5-Dichlorophenyl)-*N'*-[((*R*)-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;

58

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.

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



(IA)

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

P is phenyl, naphthyl, quinolinyl or isoquinolinyl;

P' is phenyl or pyridyl;

R^1 and R^2 are independently selected from –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, $-NO_2$, -OH, $-OCF_3$, $-CF_3$, $-NR^4R^5$, $-S(O)_mR^6$, $-S(O)_2NR^4R^5$, $-OS(O)_2R^6$, $-OS(O)_2CF_3$, $-O(CH_2)_xNR^4R^5$, $-C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, $-C(O)(CH_2)_xOR^6$, $-C(O)(CH_2)_xNR^4R^5$, -C(O)alkoxy, $-C(O)NR^4R^5$, $-(CH_2)_xC(O)$alkoxy, $-(CH_2)_xOC(O)R^6$, $-(CH_2)_xOR^6$, $-(CH_2)_xR^4R^5$, $-(CH_2)_xC(O)NR^4R^5$, $-(CH_2)_xN(R^4)C(O)R^6$, $-(CH_2)_xS(O)_2NR^4R^5$, $-(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, $-(CH_2)_xS(O)_2R^6$, $-(OCH_2)_xS(O)_2R^6$, $-N(R^4)S(O)_2R^6$, $-N(R^4)C(O)R^6$, $-(CH_2)_xN(R^4)S(O)_2R^6$, $-(CH_2)_xN(R^4)C(O)R^6$ or $-(CH_2)_xC(O)$alkyl;

R^4 and R^5 may be the same or different and represent H or alkyl or R^4 and R^5 together with the atoms to which they are attached form a C_{3-6}azacycloalkane, C_{3-6}(2-oxo)azacycloalkane ring or C_{5-8} polymethylene chain optionally interrupted by heteroatoms such as O or $-NR^7$.

Z is O, S or NR^7;

R^6 is alkyl or aryl;

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;

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 the 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;

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;

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;

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;

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;

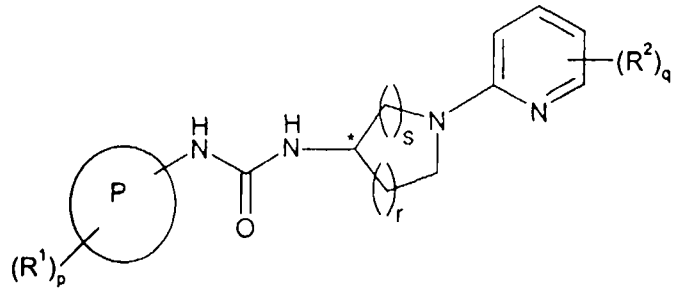
N-(2,3-Dichlorophenyl)-*N'*-[((*R*)-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea;

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;

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),



(IB)

or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein:
P is phenyl, naphthyl, quinolinyl or isoquinolinyl;
R^1 and R^2 are independently selected from –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO_2, -OH, -OCF_3, -CF_3, -NR^4R^5, -$S(O)_mR^6$, -$S(O)_2NR^4R^5$, -$OS(O)_2R^6$, -$OS(O)_2CF_3$, -$O(CH_2)_xNR^4R^5$, -$C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -$C(O)(CH_2)_xOR^6$, -$C(O)(CH_2)_xNR^4R^5$, -C(O)alkoxy, -$C(O)NR^4R^5$, -$(CH_2)_xC(O)$alkoxy, -$(CH_2)_xOC(O)R^6$, -$(CH_2)_xOR^6$, -$(CH_2)_xR^4R^5$, -$(CH_2)_xC(O)NR^4R^5$, -$(CH_2)_xN(R^4)C(O)R^6$, -$(CH_2)_xS(O)_2NR^4R^5$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, -$(CH_2)_xS(O)_2R^6$, -$(OCH_2)_xS(O)_2R^6$, -$N(R^4)S(O)_2R^6$, -$N(R^4)C(O)R^6$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -$(CH_2)_xN(R^4)C(O)R^6$ or –$(CH_2)_xC(O)$alkyl;
R^4 and R^5 may be the same or different and represent H or alkyl or R^4 and R^5 together with the atoms to which they are attached form a C_{3-6}azacycloalkane, C_{3-6}(2-oxo)azacycloalkane ring or C_{5-8} polymethylene chain optionally interrupted by heteroatoms such as O or –NR^7.
Z is O, S or NR^7;
R^6 is alkyl or aryl;

61

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;

r is 1, 2 or 3;

s is 0, 1 or 2; and

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

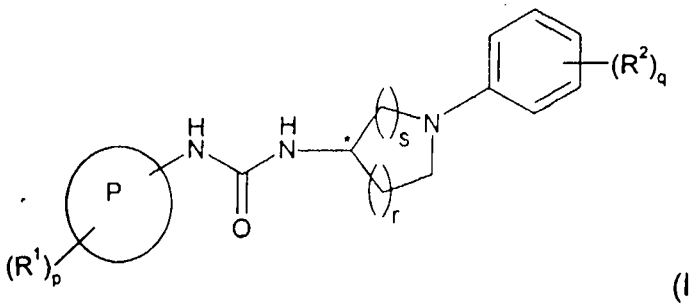
4. A compound of formula (IB) as claimed in claim 3, wherein:

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.

5. A compound of formula (I), as claimed in claim 1, of formula (IC),



(IC)

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

P is phenyl, naphthyl, quinolinyl or isoquinolinyl;

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;

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:

62

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;

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;

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;

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;

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;

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;

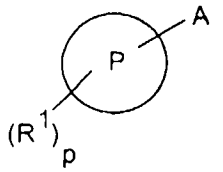
N-(2,5-Dichlorophenyl)-*N'*-[((*R*)-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea;

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.

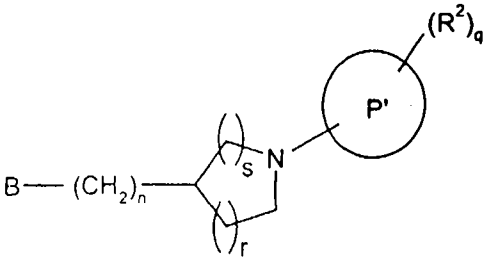
63

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):



(II)

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



(III)

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);

(ii) removing any protecting group;

(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.

64

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.

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. 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.

11. A method according to claim 11, wherein said disorders are the Disorders of the Invention.

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.

13. A use according to claim 13 wherein said disorders are the Disorders of the Invention.

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.

65

PIRROLIDINIL UREAS COMO ANTAGONISTAS DE LOS RECEPTORES VANILÓIDES

MEMORIA DESCRIPTIVA

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

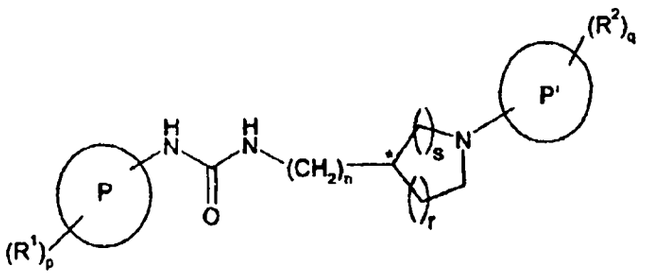
Las patentes de E.U.A. Nos. US 3,424,760 y US 3,424,761 describen una serie de 3-ureidopirrolidinas, de las que se afirma exhiben actividades analgésicas, en el sistema nervioso central y sicofarmacológicas. Específicamente, estas patentes revelan los compuestos 1-(1-fenil-3-pirrolidinil)-3-fenil-urea 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 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 vainilloide.

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



(I)

o una sal o solvato farmacéuticamente aceptable del mismo, en donde:

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

R^1 y R^2 se seleccionan independientemente de -H, halógeno, alquilo, alcoxi, cicloalquilo, aralquilo, aralcoxi, cicloalquilalquilo, cicloalquilalcoxi, -CN, -NO_2, -OH, -OCF_3, -CF_3, -NR^4R^5, -$S(O)_mR^6$, -$S(O)_2NR^4R^5$, -$OS(O)_2R^6$, -$OS(O)_2CF_3$, -$O(CH_2)_xNR^4R^5$, -$C(O)CF_3$, -C(O)alquilo, -C(O)cicloalquilo, -C(O)aralquilo, -C(O)Ar, -$C(O)(CH_2)_xOR^6$, -$C(O)(CH_2)_xNR^4R^5$, -C(O)alcoxi, -$C(O)NR^4R^5$, -$(CH_2)_xC(O)$alcoxi, -$(CH_2)_xOC(O)R^6$, -$(CH_2)_xOR^6$, -$(CH_2)_xR^4R^5$, -$(CH_2)_xC(O)NR^4R^5$, -$(CH_2)_xN(R^4)C(O)R^6$, -$(CH_2)_xS(O)_2NR^4R^5$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr,-$(CH_2)_xS(O)_2R^6$, -$(OCH_2)_xS(O)_2R^6$, -$N(R^4)S(O)_2R^6$, -$N(R^4)C(O)R^6$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -$(CH_2)_xN(R^4)C(O)R^6$ o -$(CH_2)_xC(O)$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_{3-6}, (2-oxo)azacicloalcano de C_{3-6}, o una cadena de polimetileno de C_{5-8} interrumpida opcionalmente por heteroátomos tales 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;

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;

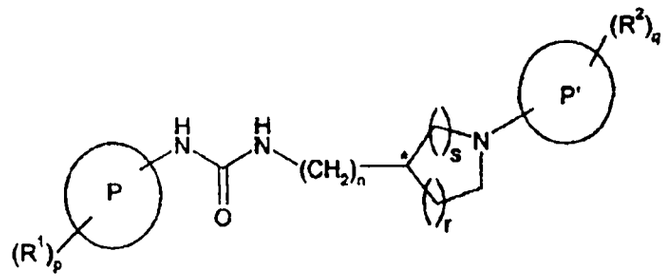
N-(2,5-diclorofenil)-*N*'-[((*R*)-1-(3,4-difluorofenil)pirrolidin-3-il)]urea;

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.

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

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



(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;

R^1 y R^2 se seleccionan independientemente de -H, halógeno, alquilo, alcoxi, cicloalquilo, aralquilo, aralcoxi, cicloalquilalquilo, cicloalquilalcoxi, -CN, -NO_2, -OH, -OCF_3, -CF_3, -NR^4R^5, -$S(O)_mR^6$, -$S(O)_2NR^4R^5$, -$OS(O)_2R^6$, -$OS(O)_2CF_3$, -$O(CH_2)_xNR^4R^5$, -$C(O)CF_3$, -C(O)alquilo, -C(O)cicloalquilo, -C(O)aralquilo, -C(O)Ar, -$C(O)(CH_2)_xOR^6$, -$C(O)(CH_2)_xNR^4R^5$, -C(O)alcoxi, -$C(O)NR^4R^5$, -$(CH_2)_xC(O)$alcoxi, -$(CH_2)_xOC(O)R^6$, -$(CH_2)_xOR^6$, -$(CH_2)_xR^4R^5$, -$(CH_2)_xC(O)NR^4R^5$, -$(CH_2)_xN(R^4)C(O)R^6$, -$(CH_2)_xS(O)_2NR^4R^5$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, -$(CH_2)_xS(O)_2R^6$, -$(OCH_2)_xS(O)_2R^6$, -$N(R^4)S(O)_2R^6$, -$N(R^4)C(O)R^6$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -$(CH_2)_xN(R^4)C(O)R^6$ o -$(CH_2)_xC$(O)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_{3-6}, (2-oxo)azacicloalcano de C_{3-6}, o una cadena de polimetileno de C_{5-8} 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;

m es 1 o 2;

n es 0, 1, 2 o 3;

70

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 (IA) 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.

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 piridilo.

Convenientemente, R^1 es halógeno, $-CF_3$ o alquilo. Preferiblemente, R^1 es flúor, cloro, bromo, $-CF_3$, metilo o *ter*-butilo.

Cuando p es 2 o 3, los grupos R^1 pueden ser iguales o diferentes.

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, R^2 es halógeno, alquilo, alcoxi, -CN o $-CF_3$. Preferiblemente, R^2 es flúor, cloro, bromo, metilo, OMe o CF_3.

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

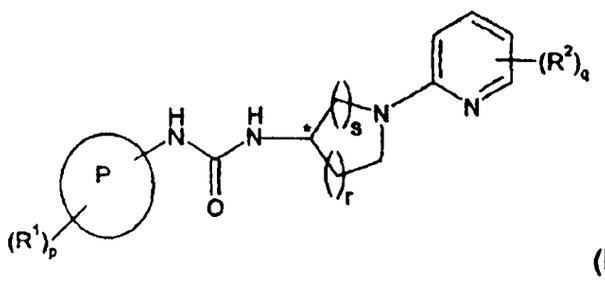
Convenientemente, x es 1, 2 o 3.

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

Cuando q es 2, los ejemplos particularmente preferidos de R^2 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 fórmula (IB):



(IB)

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

P es fenilo, naftilo, quinolinilo o isoquinolinilo;

R^1 y R^2 se seleccionan independientemente de -H, halógeno, alquilo, alcoxi, cicloalquilo, aralquilo, aralcoxi, cicloalquilalquilo, cicloalquilalcoxi, -CN, -NO_2, -OH, -OCF_3, -CF_3, -NR^4R^5, -$S(O)_mR^6$, -$S(O)_2NR^4R^5$, -$OS(O)_2R^6$, -$OS(O)_2CF_3$, -$O(CH_2)_xNR^4R^5$, -$C(O)CF_3$, -C(O)alquilo, -C(O)cicloalquilo, -C(O)aralquilo, -C(O)Ar, -$C(O)(CH_2)_xOR^6$, -$C(O)(CH_2)_xNR^4R^5$, -C(O)alcoxi, -$C(O)NR^4R^5$, -$(CH_2)_xC(O)$alcoxi, -$(CH_2)_xOC(O)R^6$, -$(CH_2)_xOR^6$, -$(CH_2)_xR^4R^5$, -$(CH_2)_xC(O)NR^4R^5$, -$(CH_2)_xN(R^4)C(O)R^6$, -$(CH_2)_xS(O)_2NR^4R^5$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, -$(CH_2)_xS(O)_2R^6$, -$(OCH_2)_xS(O)_2R^6$, -$N(R^4)S(O)_2R^6$, -$N(R^4)C(O)R^6$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -$(CH_2)_xN(R^4)C(O)R^6$ o -$(CH_2)_xC(O)$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_{3-6}, (2-oxo)azacicloalcano de C_{3-6}, o una cadena de polimetileno de C_{5-8} 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;

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.

Convenientemente, R^1 es halógeno, hidroxi, 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;

Convenientemente, R^1 es halógeno, hidroxi, 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 $-CF_3$;

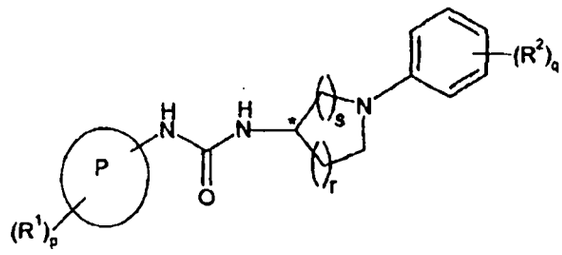
Convenientemente, p y q son independientemente 0, 1 o 2; y

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):



(IC)

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

P es fenilo, naftilo, quinolinilo o isoquinolinilo;

R^1 y R^2 se seleccionan independientemente de halógeno, hidroxi, alquilo, alcoxi, $-CF_3$, $-NO_2$, -CN, $-OCF_3$, amino, o mono- o dialquilamino;

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;

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.

Convenientemente, P es fenilo, quinolinilo o isoquinolinilo.

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.

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.

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.

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.

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, 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 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 variables de agua.

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

Los solvatos incluyen solvatos estequiométricos y solvatos no estequiométricos.

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 en particular metilo ("Me"), etilo ("Et"), n-propilo ("Pr^n"), *iso*-propilo ("Pr^i"), n-butilo ("Bu^n"), *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, $-CF_3$, -OH, $-OCF_3$, alquenilo de C_{2-6}, alquinilo de C_{3-6}, alcoxi de C_{1-6}, arilo y dialquil(C_{1-6})amino.

Como se usa aquí, el término "alcoxi", como un grupo o como parte de un grupo, se refiere a un radical de éter alquílico en donde el término "alquilo" es como se define arriba. Tales grupos alcoxi incluyen en particular 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, $-CF_3$, -OH, $-OCF_3$, alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{3-6}, arilo y dialquil(C_{1-6})amino.

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.

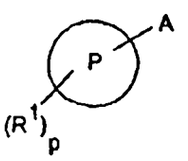
Como se usa aquí, el término "heteroarilo", como un grupo o como parte de un grupo, se refiere a un anillo aromático heterocíclico monocíclico estable de 5-7 miembros, o un anillo aromático heterocíclico bicíclico estable de 7-10 miembros, que consiste de átomos de carbono y de 1 a 4, convenientemente 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, acridinilo, azocinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, benzoimidazolilo, carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 2H,6H-1,5,2-ditiazinilo, dihidrobenzofuranilo, furanilo, furazanilo, imidazolilo, 1H-indazolilo, indolinilo, 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, 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").

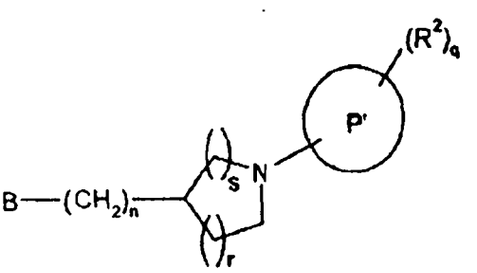
El término "naftilo" se usa aquí para denotar, a menos que se indique de otra manera, los grupos tanto 1-naftilo como 2-naftilo.

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):



(II)

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



(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:

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

fórmula (I);

(ii) remover cualquier grupo protector;

(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 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 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.

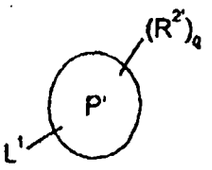
Un método de síntesis alternativo de los compuestos de urea asimétricos de fórmula (I) es a partir de un carbonato de diarilo, por medio del carbamato correspondiente. Dicho método lo describen Freer y otros (*Synthetic Communications*, 26 (2), 331-349, 1996). Será apreciado por los expertos que dicho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

Será apreciado por los expertos que puede ser necesario 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 primarias se pueden proteger como derivados ftalimida, bencilo, benciloxicarbonilo 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

81

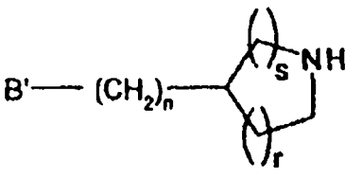
tiocetales. La desprotección de dichos grupos se logra usando procedimientos convencionales muy conocidos en la técnica.

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



(IV)

en donde P' es como se define para la fórmula (I) y $R^{2'}$ es R^2 como se define arriba, o una forma protegida del mismo, L^1 es un grupo saliente y q es como se define arriba, con un compuesto de fórmula (V):



(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.

Convenientemente, L^1 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, ciática, lesión de nervio, isquemia, neurodegeneración, ataque cerebral, dolor posterior a ataque cerebral, esclerosis múltiple, enfermedades respiratorias, asma, tos, COPD, broncoconstricción, trastornos inflamatorios, esofagitis, acedía, 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 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.

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.

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.

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, 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 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.

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 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 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 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 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

85

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 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.

Abreviaciones

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

CLAR- Cromatografía de líquidos de alto rendimiento

86

$MgSO_4$- Sulfato de magnesio

TFA- Acido trifluoroacético

DCM- Diclorometano

Descripción 1

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

A una solución de 2-cloro-5-trifluorometilpiridina (7.3 g, 0.04 mol) y 3*R*-(+)-3-(*ter*-butiloxicarbonilamino)pirrolidina (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)

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-nitroisoquinolina (D3)

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

Descripción 4

5-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 reducida para producir el compuesto del título como un sólido blanquecino.

Descripción 5

3-Metil-5-nitroisoquinolina (D5)

Una solución de 3-metilisoquinolina (5.4 g, 0.038 mol) en ácido 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 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 concentró a presión reducida para producir el compuesto de título como un sólido amarillo.

Descripción 6

5-Amino-3-metilisoquinolina (D6)

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)

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 cromatografía sobre gel de sílice eluyendo con acetato de etilo produjo el compuesto del título como un aceite.

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. 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 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)

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, 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.

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.

Descripción 11

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

Una suspensión de BINAP (1.25 g, 2 mmol), acetato de paladio (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*-butiloxicarbonilamino)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 se separó, se secó sobre

$MgSO_4$, 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.

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 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 $MgSO_4$, se filtró y se concentró a presión reducida para producir el compuesto del título como un aceite.

Descripción 13

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

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

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.

Descripción 15

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

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.

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.

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 (3*R*)-(+)-3-(*ter*-butoxicarbonilamino)pirrolidina y 4-bromo-2-fluorotolueno, usando el procedimiento indicado en la descripción 11.

Descripción 18

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

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)

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.

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 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 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)

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 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

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.

Descripción 23

Ester *ter*-butílico del ácido (1-bencil-piperidin-4-il)-carbámico (D23)

A una solución de 1-bencil-4-aminopiperidina (30 g, 0.16 mol) en 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.

Descripción 24

Ester *ter*-butílico 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/cm^2 en un hidrogenador de Parr usando catalizador de 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

Ester *ter*-butílico 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.

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.

Descripción 27

95

Ester *ter*-butílico del ácido 3-(3'-isoquinolin-5-il-ureido)-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.

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.

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*-butílico 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*-butiloxicarbonilamino)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*-butílico 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*-butiloxicarbonilamino)pirrolidina usando el procedimiento indicado en la

97

descripción 1.

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*-butílico 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 3*R*-(+)-3-(*ter*-butiloxicarbonilamino)pirrolidina usando el procedimiento indicado en la descripción 1.

Descripción 38

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

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

Descripción 39

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

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

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.

Descripción 41

Ester *ter*-butílico 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*-butiloxicarbonilamino)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*-butílico 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.

Descripción 45

Ester *ter*-butílico 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-

99

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*-butílico 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.

100

Descripción 49

Ester *ter*-butílico 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).

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

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

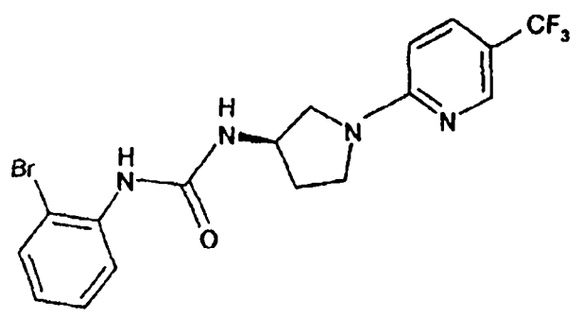
1-(3-Ciano-5-trifluorometilpiridin-2-il)-piperidin-4-ilamina (D55).

La (3*R*)-(+)-3-(*ter*-butiloxicarbonilamino)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 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 (E1)

101

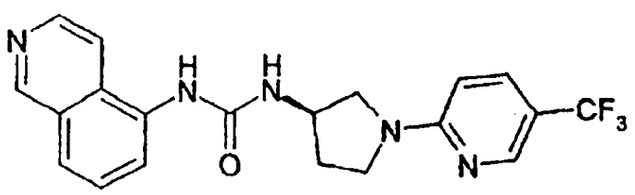


Una solución de isocianato de 2-bromofenilo (Aldrich Chemical Company) (27.4 ml, 0.222 mol) en éter dietílico seco (65 ml), se agregó gota a gota durante 0.5 horas a una solución eficazmente agitada de D2 (51.4 g, 0.222 mol) en éter dietílico seco (0.8 l) bajo argón a temperatura ambiente. Después de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

^{1}H RMN (d_6-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, 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

N-(Isoquinol-5-il)-N'-[((R)-1-(5-trifluorometil-2-piridil)pirrolidin-3-il)]urea (E2)

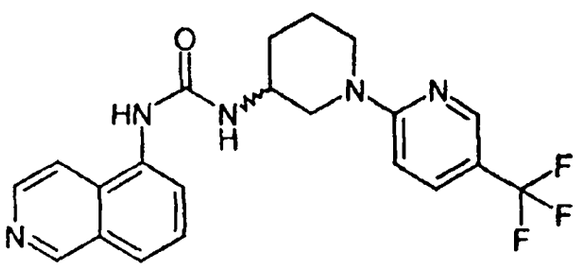


A una solución de tricarbonato de di-*ter*-butilo (0.681 g, 2.595 mmol), en DCM seco (1 ml), se le agregó una solución de D2 (0.5 g, 2.162 mmol) en DCM seco (1 ml) en una porción. Después de la efervescencia inicial, la solución se agitó a temperatura ambiente durante 0.3 horas. Se le agregó una solución 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.

^{1}H 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-il)-*N'*-[(1-(5-trifluorometil-2-piridil)piperidin-3il)]urea (E3)



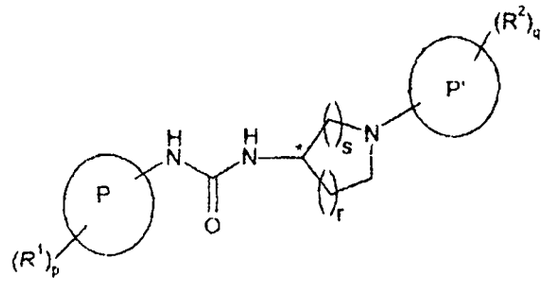
Una mezcla de D28 (0.2 g, 0.74 mmol), 2-cloro-5-trifluorometilpiridina (3 eq., 0.4 g) en dimetilformamida (10 ml) y carbonato de potasio finamente pulverizado (3 eq. 0.31 g), se calentó 18 horas a 90 °C y después se enfrió. El solvente se eliminó a presión reducida y el residuo se dividió entre acetato de etilo y agua. La fase orgánica se separó, se secó ($MgSO_4$) y se filtró. La eliminación del solvente a presión reducida dio el 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.

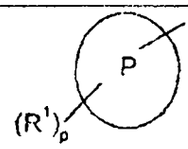
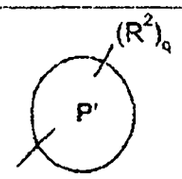
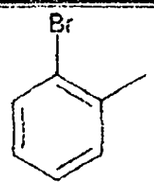
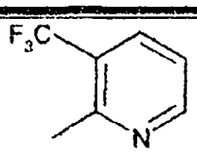
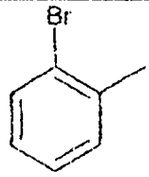
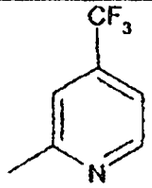
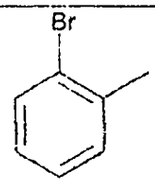
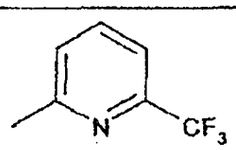
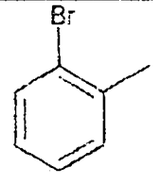
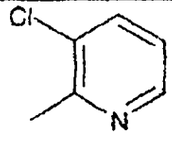
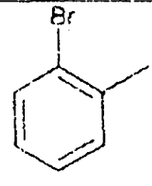
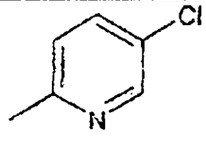
Los dos enantiómeros (E3A y E3B) se separaron por CLAR usando una columna Chiralpak AD (250 mm x 19 mm d.i.), y eluyendo con n-hexano:etanol (80:20 v/v), a una velocidad de flujo de 1 ml/min, con detección UV a 215 nm.

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

Cuadro 1

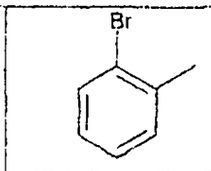
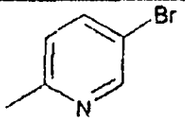
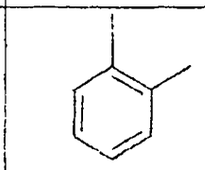
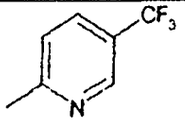
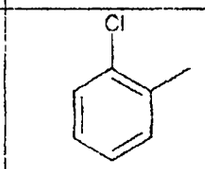
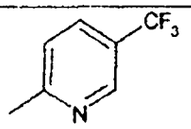
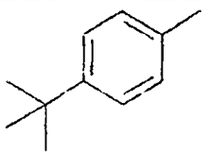
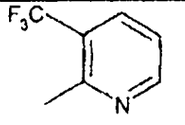
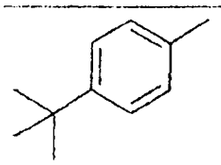
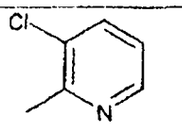
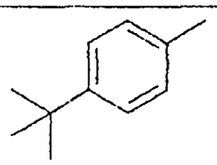
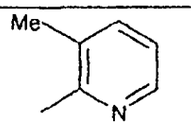
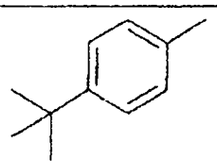
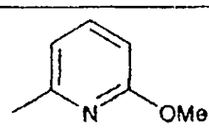
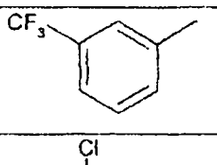
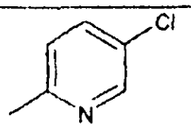
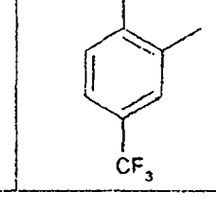
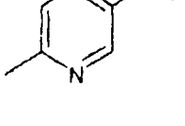


(I)

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		396, 398
8		R	1	1		396, 398

104

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		369
16		R	1	1		384, 386
17		R	1	1		452, 454

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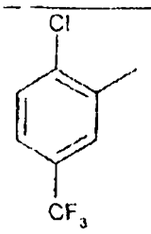
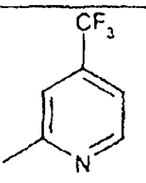
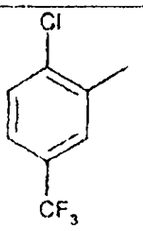
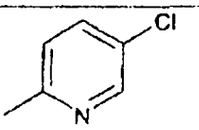
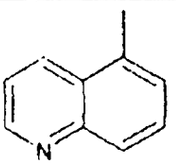
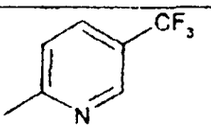
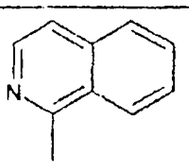
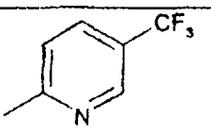
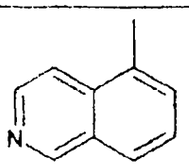
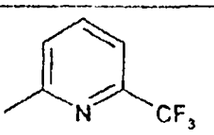
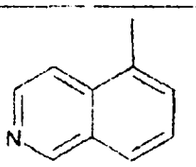
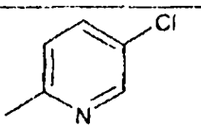
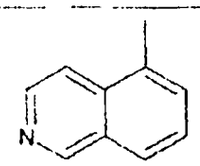
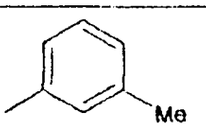
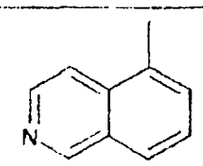
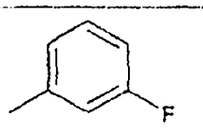
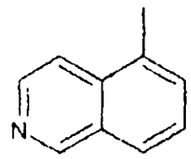
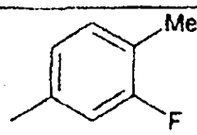
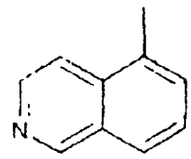
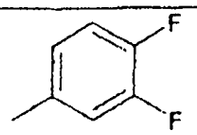
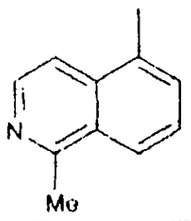
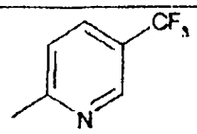
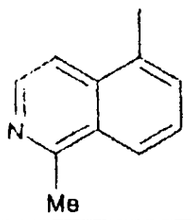
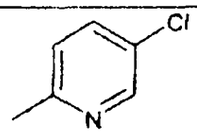
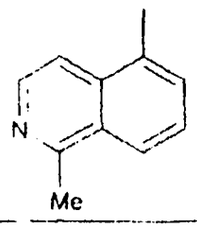
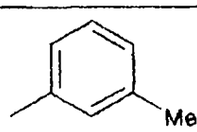
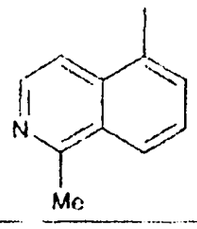
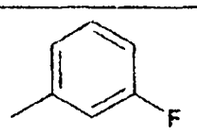
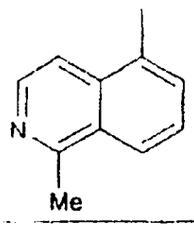
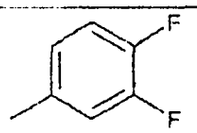
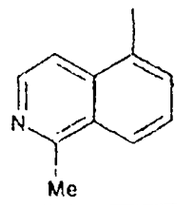
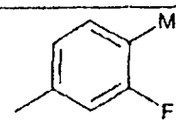
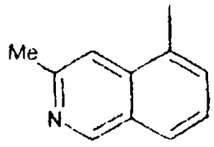
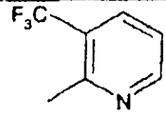
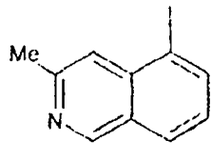
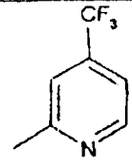
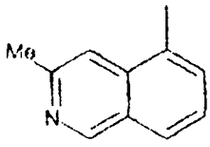
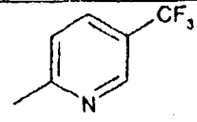
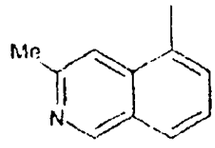
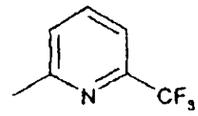
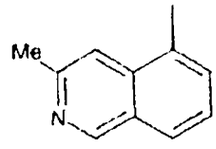
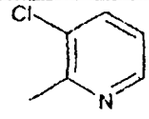
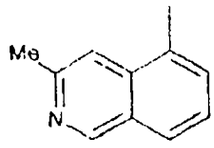
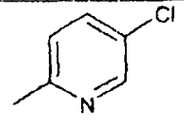
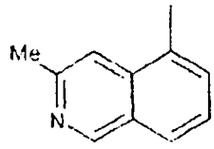
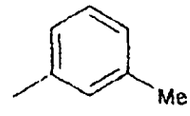
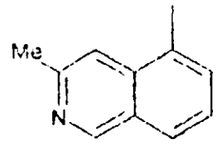
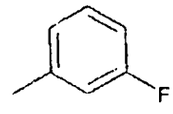
18		R	1	1		452, 454
19		R	1	1		420, 422
20		R	1	1		402
21		R	1	1		402
22		R	1	1		402
23		R	1	1		368, 370
24		R	1	1		347
25		R	1	1		351

Cuadro 1 (Continuación)

26		R	1	1		365
27		R	1	1		369
28		R	1	1		416
29		R	1	1		380, 382
30		R	1	1		361
31		R	1	1		365
32		R	1	1		383

Cuadro 1 (Continuación)

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		361
41		R	1	1		365

108

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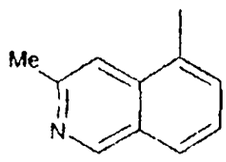
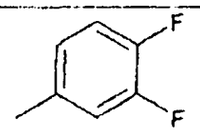
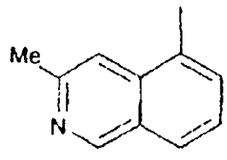
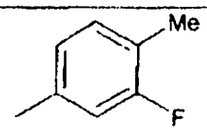
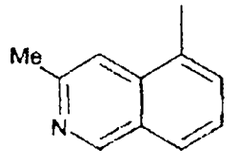
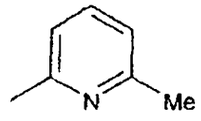
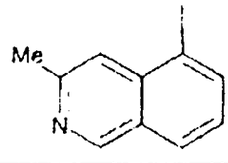
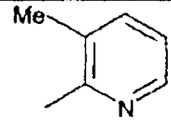
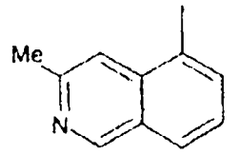
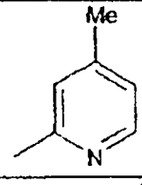
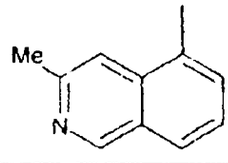
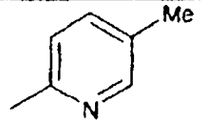
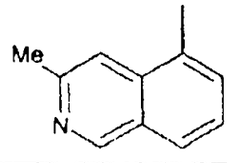
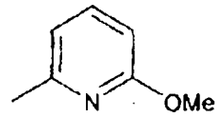
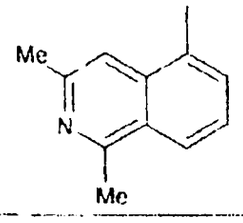
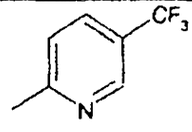
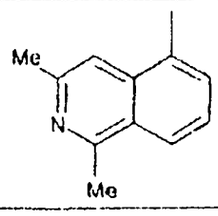
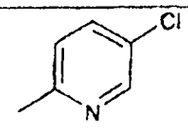
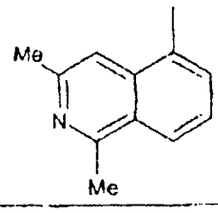
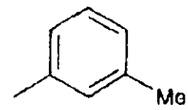
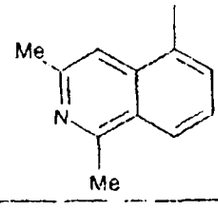
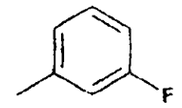
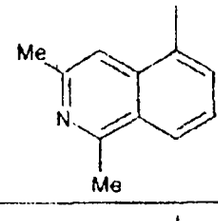
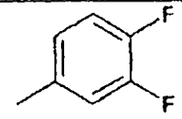
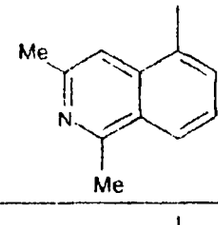
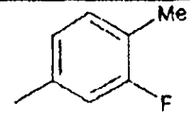
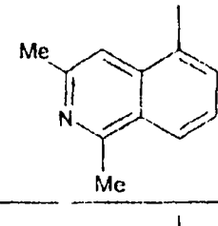
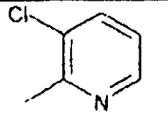
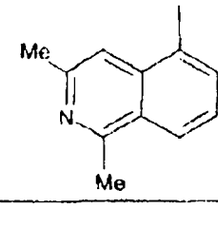
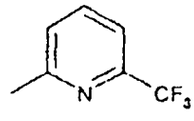
42		R	1	1		382
43		R	1	1		379
44		R	1	1		362
45		R	1	1		362
46		R	1	1		362
47		R	1	1		362
48		R	1	1		378
49		R	1	1		430

Cuadro 1 (Continuación)

50		R	1	1		396, 398
51		R	1	1		375
52		R	1	1		379
53		R	1	1		397
54		R	1	1		393
55		R	1	1		395, 397
56		R	1	1		430

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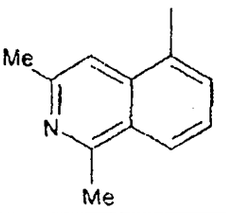
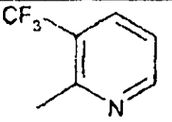
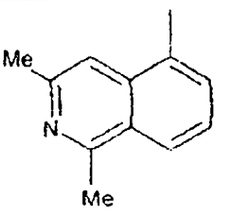
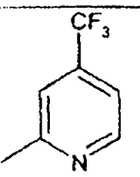
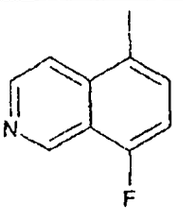
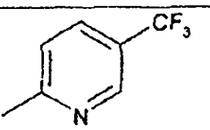
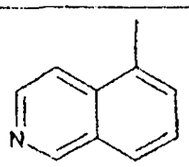
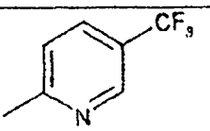
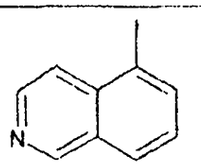
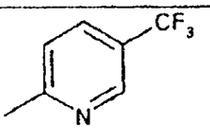
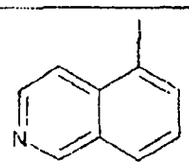
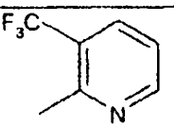
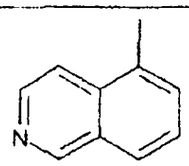
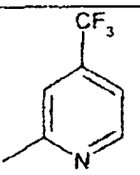
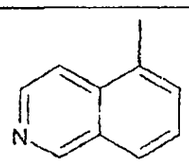
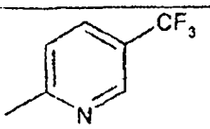
57		R	1	1		430
58		R	1	1		430
59		R	1	1		420
60			1	2		416
61			1	2		416
62		-	2	1		416
63		-	2	1		416
64		-	2	1		416

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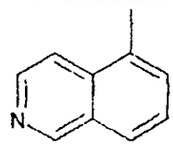
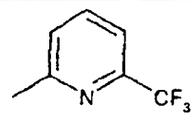
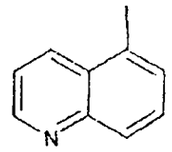
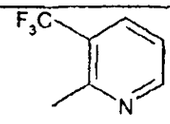
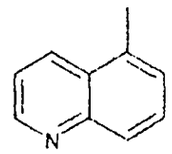
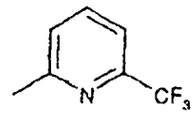
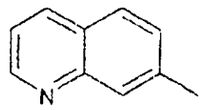
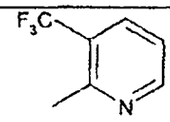
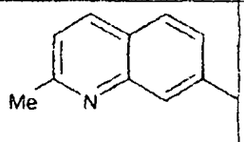
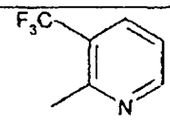
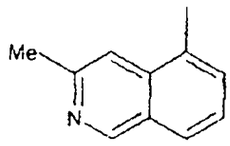
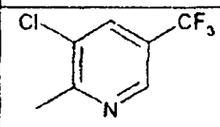
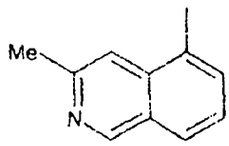
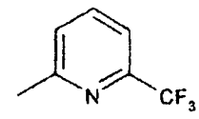
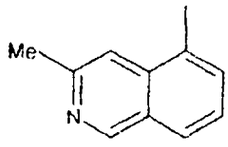
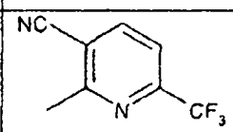
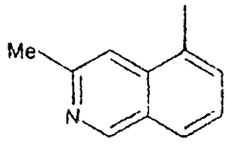
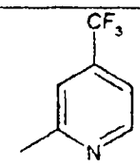
65		-	2	1		416
66		-	2	1		416
67		-	2	1		416
68		-	2	1		416
69		-	2	1		430
70		-	2	1		463, 465
71		-	2	1		430
72		-	2	1		455
74		-	2	1		430

112

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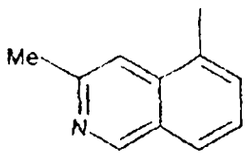
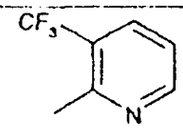
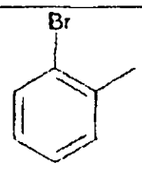
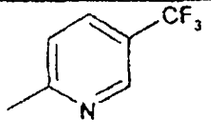
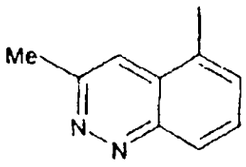
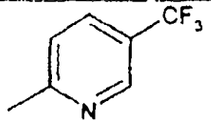
75		-	2	1		430
76		S	1	1		429, 431
77		R	1	1		417

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 4μM 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 pKb a partir de los valores de CI_{50} usando la ecuación de Cheng-Prusoff.

Todos los compuestos probados con el método anterior tenían una pKb > 6, y los compuestos preferidos tenían una pKb > 7.0.

b) Hiperalgesia inducida por FCA en conejillos de Indias

Se inyectaron 100 μl 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.

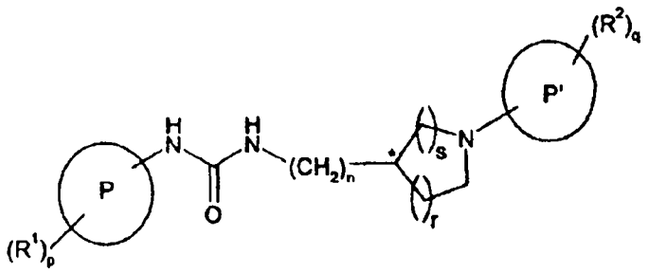
Se obtuvieron lecturas de conducta de hiperalgesia mecánica antes de la administración de FCA (lectura de animal intacto), después de administrar

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 pKb > 7.0 *in vitro* de acuerdo con el modelo (a) anterior, se probaron en este modelo y mostraron ser activos.

RESUMEN DE LA INVENCION

Se describen algunos compuestos de fórmula (I),



(I)

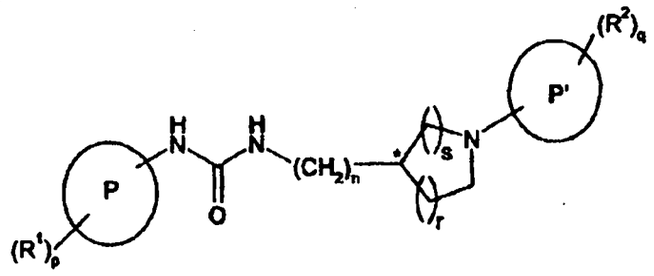
o una sal o solvato farmacéuticamente aceptable de los mismos, en donde R^1, R^2, P, P', n, p, q, r y s son como se define en la especificación; un procedimiento para preparar dichos compuestos; una composición farmacéutica que comprende dichos compuestos; y el uso de dichos compuestos y composición en medicina.

116

CAPÍTULO REIVINDICATORIO

(solicitud divisional)

1. Un compuesto de fórmula (I):



(I)

o una sal o solvato farmacéuticamente aceptable del mismo, en donde:

P representa isoquinolinil;

P' representa fenil;

R^1 y R^2 se seleccionan independientemente de -H, halógeno, alquilo, alcoxi, cicloalquilo, aralquilo, aralcoxi, cicloalquilalquilo, cicloalquilalcoxi, -CN, $-NO_2$, -OH, $-OCF_3$, $-CF_3$, $-NR^4R^5$, $-S(O)_mR^6$, $-S(O)_2NR^4R^5$, $-OS(O)_2R^6$, $-OS(O)_2CF_3$, $-O(CH_2)_XNR^4R^5$, $-C(O)CF_3$, -C(O)alquilo, -C(O)cicloalquilo, -C(O)aralquilo, -C(O)Ar, $-C(O)(CH_2)_xOR^6$, $-C(O)(CH_2)_XNR^4R^5$, -C(O)alcoxi, $-C(O)NR^4R^5$, $-(CH_2)_XC(O)$alcoxi, $-(CH_2)_XOC(O)R^6$, $-(CH_2)_XOR^6$, $-(CH_2)_XR^4R^5$, $-(CH_2)_XC(O)NR^4R^5$, $-(CH_2)_XN(R^4)C(O)R^6$, $-(CH_2)_XS(O)_2NR^4R^5$, $-(CH_2)_XN(R^4)S(O)_2R^6$, -ZAr, $-(CH_2)_XS(O)_2R^6$, $-(OCH_2)_XS(O)_2R^6$, $-N(R^4)S(O)_2R^6$, $-N(R^4)C(O)R^6$, $-(CH_2)_XN(R^4)S(O)_2R^6$, $-(CH_2)_XN(R^4)C(O)R^6$ o $-(CH_2)_XC(O)$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_{3-6}, (2-oxo)azacicloalcano de C_{3-6}, o una cadena de polimetileno de C_{5-8} interrumpida opcionalmente por heteroátomos tales 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;

m es 1 o 2;

n es 0:

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

r es 1;

s es 1; y

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

2. Un compuestos según la Reivindicación 1 donde:

R^1 y R^2 se seleccionan independientemente de halógeno, alquilo, alcoxi, -CN y $-CF_3$;

p y q son independientemente 0, 1 o 2.

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

****

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

RECEIVED
16 DEC 2003
WIPO PCT

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
LLK/P32894A		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB02/04206	13.09.2002	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	Date of completion of this report
04.04.2003	15.12.2003
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Seitner, I Telephone No. +31 70 340-2389

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:

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

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

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

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.

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-SUBSITUTED 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-

piperidinyl]-N'-(4-fluorophenyl)-urea and N-[1-[4,cyano-3-(trifluoromethyl)phenyl]-4-piperidinyl]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-NO_2-4-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).**

United States Patent Office 3,424,760 Patented Jan. 28, 1969

3,424,760

3-UREIDOPYRROLIDINES

Grover C. Helsley and William J. Welstead, Jr., Richmond, Va., assignors to A. H. Robins Company, Incorporated, Richmond, Va., a corporation of Virginia

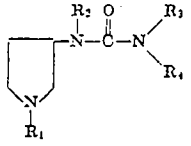
No Drawing. Filed Mar. 7, 1966, Ser. No. 532,093
U.S. Cl. 260—326.3 10 Claims
Int. Cl. C07d 27/04; A61k 27/00

ABSTRACT OF THE DISCLOSURE

New compounds which are 1-(1-substituted-3-pyrrolidinyl)-3-substituted ureas, the 1 substituent being phenyl, phenyllower-alkyl, or lower-cycloalkyl, and the 3 substituents (on the nitrogen atom) being on the one hand hydrogen or lower-alkyl and on the other hand hydrogen, lower-alkyl, or phenyl, the compounds exhibiting analgetic, central nervous system, and psychopharmacologic activities.

The present invention relates to certain novel heterocyclic organic compounds which may be referred to as substituted 3-ureidopyrrolidines, and is more particularly concerned with 1-(1-substituted-3-pyrrolidinyl)-3-substituted ureas, compositions thereof, and methods of making and using the same.

The invention is especially concerned with novel 3-ureidopyrrolidines having the formula:



(I)

wherein R_1 is selected from the group consisting of phenyl, phenyllower-alkyl, and lower-cycloalkyl,
wherein R_2 is selected from the group consisting of hydrogen, lower-alkyl, and phenyl,
wherein R_3 is selected from the group consisting of hydrogen and lower-alkyl, and
wherein R_4 is selected from the group consisting of hydrogen, lower-alkyl, and phenyl,
and acid addition salts thereof.

The compounds of the invention having the foregoing Formula I are generally characterized by important pharmacological activity, and exhibit analgetic, central nervous system and psychopharmacologic activities. More specifically, the present compounds may be utilized in such applications as appetite suppression, CNS stimulation, anticonvulsant activity, and sedation. In addition, the compounds are relatively non-toxic and exhibit advantageous therapeutic ratios.

The activity of the active agents of the present invention has been evidenced by tests in lower animals. It will be clearly understood that the distribution and marketing of any compound or composition falling within the scope of the present invention for use in human beings will of course have to be predicated upon prior approval by governmental agencies, such as the U.S. Federal Food and Drug Administration, which are responsible for and authorized to pass judgment on such questions.

It is accordingly an object of the present invention to provide certain new and useful 1-(1-substituted-3-pyrrolidinyl)-3-substituted ureas, compositions thereof, and methods of making and using the same. Other objects of the invention will be aparent to one skilled in the art, and still other objects will become apparent hereinafter.

In the definition of symbols in the foregoing Formula I and where they appear elsewhere thrughout this specification, the terms have the following significance.

The term "lower-alkyl" as used herein includes straight and branched chain radicals of up to eight carbon atoms inclusive and is exemplified by such groups as methyl, ethyl, propyl, isopropyl, butyl, sec. butyl, tertiary butyl, amyl, isoamyl, hexyl, heptyl, octyl, and the like. "Lower-alkoxy" has the formula -0-lower-alkyl. The term "lower-cycloalkyl" as used herein includes primarily cyclic alkyl radicals containing three up to nine carbon atoms inclusive and encompasses such groups as cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, methylcyclohexyl, propylcyclohexyl, ethylcylopentyl, propylcyclopentyl, dimethylcyclohexyl, cycloheptyl, and cyclooctyl. "Phenyllower-alkyl" are groups such as benzyl, phenethyl, methylbenzyl, phenpropyl, and the like.

When halogen is referred to herein, preferably but not necessarily a halogen of atomic weight in excess of nineteen but not greater than eighty is employed. Of the halogens, chlorine is preferred.

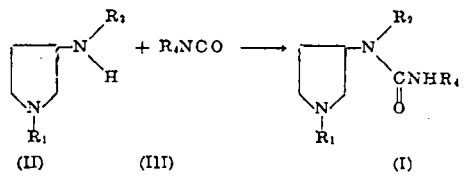
The compounds of Formula I may be converted to and are most conveniently employed in the form of nontoxic pharmaceutically acceptable acid addition salts. Such salts also have improved water-solubility. Although the nontoxic salts are preferred, any salt may be prepared for use as a chemical intermediate, as in the preparation of another but nontoxic acid addition salt. The free basic compounds of Formula I may be conveniently converted to their acid addition salts by reaction of the free base with the selected acid, preferably in the presence of an organic solvent inert to the reactants and reaction products under the conditions of the reaction. The acids which can be used to prepare the preferred nontoxic acid addition salts are those which produce, when combined with the free bases, salts the anions of which are relatively innocuous to the animal organism in therapeutic doses of the salts, so that beneficial physiological properties inherent in the free bases are not vitiated by side-effects ascribable to the anions.

Appropriate acid atddition salts are those derived from mineral acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, nitric acid, sulfuric acid, and phosphoric acid; and organic acids such as acetic acid, citric acid, lactic acid, fumaric acid, and tartaric acid. The preferred acid addition salt is the hydrochloride.

The acid addition salts are prepared either by dissolving the free base in an aqueous solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and the selected acid in an organic solvent, in which case the salt ordinarily separates directly or can be conventionally recovered by concentration of the solution or the like. Conversely the free base may be obtained conventionally by neutralizing the acid addition salt with an appropriate base such as ammonia, amonium hydroxide, sodium carbonate or the like (extracting the liberated base with a suitable solvent, illustratively ethyl acetate or benzene, drying the extract and evaporating to dryness or fractionally distilling, or in other conventional manner.

Methods of preparation

The preparation of 1-substituted-3-ureidopyrrolidines (I) when R_3 is hydrogen may be accomplished by mixing and reacting the appropriately substituted 3-aminopyrrolidine (II) with the appropriate isocyanate (III). The reaction sequence is illustrated by the following equation:



(II) (III) (I)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., 29/02/2008

Abogado
CARLOS OLARTE

ASUNTO		
	Radicación	04-22055-A
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	3975
	Folios	005

Patente de Invención	X	Patente de Modelo de Utilidad			
Vía Nacional					
Vía PCT (Fase Nacional)	X	Cap. I		Cap. II	X

No. Sol. Internacional PCT/US01/49355
Fecha de Presentación Internacional. 17/12/2001

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

La presente solicitud de patente se aceptó como divisional de la solicitud 04-22055 radicada el 2004-03-11.

1.1. Descripción: Folios: 65 a 115 como se radicó inicialmente.

1.2. Reivindicaciones: Folios 116 117 como se radicó inicialmente.

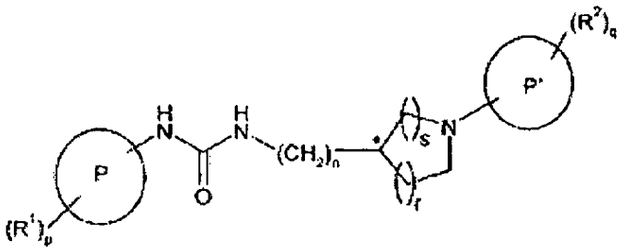
1.3. Prioridad: Folio 1 GB 0122156.3(13/09/2001); GB 0130547.3 (20/12/2001); GB 0130503.6 (20/12/2001) y GB 0130505.1 (20/12/2001).

2. Objeto de la invención

Título de la solicitud: PIRROLIDINIL UREAS COMO ANTAGONISTAS DE LOS RECEPTORES VANILOIDES.

Objeto de la invención:

El objeto de la presente solicitud de patente de invención consiste en compuestos de fórmula general (I) y a composiciones farmacéuticas de los mismos:



(I)

Reivindicaciones 1 y 2: Compuestos de fórmula (I) donde P= isoquinolil y P'= piridil.

Reivindicación 3: Una composición farmacéutica que comprende un compuesto de fórmula (I) y un vehículo farmacéuticamente aceptable.

El problema planteado en esta solicitud de patente es la necesidad de proveer compuestos con actividad antagónica al receptor vaniloide (VR1) útiles en el tratamiento del dolor.

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos de fórmula general (I), así como sus sales farmacéuticamente aceptables.

Se catalogó el objeto de la invención según la IPC en las categorías C07D 401/00, A61K 31/40 y A61P 29/00.

3. De la solicitud de Patente

3.1. Reivindicaciones *(artículo 30 D 486)*

Los sustituyentes R^1 y R^2 de la reivindicación 1 comprenden muchos sustituyentes con los cuales se pueden generar un número muy elevado de compuestos de fórmula (I), con lo cual no se delimita de manera concisa la materia que de acuerdo al capítulo descriptivo se desea proteger en esta solicitud de patente. De la misma manera, se utilizan términos como alquilo, alcoxi, aralquilo y cicloalquilo que son muy generales y poco concisos.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 13/09/2001, se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

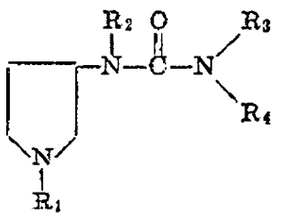
N°	Documento	Título	Fecha de publicación
D1	US 3424760	3-UREIDOPYRROLIDINES	28/01/1968

5. Análisis de patentabilidad *(artículo 14 D 486)*

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

5.1. Nivel Inventivo: *(artículo 18 D 486)*

El documento D1 describe compuestos de fórmula:



Si se remplazan los sustituyentes R_1 y R_4 por fenilo se obtienen 3-ureidopirrolidinas sustituidas similares a las de fórmula (I) de la presente solicitud, diferenciándose solamente en el sustituyente isoquinolinil del núcleo de 3-ureopirrolidina. Además de la similitud en la estructura, estos compuestos también tienen actividad analgésica.

Esta diferencia estructural no parecen concederle a los compuestos reivindicados un efecto técnico inesperado, ventaja o mejoría con respecto a los presentes en el estado de la técnica, ya que tienen el mismo núcleo básico de 3-ureopirrolidina que los hace útiles como analgésicos y los datos indicados en el capítulo descriptivo no demuestran mayor eficacia de los compuestos reivindicados en la presente solicitud con respecto a los del arte previo, por lo tanto se les puede considerar compuestos alternativos a los ya conocidos.

Teniendo en cuenta el problema técnico de la presente solicitud, el cual es la necesidad de proveer compuestos con actividad antagónica al receptor vaniloide (VR1) que sean útiles en el tratamiento del dolor, vemos que la información de la anterioridad citada le sugiere al experto en la materia, utilizando sus conocimientos generales, solucionar este problema técnico de manera obvia, por lo tanto se puede considerar que el objeto de la solicitud carece de nivel inventivo.

6. Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	US 3424760	1 a 3	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 14 MAR. 2008

CONCEPTO TECNICO No. 444	**EXAMINADOR TECNICO** Código No. 202077

V° OR