CSA625416

Industria y Comercio

SUPERINTENDENCIA

Organizacion y Digitalizacion CSA Ltda

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 08-52891

54. **TÍTULO** *DERIVADOS DE OXADIAZOL*

51. **CLASIFICACIÓN INTERNACIONAL** *C07D 271/06, A61K 31/4245,*

71. **SOLICITANTE** *7TM PHARMA A/S*

DOMICILIO *HOERSHOIM, DINAMARCA*

74. **APODERADO** *DILIA RODRIGUEZ D'ALEMAN*

22. **BOGOTÁ, D. C.,**

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-052891- -00000-0000
Fecha: 2008-05-23 15:11:09 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 92

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

[x] Patente de Invención [ ] Patente de Modelo de Utilidad

[x] Capítulo I. [ ] Capítulo II.

2 SOLICITANTE (71)	**Nombre:** 7TM PHARMA A/S **Dirección:** Fremtidsvej 3, DK-2970 Hoersholm, Dinamarca **Nacionalidad o domicilio:** Hoersholm, Dinamarca **Lugar de Constitución:** Dinamarca **Teléfono:** **Fax:** **E-mail**	**IDENTIFICACIÓN** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] **Número**
3 REPRESENTANTE O APODERADO (74)	Nombre: DILIA MARÍA RODRÍGUEZ D´ALEMAN Dirección: Carrera 11 No. 86-53, piso 6 Teléfono: 6 181088 Fax: 6350824 E-mail: clarkemodet@clarkemodet.com.co	**IDENTIFICACIÓN** C.C. [x] NIT [ ] C.E. [ ] Otro [ ] Número 41.654.882 TP 20824 CSJ
4 INVENTOR (ES) (72)	Nombre: **VER ANEXOS** Dirección: Nacionalidad o domicilio:	

5 PCT (86)

Solicitud Internacional No. **PCT/EP2006/011216** Fecha **22 de noviembre de 2006**

Publicación Internacional No. **WO 2007/062773 A1** Fecha **07 de junio de 2007**

6 TITULO (54) **DERIVADOS DE OXADIAZOL**

7 Clasificación Internacional (51) C07D 271/06

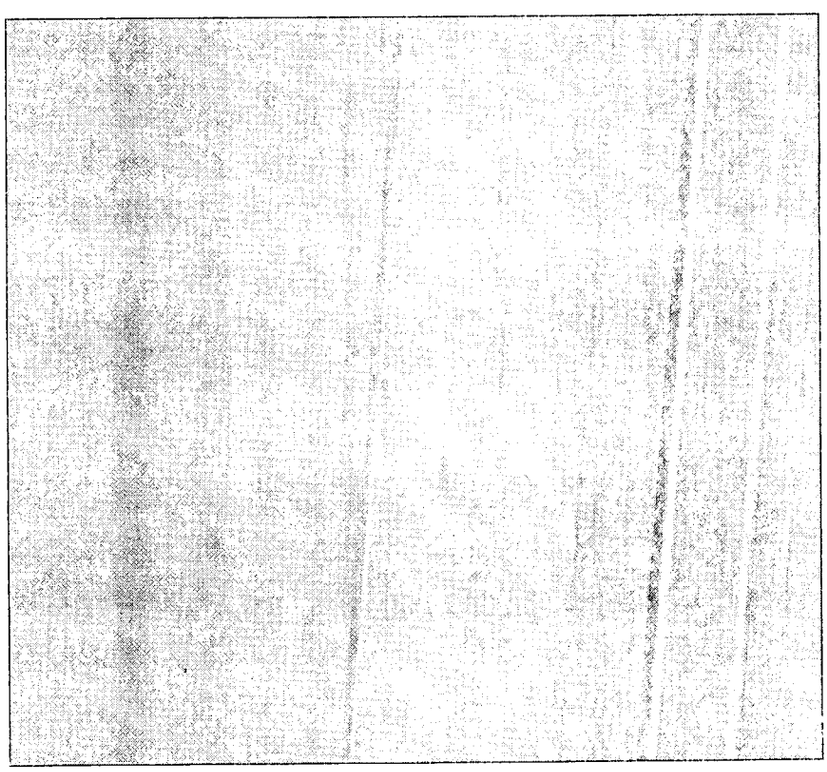
8 Prioridad SI [x] NO [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	GRAN BRETAÑA	**30 de noviembre de 2005**	**0524428.0**

9 Comprobante de pago No. 08 - 41.047 **Fecha** 21 de mayo de 2008

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
- [ ] Poderes si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso copia de 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 deposito 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 Opinión escrita, Request.

11 FIGURA CARACTERÍSTICA



12 Solicito la concesión de la patente

NOMBRE : DILIA MARÍA RODRÍGUEZ D'ALEMAN

FIRMA:

C.C. 41.654.882 **T.P. 20824**

As. P-1234

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-052891- -00000-0000

Fecha: 2008-05-23 15:11:09 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 92

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 41,047
FECHA : MAYO 21 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	693066	21/05/2008	27,730,000.00

***** 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	501,000.00
			TOTAL : $	501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

P-1234

2

ANEXOS

INVENTORES

1.) **RECEVEUR, Jean-Marie**
(7TM Pharma A/S, Fremtidsvej 3, DK-2970 Hoersholm, Dinamarca);

2.) **CHRISTENSEN, Ann**
(7TM Pharma A/S, Fremtidsvej 3, DK-2970 Hoersholm, Dinamarca);

3.) **GRIMSTRUP, Marie**
(7TM Pharma A/S, Fremtidsvej 3, DK-2970 Hoersholm, Dinamarca);

4.) **HOEGBERG, Thomas**
(7TM Pharma A/S, Fremtidsvej 3, DK-2970 Hoersholm, Dinamarca).

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 June 2007 (07.06.2007)

PCT

(10) International Publication Number
WO 2007/062773 A1

(51) International Patent Classification:
C07D 271/06 (2006.01) *A61K 31/4245* (2006.01)
C07D 413/04 (2006.01) *A61P 11/00* (2006.01)

(21) International Application Number:
PCT/EP2006/011216

(22) International Filing Date:
22 November 2006 (22.11.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0524428.0 30 November 2005 (30.11.2005) GB

(71) Applicant *(for all designated States except US)*: **7TM PHARMA A/S** [DK/DK]; Fremtidsvej 3, DK-2970 Hoersholm (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **RECEVEUR, Jean-Marie** [FR/DK]; 7TM Pharma A/S, Fremtidsvej 3, DK-2970 Hoersholm (DK). **CHRISTENSEN, Ann** [DK/DK]; 7TM Pharma A/s, Fremtidsvej 3, DK-2970 Hoersholm (DK). **GRIMSTRUP, Marie** [DK/DK]; 7TM Pharma A/S, Fremtidsvej 3, DK-2970 Hoersholm (DK). **HOEGBERG, Thomas** [SE/SE]; 7TM Pharma A/S, Fremtidsvej 3, DK-2970 Hoersholm (DK).

(74) Agent: **WALLS, Alan, James**; P.O. Box 223, Tadworth, Surrey KT20 5YF (GB).

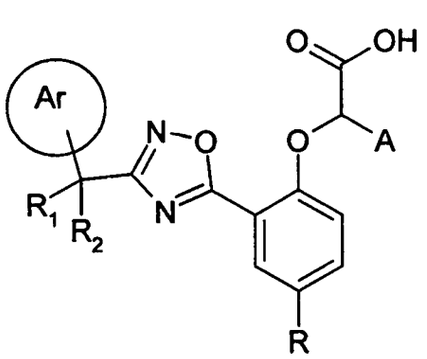
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search 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: OXADIAZOLE DERIVATIVES WITH CRTH2 RECEPTOR ACTIVITY



(I)

(57) Abstract: Compounds of formula (I) are CRTH2 ligands, useful for treatment of inflammatory, autoimmune, respiratory or allergy disease: wherein R_1 is hydrogen or methyl and R_2 is optionally substituted cycloalkyl, or optionally substituted non-aromatic heterocyclyl having 4 to 6 ring atoms; or R_1 and R_2, taken together with the carbon atom to which they are attached form an optionally substituted cycloalkyl, or optionally substituted non-aromatic heterocyclyl ring having 4 to 6 ring atoms; R is hydrogen or an optional substituent; the phenyl ring containing the substituent R is optionally substituted by 1 , 2 or 3 optional substituents; A is hydrogen or C_1-C_3 alkyl; and ring Ar is an optionally substituted phenyl or 5- or 6- membered monocyclic heteroaryl ring.

WO 2007/062773 A1

OXADIAZOLE DERIVATIVES WITH CRTH2 RECEPTOR ACTIVITY

This invention relates to the use of a class of compounds which are ligands of the CRTH2 receptor (Chemoattractant Receptor-homologous molecule expressed on T Helper cells type 2), in the treatment of diseases responsive to modulation of CRTH2 receptor activity, principally diseases having a significant inflammatory component. The invention also relates to novel members of that class of ligands and pharmaceutical compositions containing them.

Many classes of antiinflammatory agents are known, including the non-steroidal antiinflammatory compounds known as NSAIDs and the inhibitors of cyclooxygenase (COX-1 and COX-2). Benzoylphenylacetic acid and some benzophenone derivatives with carboxymethoxy substituents in one of the rings have been identiified as antiinfammatory agents (see, for example, Khanum et. al. Bioorganic Chemistry Vol 32, No. 4, 2004, pages 211-222 and the references cited therein). Some o-phenyl carbamoyl-phenoxyacetic acids and o-benzamido-phenoxymethyl tetrazoles have been reported as potential antiinflammatory agent, see for example Drain et. al. J. Pharm. Pharmac., 1971, 23, 857-864, and ibid 1970, 22, 684-693. WO 99/15520 discloses a few benzophenone derivatives with carboxymethoxy or tetrazolylmethoxy substituents in one of the rings, synthesised as members of a group of compounds said to have activity as inhibitors of peroxisome proliferator-activated receptor (PPAR), and utility in a variety of disease states including diabetes, cardiac disease, andcirculatory disease.

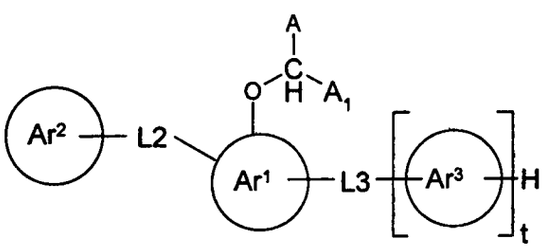
The natural ligand of the G-protein coupled receptor CRTH2 is prostaglandin D2. As its name implies, CRTH2 is expressed on T helper cells type 2 (Th2 cells) but it is also known to be expressed on eosinophils and basophil cells. Cell activation as a result of binding of PGD2 to the CRTH2 receptor results in a complex biological response, including release of inflammatory mediators. Elevated levels of PGD2 are therefore associated with many diseases which have a strong inflammatory component, such as asthma, rhinitis and allergies. Blocking binding of PGD2 to the CRTH2 receptor is therefore a useful therapeutic strategy for treatment of such diseases.

Some small molecule ligands of CRTH2, apparently acting as antagonists of PGD2, are known, for example as proposed in the following patent publications: WO

03/097042, WO 03/097598, WO 03/066046, WO 03/066047, WO 03/101961, WO 03/101981, GB 2388540, WO 04/089885 and WO 05/018529.

The structures of PGD2 antagonist compounds referred to in some of the foregoing publications have a bicyclic or tricyclic core ring system related to the indole core of indomethacin, a known anti-inflammatory agent, now known to bind to CRTH2. The present invention arises from the identification of a class of compounds having a monocyclic core whose substituent moieties are selected and orientated by the monocyclic core to interact with and bind to CRTH2. The class of compounds with which this invention is concerned are thus capable of modulating CRTH2 activity, and are useful in the treatment of diseases which benefit from such modulation, for example asthma, allergy and rhinitis.

Our copending international application PCT/EP2005/005884 is concerned with the use of a compound of formula (IA) or a salt, hydrate or solvate thereof in the manufacture of a composition for the treatment of disease responsive to modulation of CRTH2 receptor activity:



(IA)

wherein

A represents a carboxyl group –COOH, or a carboxyl bioisostere;

A_1 is hydrogen or methyl;

ring Ar^1 is an optionally substituted phenyl ring or 5- or 6-membered monocyclic heteroaryl ring, in which AA_1CHO- and L2 are linked to adjacent ring atoms;

rings Ar^2, Ar^3 each independently represent a phenyl or 5- or 6-membered monocyclic heteroaryl ring, or a bicyclic ring system consisting of a 5- or 6-membered carbocyclic or heterocyclic ring which is benz-fused or fused to a 5- or 6-membered monocyclic heteroaryl ring, said ring or ring system being optionally substituted;

t is 0 or 1;

L2 and L3 each independently represents a divalent radical of formula $-(Alk^1)_m-(Z)_n-(Alk^2)_p$ wherein

m, n and p are independently 0 or 1,

Alk^1 and Alk^2 are independently optionally substituted straight or branched chain C_1-C_3 alkylene or C_2-C_3 alkenylene radicals which may contain a compatible –O-, -S- or –NR- link wherein R is hydrogen or C_1-C_3 alkyl, and

Z is –O-; -S-; -C(=O)-; -SO_2-; -SO-; -NR-, -$NRSO_2$-, -SO_2NR-, -C(=O)NR-, -NRC(=O)-, -NRCONH-, -NHCONR-, -NRC(=NR)NH-, -NHC(=NR)NR-, –C(R)=N-NR-, or –NR-N=C(R)- wherein R is hydrogen or C_1-C_3 alkyl; or a divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical,

PROVIDED THAT

(A) the total length of L2 and L3 does not exceed that of an unbranched saturated chain of 10 carbon atoms; and

(B) L2 is not –C(=O)-, -C(=O)NR-, or -NRC(=O)- when Ar^2 is optionally substituted phenyl; and

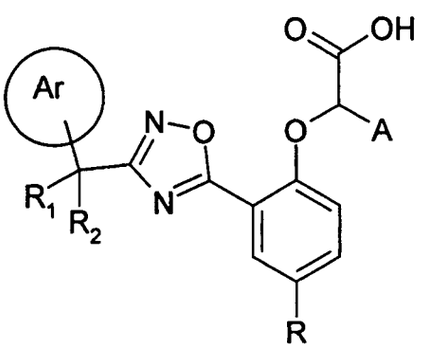
(C) (a) L2 is not a bond and (b) p in L2 is not 0 when n is 1 and Z is aryl or heteroaryl, and

(D) (a) L2 is not –O-, -SO_2-, -NR-, -CHR^XR^Y- or –$CH(R^X)(OR^Y)$-, wherein R^X and R^Y are independently hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_7 cycloalkyl, or join to form a ring, and (b) when p is 1 and n is 1 and Z is aryl or heteroaryl then Alk^2 is not -CHR^XR^Y- or –$CH(R^X)(OR^Y)$-, wherein R^X and R^Y are independently hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_7 cycloalkyl, or join to form a ring.

Since it is not yet published, a copy of the description part of the above-mentioned document PCT/EP2005/005884 is attached as an APPENDIX.

The present invention is concerned with a compounds related to those of PCT/EP2005/005884, having an arylmethyloxadiazolyl radical attached to a phenyl ring corresponding to ring Ar^1 of the compounds of PCT/EP2005/005884, said radical having a specific substitution as described below, on the carbon atom between the aryl and oxadiazole rings.

According to the present invention, there is provided compound of formula (I) or a salt, hydrate or solvate thereof other than {4-bromo-2-[3-(1-phenylcyclopropyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid or a salt, hydrate or solvate thereof:



(I)

wherein

R_1 is hydrogen or methyl and R_2 is optionally substituted cycloalkyl, or optionally substituted non-aromatic heterocyclyl having 4 to 6 ring atoms; or **R_1 and R_2**, taken together with the carbon atom to which they are attached form an optionally substituted cycloalkyl, or optionally substituted non-aromatic heterocyclyl ring having 4 to 6 ring atoms;

R is hydrogen or an optional substituent;

the phenyl ring containing the substituent R is optionally substituted by 1, 2 or 3 optional substituents;

A is hydrogen or C_1-C_3 alkyl;

ring Ar is an optionally substituted phenyl or 5- or 6-membered monocyclic heteroaryl ring.

The compound {4-bromo-2-[3-(1-phenylcyclopropyl)-[1,2,4]oxadiazol-5-yl]phenoxy}-acetic acid (and its salts, hydrates and solvates) has formula (I) above wherein A is

hydrogen, Ar is phenyl, R is bromo, and R_1 and R_2 taken together with the carbon atom to which they are attached form a cyclopropyl ring. That compound is excluded from all aspects of the present invention because it is specifically disclosed in PCT/EP2005/005884.

In another aspect, the invention provides a method of treatment of a subject suffering from a disease responsive to modulation of CRTH2 receptor activity, which comprised administering to the subject an amount of a compound (I) as defined and described above effective to ameliorate the disease.

In particular, compounds with which the invention is concerned are useful in the treatment of disease associated with elevated levels of prostaglandin D2 (PGD2) or one or more active metabolites thereof.

Examples of such diseases include asthma, rhinitis, allergic airway syndrome, allergic rhinobronchitis, bronchitis, chronic obstructive pulmonary disease (COPD), nasal polyposis, sarcoidosis, farmer's lung, fibroid lung, cystic fibrosis, chronic cough, conjunctivitis, atopic dermatitis, Alzheimer's disease, amyotrophic lateral sclerosis, AIDS dementia complex, Huntington's disease, frontotemporal dementia, Lewy body dementia, vascular dementia, Guillain-Barre syndrome, chronic demyelinating polyradiculoneurophathy, multifocal motor neuropathy, plexopathy, multiple sclerosis, encephalomyelitis, panencephalitis, cerebellar degeneration and encephalomyelitis, CNS trauma, migraine, stroke, rheumatoid arthritis, ankylosing spondylitis, Behçet's Disease, bursitis, carpal tunnel syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, dermatomyositis, Ehlers-Danlos Syndrome (EDS), fibromyalgia, myofascial pain, osteoarthritis (OA), osteonecrosis, psoriatic arthritis, Reiter's syndrome (reactive arthritis), sarcoidosis, scleroderma, Sjogren's Syndrome, soft tissue disease, Still's Disease, tendinitis, polyarteritis Nodossa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis, lupus erythematosus, systemic lupus erythematosus (SLE), type I diabetes, nephritic syndrome, glomerulonephritis, acute and chronic renal failure, eosinophilia fascitis, hyper IgE syndrome, sepsis, septic shock, ischemic reperfusion injury in the heart, allograft rejection after transplantations, and graft versus host disease.

However, the compounds with which the invention is concerned are primarily of value for the treatment asthma, rhinitis, allergic airway syndrome, and allergic rhinobronchitis.

As used herein, the term "(C_a-C_b)alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus when a is 1 and b is 6, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "cycloalkyl" refers to a monocyclic saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the unqualified term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical, and includes radicals having two monocyclic carbocyclic aromatic rings which are directly linked by a covalent bond. Illustrative of such radicals are phenyl, biphenyl and napthyl.

As used herein the unqualified term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O, and includes radicals having two such monocyclic rings, or one such monocyclic ring and one monocyclic aryl ring, which are directly linked by a covalent bond. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyridazinyl, triazinyl, indolyl and indazolyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in addition means a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O, and to groups consisting of a monocyclic non-aromatic radical containing one or more such heteroatoms which is covalently linked to another such radical or to a monocyclic carbocyclic radical. Illustrative of such radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl,

benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four compatible substituents, each of which independently may be, for example, $(C_1\text{-}C_6)$alkyl, cycloalkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy, hydroxy$(C_1\text{-}C_6)$alkyl, mercapto, mercapto$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylthio, halo (including fluoro, bromo and chloro), fully or partially fluorinated $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy or $(C_1\text{-}C_3)$alkylthio such as trifluoromethyl, trifluoromethoxy, and trifluoromethylthio, nitro, nitrile (-CN), oxo, phenyl, phenoxy, $-COOR^A$, $-COR^A$, $-OCOR^A$, $-SO_2R^A$, $-CONR^AR^B$, $-SO_2NR^AR^B$, $-NR^AR^B$, $OCONR^AR^B$, $-NR^BCOR^A$, $-NR^BCOOR^A$, $-NR^BSO_2OR^A$ or $-NR^ACONR^AR^B$ wherein R^A and R^B are independently hydrogen or a $(C_1\text{-}C_6)$alkyl group or, in the case where R^A and R^B are linked to the same N atom, R^A and R^B taken together with that nitrogen may form a cyclic amino ring. Where the substituent is phenyl or phenoxy, the phenyl ring thereof may itself be substituted by any of the above substituents except phenyl or phenoxy. An "optional substituent" may be one of the foregoing substituent groups.

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically acceptable salts, with bases such as ammonium hydroxide; alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-methyl-D-glucamine, choline tris(hydroxymethyl)amino-methane, L-arginine, L-lysine, N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic, p-toluenesulphonic, benzoic, benzenesunfonic, glutamic, lactic, and mandelic acids and the like.

Compounds with which the invention is concerned which may exist in one or more stereoisomeric form, because of the presence of asymmetric atoms or rotational restrictions, can exist as a number of stereoisomers with R or S stereochemistry at each chiral centre or as atropisomeres with R or S stereochemistry at each chiral

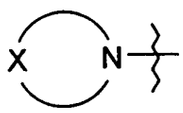
axis. The invention includes all such enantiomers and diastereoisomers and mixtures thereof.

Use of prodrugs, such as esters, of compounds (I) with which the invention is concerned is also part of the invention.

For use in accordance with the above aspects of the invention the following structural characteristics may be present, in any compatible combination, in the compounds (I):

In the case where R_1 is hydrogen or methyl, and R_2 is optionally substituted cycloalkyl, R_2 may be, for example, optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl;

In the case where R_1 is hydrogen or methyl, and R_2 is optionally substituted non-aromatic heterocyclyl having 4 to 6 ring atoms, the R_2 ring radical may be, for example, of formula

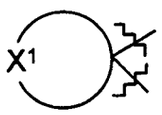


wherein the ring contains 4 to 6 ring atoms, and X is selected from $-CH_2-$, $-CH(C_1-C_3alkyl)-$, $-C(C_1-C_3alkyl)_2-$, $-CH(cycloalkyl)$, $-CH(NH_2)-$, $-C(CH_3)(NH_2)-$, $-CH(NH(C_1-C_3alkyl))-$, $-CH(N(C_1-C_3alkyl)_2)-$, $-CH(NH(cycloalkyl))-$, $-CH(NHCO(C_1-C_3alkyl))-$, $-CH(NHCO(cycloalkyl))-$, $-CH(NHSO_2(C_1-C_3alkyl))-$, $-CH(NHSO_2(cycloalkyl))-$, $-CH(OH)-$, $-CH(C_1-C_3alkoxy)-$, $-CH(cycloalkyloxy)-$, $-CO-$, $-SO_2-$, $-O-$, $-NH-$, $-N(C_1-C_3alkyl)-$, $-N(cycloalkyl)-$, $-CONH-$, $-CON(C_1-C_3alkyl)-$, $-CON(cycloalkyl)-$, $-N(CO(OC_1-C_3alkyl))-$, $-N(CO(O-cycloalkyl))-$, $-N(CO(CH_2OH))-$, $-SO_2NH-$, $-SO_2N(C_1-C_6alkyl)-$, $-SO_2N(cycloalkyl)-$, $-N(SO_2(C_1-C_3alkyl))-$, $-N(SO_2(cycloalkyl))-$, $-N(CO(C_1-C_3alkyl))-$, or $-N(CO(cycloalkyl))-$. Of the foregoing options for X, the following are presently preferred: $-CH_2-$, $-SO_2-$, $-CO-$, $-O-$, $-N(SO_2(C_1-C_3alkyl))-$, $-N(SO_2(cycloalkyl))-$, $-N(CO(C_1-C_3alkyl))-$, $-N(CO(cycloalkyl))-$, $-CONH-$, $-CON(C_1-C_3alkyl)-$, and $-CON(cycloalkyl)-$. Where, in the foregoing options for X, a C_1-C_3alkyl group is present, methyl is often preferred, and where a cycloalkyl group is present, cyclopropyl is often preferred.

In compounds of the invention, when R_1 is hydrogen or methyl, specific examples of groups R_2 include those present in the compounds of the examples herein.

In the case where R_1 and R_2, taken together with the carbon atom to which they are attached form an optionally substituted cycloalkyl ring, that ring may be, for example, optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

In the case where R_1 and R_2, taken together with the carbon atom to which they are attached form an optionally substituted non-aromatic heterocyclyl ring having 4 to 6 ring atoms, that ring may be, for example, of formula



wherein the ring contains 4 to 6 ring atoms and X^1 is selected from $-CH_2-$, $-CH(C_1-C_3alkyl)-$, $-C(C_1-C_3alky])_2-$, -CH(cycloalkyl), $-CH(NH_2)-$, $-CMe(NH_2)-$, $-CH(NH(C_1-C_3alkyl))-$, $-CH(N(C_1-C_3alkyl)_2)-$, -CH(NH(cycloalkyl))-, $-CH(NHCO(C_1-C_3alkyl))-$, -CH(NHCO(cycloalkyl))-, $-CH(NHSO_2(C_1-C_3alkyl))-$, $-CH(NHSO_2(cycloalkyl))-$, $-CH(OH)-$, $-CH(C_1-C_3alkoxy)-$, -CH(cycloalkyloxy])-, $-SO_2-$, -O-, -NH-, $-N(C_1-C_3alkyl)-$, -N(cycloalkyl)-, -CONH-, $-CON(C_1-C_3alkyl)-$, -CON(cycloalkyl)-, $-SO_2NH-$, $-SO_2N(C_1-C_6alkyl)-$, $-SO_2N(cycloalkyl)-$, $-N(SO_2(C_1-C_3alkyl))-$, $-N(SO_2(cycloalkyl))-$, $-N(CO(OC_1-C_3alkyl))-$, -N(CO(O-cycloalkyl))-, $-N(CO(CH_2OH))-$, $-N(CO(C_1-C_3alkyl))-$, or -N(CO(cycloalkyl))-. Of the foregoing options for X^1, the following are presently preferred: $-CH_2-$, $-SO_2-$, -O-, -CONH-, $-CON(C_1-C_3alkyl)-$, -CON(cycloalkyl)-, $-N(SO_2(C_1-C_3alkyl))-$, $-N(SO_2(cycloalkyl))-$, $-N(CO(C_1-C_3alkyl))-$, and -N(CO(cycloalkyl))-. Where, in the foregoing options for X^1, a C_1-C_3alkyl group is present, methyl is often preferred, and where a cycloalkyl group is present, cyclopropyl is often preferred

In compounds of the invention, when R_1 and R_2, taken together with the carbon atom to which they are attached form a ring, specific examples such rings include those present in the compounds of the examples herein.

A may be hydrogen, methyl, ethyl, n- or iso-propyl. Presently preferred are compounds wherein A is hydrogen or methyl.

R may be, for example, a substituent selected from fluoro, chloro, bromo, (C_1-C_3)alkyl, cycloalkyl, trifluoromethyl, (C_1-C_3)alkoxy, (C_1-C_3)alkylmercapto, trifluoromethoxy, trifluoromethylthio, cyano, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, (cycloalkyl)$NHSO_2$-, NH_2CO-, (C_1-C_3alkyl)NHCO-, (C_1-C_3alkyl)$_2$NHCO-, and (cycloalkyl)NHCO-.

Ring Ar corresponds to the ring Ar^2 of the compounds of APPENDIX 1, and may be, for example, any of the Ar^2 groups mentioned therein or present in the exemplified compounds of APPENDIX 1. Thus, the present Ar group may be, for example, optionally substituted phenyl, pyridyl, pyrimidyl, diazolyl, oxazolyl, triazinyl, quinolinyl, pyrrollyl, furanyl, or thiazolyl.

Likewise, optional substituents in Ar may be, for example, any of the optional Ar^2 substituents mentioned in, or present in the exemplified compounds of, APPENDIX 1. Thus, optional substituents in the present ring Ar may be selected from fluoro, chloro, bromo, (C_1-C_3)alkyl, trifluoromethyl, (C_1-C_3)alkoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, cyano, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, and (C_1-C_3alkyl)$_2NSO_2$-,

The phenyl ring containing R in the present compounds of formula (I) corresponds to the ring Ar^1 of the compounds of APPENDIX 1, so any of the optional Ar^1 substituents mentioned in, or present in the exemplified compounds of, APPENDIX 1 may also be present in the R-containing phenyl ring of the compounds of this invention, Thus, such optional substituents may be selected from fluoro, chloro, bromo, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, NH_2CO-, (C_1-C_3alkyl)NHCO-, (C_1-C_3alkyl)$_2$NHCO-, (cycloalkyl)NHCO-, C_1-C_6 alkyl, C_1-C_6 alkoxy, cycloalkyl, aryl, aryloxy, aryl(C_1-C_6)- or aryl(C_1-C_6 alkoxy)-.

The invention also includes pharmaceutical compositions comprising a compound belonging to the above described compounds of formula (I) together with a pharmaceutically acceptable carrier.

Compositions

As mentioned above, the compounds with which the invention is concerned are capable of modulating CRTH2 activity, and are useful in the treatment of diseases which benefit from such modulation. Examples of such diseases are referred to above, and include asthma, allergy and rhinitis.

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing treatment. Optimum dose levels and frequency of dosing will be determined by clinical trial, as is required in the pharmaceutical art.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets 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 suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

For topical application to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The drug may also be formulated for inhalation, for example as a nasal spray, or dry powder or aerosol inhalers.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

The compounds with which the invention is concerned may be administered alone, or as part of a combination therapy with other drugs used for treatment of diseases with a major inflammatory component. In the case of asthma, rhinitis, and allergic airway syndrome such drugs include corticosteroids, long-acting inhaled beta agonists, cromolyn, nedocromil, theophylline, leukotriene receptor antagonists, antihistamines, and anticholinergics (e.g. ipratropium), and are often administered as nasal sprays, dry powder or aerosol inhalers.

In the case of arthritis and related inflammatory diseases other known drugs include glucocorticoids, NSAIDs (Non Steroidal Anti-Inflammatory Drugs – conventional prostaglandin synthesis inhibitors, COX-2 inhibitors, salicylates), and DMARDs (disease-modifying anti-rheumatic drugs such as methotrexate, sulfasalazine, gold, cyclosporine).

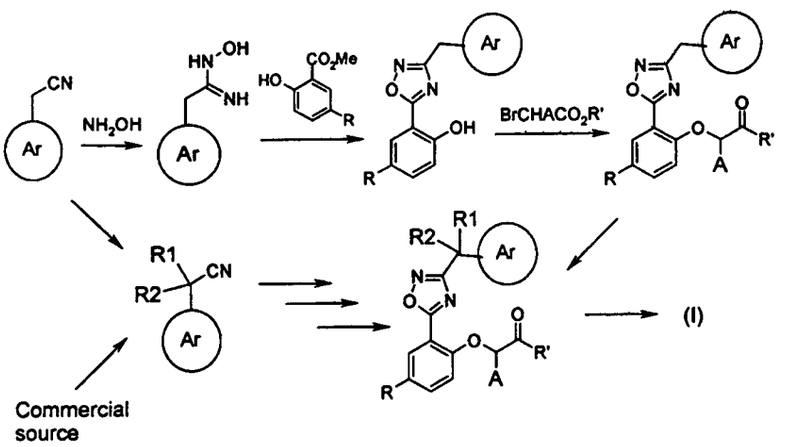
Synthetic Routes

There are multiple synthetic strategies for the synthesis of the compounds (I) with which the present invention is concerned, but all rely on known chemistry, known to

the synthetic organic chemist. Thus, compounds according to Formula I can be synthesised according to procedures described in the standard literature and are well-known to the one skilled in the art. Typical literature sources are "*Advanced organic chemistry*", 4th Edition (Wiley), J March, "*Comprehensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock , "*Handbook of Heterocyclic Chemistry*", 2nd Edition (Pergamon), A.R. Katritzky), review articles such as found in "*Synthesis*", "*Acc. Chem. Res.*" , "*Chem. Rev*", or primary literature sources identified by standard literature searches online or from secondary sources such as "*Chemical Abstracts*" or "*Beilstein*".

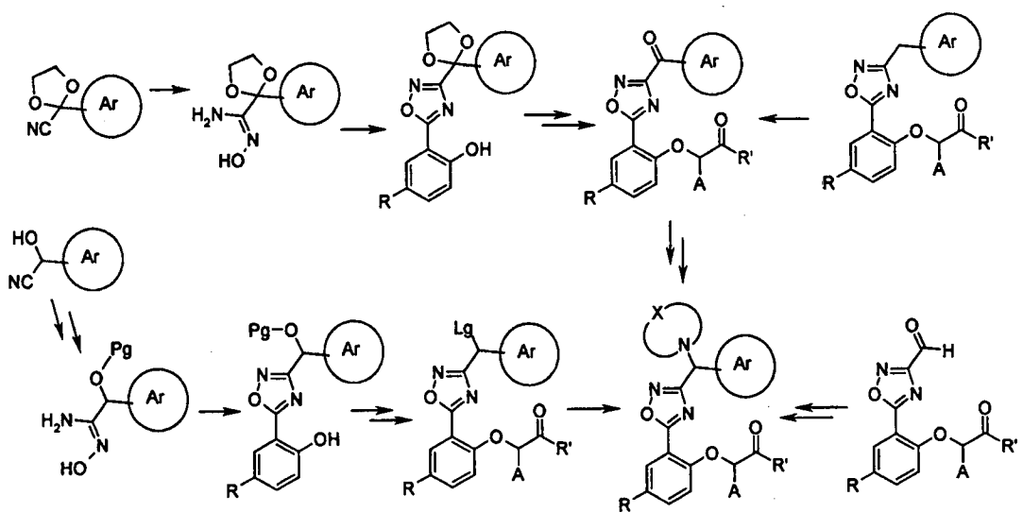
In particular, the compounds of the present invention may be synthesised by the method described in the general routes summarised in the following three paragraphs, and in the Examples below, or by methods generally described in relation to the compounds of APPENDIX 1.

The core oxadiazole of Formula I is normally formed by condensation of amidoximes and optionally substituted methyl benzoates. The acidic side chains are introduced by base catalysed substitution of the phenol with e.g. bromoacetate or 2-bromoproprionate esters followed by alkaline hydrolysis of the ester. The R1 and R2 groups are either available in commercial starting materials or introduced at the nitrile stage utilising base catalysed nucleophilic substitutions or R_1 and R_2 are introduced after assembly of the oxadiazole system.

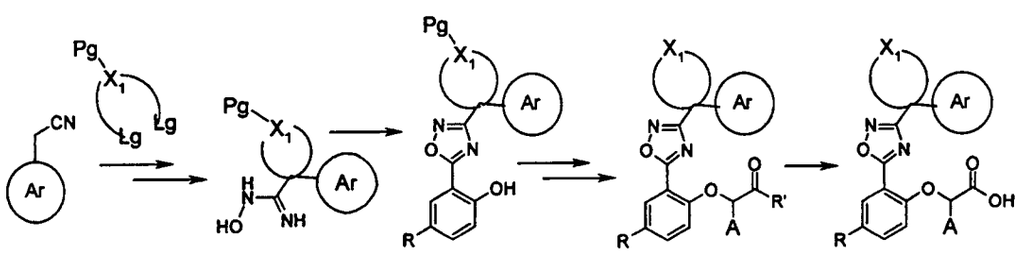


The R_2 group containing a cyclic nitrogen ring can be introduced from the corresponding ketone, obtained by standard oxidation conditions, by e.g. reductive alkylation. Optionally the ketone may be introduced in a protected form such as ketal at an earlier stage of the syntehesis. Alternatively, the R_2 group may be introduced by nucleophilic displacement of a corresponding compound containing a leaving

group Lg such as chlorine, bromine, mesyl,or tosyl as illustrated. Optionally the leaving group may be introduced in a protected form at an earlier stage of the syntehesis, e.g. from a cyanohydrin that is protected as acetal prior to the transformation of the nitrile into the oxadiazole. Another approach utilise an aldehyde function on the oxadiazole that is functionalised by a suitable metalorganic species containing the Ar moiety followed by conversion of the resulting hydroxyl group into the nitrogen containing ring.



The compounds having R_1 and R_2 adjoined in a common ring can for example be introduced by the following strategy where Lg denotes a leaving group such as chlorine, bromine, mesyl or tosyl and Pg denotes a protecting group when needed, such as t-Boc for nitrogen. After deprotection the X_1 group can be further manipulated by standard reactions, e.g. for X_1 being secondary amine, alkylation or acylation with a sulfonyl chlorides or acyl chlorides to produce alkylated amines, sulfonamides or carboxamides, respectively.

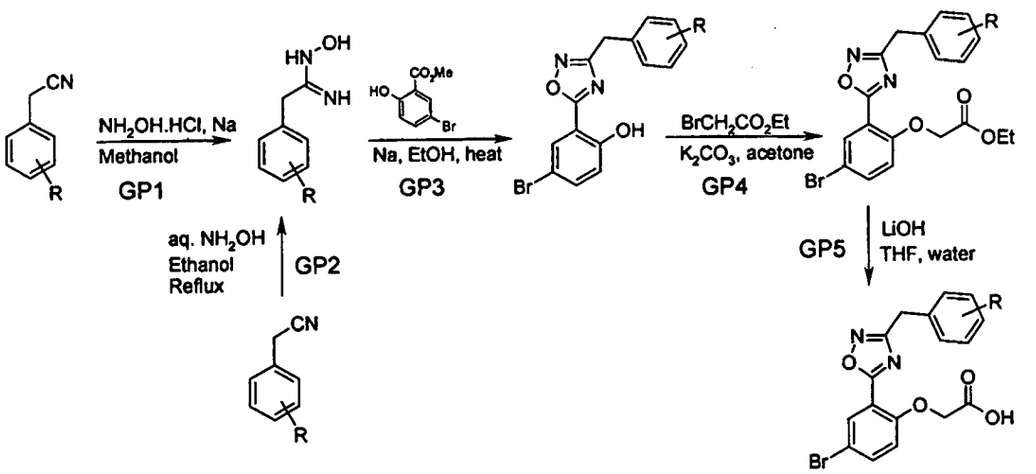


The following Examples illustrate the preparation of compounds with which this invention is concerned.

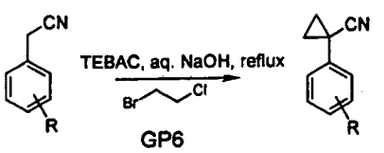
General comments:

Microwave chemistry was performed in a Personal Chemistry Emrys Optimizer. NMR spectra were obtained on a Bruker Avance AMX 300 MHz instrument. LC/MS was performed on an Agilent 1100-series instrument. LC/MS methods are as follows: An10p8: Column: XTerra MS C18; Flow: 1.0 mL/min; Gradient: 0-5 min: 15-100% MeCN in water, 5-7½ min: 100% MeCN; Modifier: 5 mM ammonium formate; MS-ionisation mode: API-ES (pos.). An10n8: Column: XTerra MS C18; Flow: 1.0 mL/min; Gradient: 0-5 min: 15-100% MeCN in water, 5-7½ min: 100% MeCN; Modifier: 5 mM ammonium formate; MS-ionisation mode: API-ES (neg.). TFA20p5: Column: Gemini 5µ C18 50x2.00mm; Flow: 1.2 mL/min; Gradient: 0-3½ min: 10-95% MeCN in water, 3½-4½ min: 95% MeCN; Modifier: 0.1% TFA; MS-ionisation mode: API-ES (pos.).

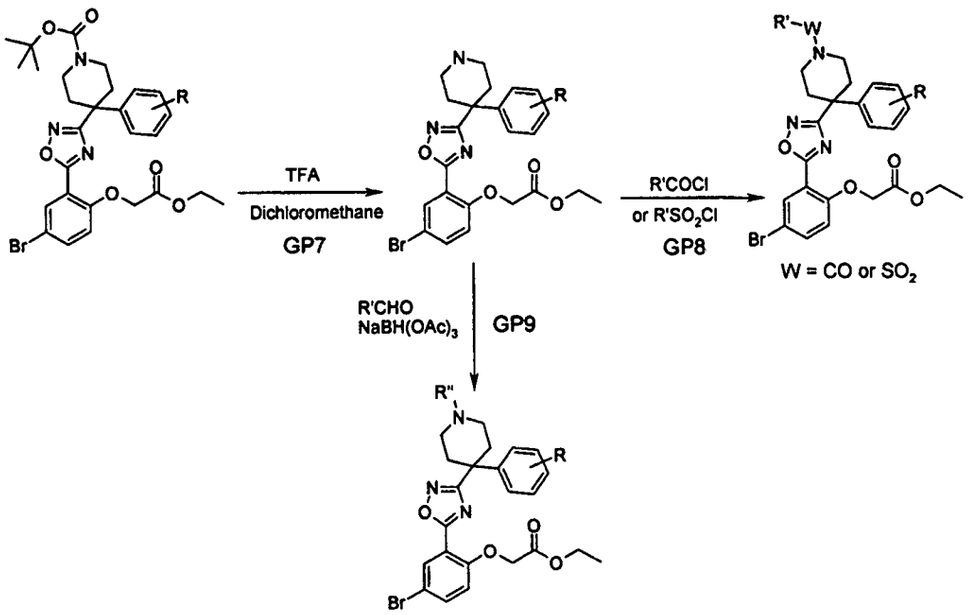
General Synthetic Route I



General Synthetic Route II



General Synthetic Route III



General procedure 1 (GP1)

Synthesis of amidoximes

Sodium (1.25 mmol) was added to dry methanol (1ml) to give solution A. Hydroxylamine hydrochloride (1.2 mmol) was dissolved in dry methanol (1mL) to give solution B. Solution A and B were mixed, cooled in an ice-bath and filtered. To the filtrate was then added the nitrile (1 mmol) and the reaction mixture was stirred over night at room temperature. The solvent was removed *in vacuo* to give the corresponding amidoxime. The compound was purified over silica gel chromatography (EtOAc/Heptane: 1/2) or used without further purification.

General procedure 2 (GP2)

Synthesis of amidoximes

To 50 ml of 96 % ethanol was added the nitrile (10 mmol) and 50 % hydroxylamine (40mmol) in water. The mixture was heated to reflux for 2 hours. After cooling, the solvent was removed *in vacuo* and water was added and the mixture was stirred until precipitation occurred. The precipitate was filtered and dried *in vacuo*.

General procedure 3 (GP3)

Synthesis of oxadiazoles

To a solution of sodium (3.3 mmol) in dry ethanol (10 mL) were successively added the amidoxime (1.15 mmol), molecular sieves (1g) and methyl benzoate (1 mmol).

After stirring for 12 h under reflux, the reaction mixture was cooled and filtered through a celite pad. The celite pad was washed with methanol and CH_2Cl_2. The solvent was removed *in vacuo* and the residue was stirred with water. The precipitate was filtered off and dried to give the corresponding oxadiazole. The compound was purified over silica gel chromatography (EtOAc:Heptane, 1:2) or used without further purification.

General procedure 4 (GP4):

Alkylation of phenol

The phenol (0.5 mmol) in acetone (1 mL) was added ethyl bromoacetate (85 mg, 0.5 mmol) or ethyl 2-bromopropionate (91 mg, 0.5 mmol) or ethyl-2-(trifluoromethylsulfonyl)propionate (125 mg, 0.5 mmol) and K_2CO_3 (75 mg, 0.54 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then concentrated in vacuo and the residue was partitioned between water and ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The product was used directly or purified by recrystallization from MeOH or by flash chromatography.

General procedure 5 (GP5):

Hydrolysis of ester

To the ester (0.10 mmol) in THF (0.5 mL) was added $LiOH \cdot H_2O$ (6.3 mg, 0.15 mmol) in water (0.5 mL). The reaction was stirred at room temperature for >2 h, 3% HCl was added until pH <1, and the mixture was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated to give the product.

General procedure 6 (GP6):

Synthesis of cyclopropyl

To a mixture of phenylacetonitrile (20 mmol) and triethylbenzylammoniumchloride (2 mmol) in 50 % aqueous sodium hydroxide (10 ml), was slowly added 1-bromo-2-chloroethane (30 mmol). The mixture was refluxed for 12 hours. After cooling, the mixture was partitioned between water and ethylacetate. The organic phase was dried (Na_2SO_4), reduced *in vacuum* and purified by flash chromatography (EtOAc:Heptane, 1:4).

General procedure 7 (GP7):

Removal of Boc protecting group

The Boc. Protected compound (2.6 mmol) was stirred in 10% TFA in dichloromethane (15ml) at room temperature for 12 hours. Sat. aqueous sodium carbonate was added and dichloromethane was removed *in vacuo*. The residue was partitioned between water and ethylacetate. The organic phase was dried (Na_2SO_4), reduced *in vacuo* and purified by flash chromatography (EtOAc, then EtOAc:MeOH, 1:1).

General procedure 8 (GP8):

Alkylation of piperidine nitrogen with RCOCl or RSO2Cl

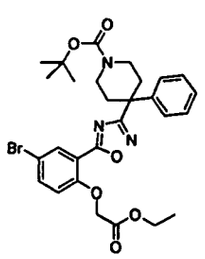
To a cooled (0°C) mixture of the" piperidine" (0.3 mmol) and triethylamine (0.33mmol) in dichlorometane (5 ml) was added the acid chloride or sulfonyl chloride (0.33mmol). The reaction mixture was stirred at room temperature for 2 hours. Solvent was removed in vacuo. The residue was partitioned between water and dichloromethane. The organic phase was dried (Na_2SO_4), reduced *in vacuo* and purified by flash chromatography (EtOAc:Heptane, 1:1) or used without further purification.

General procedure 9 (GP9):

Reductive alkylation of piperidine nitrogen

To a mixture of the "piperidine" (0.2 mmol) and sodium triacetoxyborohydride (0.9 mmol) in dichloromethane (8 ml) was added formaldehyde 37 % (0.9 mmol). The reaction mixture was stirred at room temperature overnight. Sat. aqueous sodium hydrogencarbonate was added and the compound extracted with dichloromethane. The organic phase was dried (Na_2SO_4), reduced *in vacuo* and used without further purification.

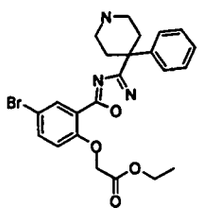
Preparation of Intermediates



IM1

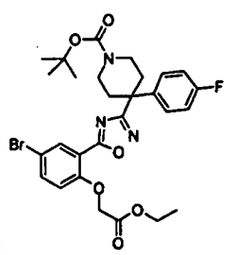
4-[5-(5-Bromo-2-ethoxycarbonylmethoxy-phenyl)-[1,2,4]oxadiazol-3-yl]-4-phenyl-piperidine-1-carboxylic acid tert-butyl ester. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 4-Cyano-4-phenyl-

piperidine-1-carboxylic acid tert-butyl ester according to GP2, GP3 and GP4: LC/MS (tfa20p5.m) Rt 3.22 min, *m/z* 566 $[M+H]^+$;



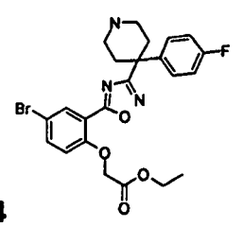
IM2

{4-Bromo-2-[3-(4-phenyl-piperidin-4-yl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid ethyl ester. Title compound was prepared from intermediate **IM1** according to GP7: LC/MS (tfa20p5.m) Rt 2.194 min, *m/z* 502 $[M+H]^+$;



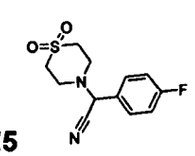
IM3

4-[5-(5-Bromo-2-ethoxycarbonylmethoxy-phenyl)-[1,2,4]oxadiazol-3-yl]-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 4-Cyano-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester according to GP2, GP3 and GP4: LC/MS (tfa20p5.m) Rt 3.75 min, *m/z* 628[M+Na].



IM4

(4-Bromo-2-{3-[4-(4-fluoro-phenyl)-piperidin-4-yl]-[1,2,4]oxadiazol-5-yl}-phenoxy)-acetic acid ethyl ester. Title compound was prepared from intermediate **IM3** according to GP7: LC/MS (tfa20p5.m) Rt 2.3 min, *m/z* 506 $[M+H]^+$;

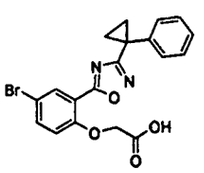


IM5

(1,1-Dioxo-1lambda*6*-thiomorpholin-4-yl)-(4-fluoro-phenyl)-acetonitrile. Title compound was prepared from 4-Fluoro-benzaldehyde and Thiomorpholine 1,1-dioxide as follow:

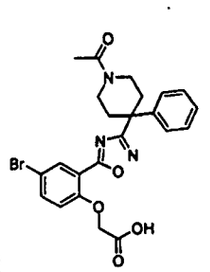
To a solution of Thiomorpholine 1,1-dioxide (2.52g, 18.64 mmol) in 1N aqueous HCl (18.64 ml, 18.64 mmol) was added sodium cyanide (0.822g, 16.78 mmol). After dissolution of sodium cyanide, a solution of 4-Fluoro-benzaldehyde (1ml, 9.32 mmol) in acetonitrile (38 ml) was added dropwise. The reaction mixture was stirred at room temperature for 3 days. Solvent was removed in vacuo and water was added. The mixture was stirred for ~10 minutes and the white precipitate was filtered off, washed with water and dried in vacuo to give title compound (1.74g, 6.48mmol, 70%). LC/MS (tfa20p5.m) Rt 2.01 min, *m/z* 269 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 3.12 (m, 8H), 4.94 (s, 1H), 7.16 (t, 2H), 7.53 (dd, 2H).

Examples



D1

{4-Bromo-2-[3-(1-phenylcyclopropyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxy-benzoic acid methyl ester and 1-phenyl-1-cyclopropanecarbonitrile according to GP1, GP3, GP4 and GP5: LC/MS (an10n8) Rt.2.756 *m/z* 413.4 $[M-H]^-$; ^1H NMR (DMSO-d_6): δ 0.92 (m, 2H), 1.11 (m, 2H), 4.38 (s, 2H), 6.63-6.66 (d, 1H), 6.79-6.88 (m, 3H), 6.93-6.95 (m, 2H), 7.25-7.29 (dd, 1H), 7.50-7.51 (d, 1H).

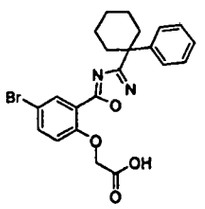


D2

{2-[3-(1-Acetyl-4-phenyl-piperidin-4-yl)-[1,2,4]oxadiazol-5-yl]-4-bromo-phenoxy}-acetic acid. Title compound was prepared from example **D5** and acetic anhydride as follow:

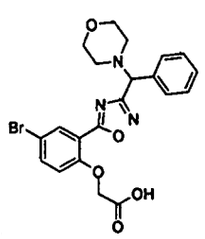
A suspension of example **D5** (0.04mmol) in acetic anhydride (0.5ml) was heated to 50°C for 1 hour. Solvent was removed *in vacuo* to give a colourless gum. Water was

added and the mixture was stirred vigorously until of a fine precipitate was formed. The precipitate was filtered off, washed with water and dried *in vacuo* to give title compound: LC/MS (an10p8.n) Rt 2,507 min, *m/z* 500 $[M-H]^-$; ^1H NMR (DMSO): δ 2.0 (s, 3H), 1.95-2.3 (m, 2H), 2.6-2.7 (m,2H), 2.8-2.9 (m,1H), 3.2-3.3 (m,1H), 3,75-3,85 (m,1H), 4,15-4,3 (m,1H), 4,9 (s,3H), 7,15-7.19 (d, 1H), 7.21-7,28 (1H), 7.31-7.43 (m,4H), 7.75-7.81(dd,1H), 8.05-8.07(d,1H).



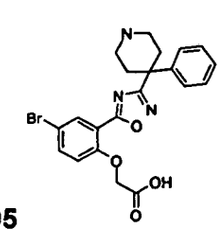
D3

{4-Bromo-2-[3-(1-phenyl-cyclohexyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 1-Phenyl-cyclohexanecarbonitrile according to GP1, GP3, GP4 and GP5: LC/MS (an10p8.m) Rt 3.21 min, *m/z* 457 $[M+H]^-$; ^1H NMR (DMSO): δ 1.3-1.7 (m, 6H), 2.0-2.1 (m, 2H), 2.5-2.6 (m, 2H), 4.9 (m, 2H), 7.13-7.25 (m, 2H), 7.28-7.41(m, 4H) , 7.74-7.80 (dd,1H), 8.00-8.03 (d,1H)



D4

{4-Bromo-2-[3-(morpholin-4-yl-phenyl-methyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and Morpholin-4-yl-phenyl-acetonitrile according to GP1, GP3, GP4 and GP5: LC/MS (an10n8.m) Rt 2,39 min, *m/z* 474 $[M-H]^-$; ^1H NMR (DMSO): δ 1.9 (s, 1H), 2.3-2.5 (m, 3H), 3.6 (s, 4H), 4.85 (s, 1H), 4.9 (s, 2H), 7.13-7.2 (d, 1H), 7.27-7.45 (m, 4H), 7.5-7.6 (m, 2H), 7.75-7.83 (d, 1H), 8.05-8.1 (s, 1H).

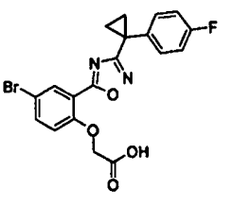


D5

{4-Bromo-2-[3-(4-phenyl-piperidin-4-yl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from intermediate **IM2** and lithium hydroxide as follow:

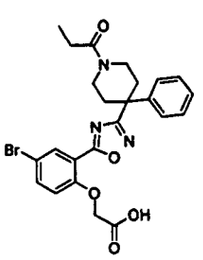
To the ester (0.10 mmol) in THF (0.5 mL) was added $LiOH \cdot H_2O$ (6.3 mg, 0.15 mmol) in water (0.5 mL). The reaction was stirred at room temperature for >2 h, aq. HCl was added until precipitation occurred. The precipitate was filtered off and dried *in vacuo* to give title compound.

. LC/MS (an10n8.m) Rt 2.33 min, *m/z* 458 $[M-H]^-$; ^1H NMR (DMSO): δ 2.3 (m, 2H), 2.8 (m, 2H), 2.95 (m, 2H), 3.2 (m, 2H), 4.4 (s, 2H), 6.9 (s, 1H), 7.3 (m, 1H), 7.4 (m, 4H), 7.65 (d, 1H), 8.0(s, 1H),



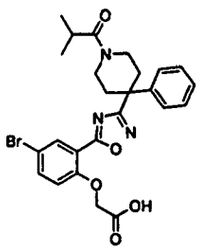
D6

(4-Bromo-2-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-yl}-phenoxy)-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 1-(4-Fluoro-phenyl)-cyclopropanecarbonitrile according to GP6, GP2, GP3, GP4 and GP5 LC/MS (tfa20p5.m) Rt 3.09 min, *m/z* 436 $[M+H]^+$; ^1H NMR (DMSO): δ 1.45 (m, 2H), 1.65 (m, 2H), 4.9 (s, 2H), 7.1-7.2 (m, 3H), 7.4-7.55 (m, 2H), 7.8 (dd, 1H), 8.0 (d, 1H).



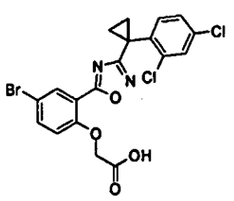
D7

{4-Bromo-2-[3-(4-phenyl-1-propionyl-piperidin-4-yl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from intermediate **IM2** and Propionyl chloride according to GP8 and GP5 LC/MS (tfa20p5.m) Rt 2.78 min, *m/z* 514 $[M+H]^+$; ^1H NMR (DMSO): δ 0.95-1.0 (t, 3H), 2.0-2.2 (m, 2H), 2.3-2.4 (m, 2H), 2.55-2.70 (m, 2H), 2.8-2.95(m, 1H),3.15-3.3(m, 1H), 3.75-3.9 (m, 1H), 4.15-4.3 (m, 1H), 4.85 (s, 2H), 7.13-7.18 (d, 1H), 7.2-7.28 (m, 1H), 7.31-7.43 (m, 4H), 7.74-7.80 (dd, 1H), 8.03-8.06 (d, 1H).



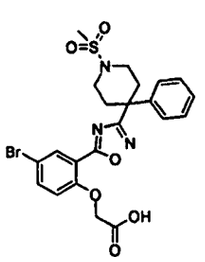
D8

{4-Bromo-2-[3-(1-isobutyryl-4-phenyl-piperidin-4-yl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from intermediate **IM2** and Isobutyryl chloride according to GP8 and GP5: LC/MS (tfa20p5.m) Rt 2.947min, *m/z* 528 $[M+H]^+$; ^1H NMR (DMSO): δ 0.95 1,05(m, 6H), 1.95-2.02 (m, 2H), 2.6-2.75 (m, 2H), 2.8-2.95 (m, 2H), 3.2-3.3 (m, 1H), 3.85-3.95 (m, 1H), 4.2-4.3 (m, 1H), 4.85 (s, 2H), 7.1-7.17 (d, 1H), 7,2-7.28 (m, 1H), 7.31-7.44 (m, 4H), 7.73-7.78 (dd, 1H), 8.5(d, 1H).



D9

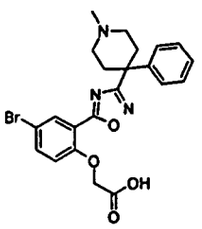
(4-Bromo-2-{3-[1-(2,4-dichloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-yl}-phenoxy)-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 1-(2,4-Dichloro-phenyl)-cyclopropanecarbonitrile according to GP6, GP2, GP3, GP4 and GP5: : LC/MS (tfa20p5.m) Rt 3.483 min, *m/z* 485 $[M+H]^+$; ^1H NMR (DMSO): δ 1.4-1.5 (m, 2H), 1,7-1.8(m, 2H), 4.6 (s, 2H), 7.0-7.04 (d, 1H), 7.44-7.49 (dd, 1H), 7.58-7.62 (d, 1H), 7.66-7.68 (d, 1H), 7.69-7.75 (dd, 1H), 7.96-7.99 (d, 1H).



D10

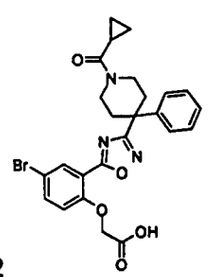
{4-Bromo-2-[3-(1-methanesulfonyl-4-phenyl-piperidin-4-yl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from intermediate **IM2** and Methanesulfonyl chloride according to GP8 and GP5:LC/MS (tfa20p5.m) Rt 2.725 min, *m/z* 538 $[M+H]^+$; ^1H NMR (DMSO): δ 2.2-2.3 (m, 2H), 2.7-3.0(m, 7H), 3.5-3.6 (m,

2H), 4.9(s, 2H), 7.14-7.19 (d, 1H), 7.21-7.29 (m, 1H), 7.32-7.44 (m, 4H), 7.75-7.80 (dd, 1H), 8.05-8.08 (d, 1H).



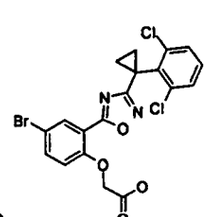
D11

{4-Bromo-2-[3-(1-methyl-4-phenyl-piperidin-4-yl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from intermediate **IM2** and formaldehyde according to GP9 and GP5: LC/MS (tfa20p5.m) Rt 1.849 min, *m/z* 474[M+H]$^+$; ^{1}H NMR (DMSO): δ 2.25-2.4 (m, 5H), 2.5 (m, 2H), 2.65-2,75 (m, 2H), 2.95-3.05(m, 2H), 4.7 (s, 2H), 7.03-7.1 (d, 1H), 7.2-7.29 (m, 1H), 7.3-7.45(m, 4H), 7.67-7.73 (dd, 1H), 8.01-8.04(d, 1H).



D12

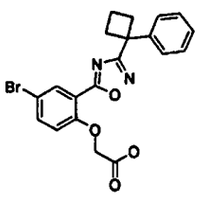
{4-Bromo-2-[3-(1-cyclopropanecarbonyl-4-phenyl-piperidin-4-yl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from intermediate **IM2** and Cyclopropanecarbonyl chloride according to GP8 and GP5: LC/MS (tfa20p5.m) Rt 2.82min, *m/z*528 [M+H]$^+$; ^{1}H NMR (DMSO): δ 0.68-0.70 (m,4H), 2.00-2.27 (m, 2H), 2.72 (m, 2H), 3.1 (m,1H), 4.08 (m, 1H), 4.18 (m, 2H), 4.91 (s, 2H), 7.15-7.18 (d, 1H), 7.25-7.27(m, 1H), 7.32-7.42 (m, 4H), X (7.76-7.80(dd, 1H), 8.05-8.06 (d, 1H),



D13

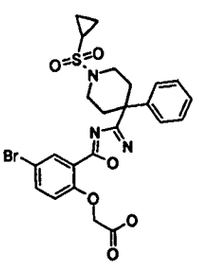
(4-Bromo-2-{3-[1-(2,6-dichloro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-yl}-phenoxy)-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 1-(2,6-Dichloro-phenyl)-cyclopropanecarbonitrile according to GP6, GP2, GP3, GP4 and GP5: : LC/MS (tfa20p5.m) Rt 3.313 min, *m/z* 485 [M+H]$^+$; ^{1}H NMR (DMSO): δ 1.54-1,58 (m, 2H),

1.93-1.98 (m, 2H), 4.89 (s, 2H), 7.15-7.19 (d, 1H), 7.39-7.55 (m, 2H), 7.77-7.81 (dd, 1H), 8.04-8.05 (d, 1H).



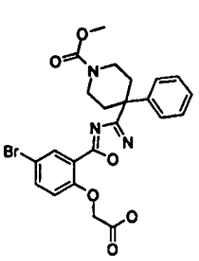
D14

{4-Bromo-2-[3-(1-phenyl-cyclobutyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 1-Phenyl-cyclobutanecarbonitrile according to GP6, GP2, GP3, GP4 and GP5: : LC/MS (an10p.8.m) Rt 2.90 min, *m/z* 429 $[M+H]^-$; ^1H NMR (DMSO): δ 1.97 (m, 1H), 2.08 (m, 1H), 2.68-2.72 (m, 2H), 2.87 (m, 2H), 4.90 (s,2H), 7.14-7.17 (d, 1H), 7.22-7.26 (m, 1H), 7.35-7.36 (m, 4H), 7.75-7.79 (dd, 1H), 8.00-8.02 (d, 1H), 13.17 (s, 1H).



D15

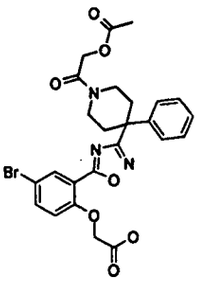
{4-Bromo-2-[3-(1-cyclopropanesulfonyl-4-phenyl-piperidin-4-yl)-[1,2,4] oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from intermediate **IM2** and Cyclopropanesulfonyl chloride according to GP8 and GP5:LC/MS (tfa20p5.m) Rt 2.9 min, *m/z* 564 $[M+H]^-$; ^1H NMR (DMSO): δ 0.98 (m,4H) , 2.2 (m,2H), 2.56 (m,1H), 2.75 (m,2H), 3.04 (m,2H), 3.58 (m,2H), 4.9 (s,2H), 7.15-7.18 (d,1H), 7.25-7.28 (m,1H), 7.33-7.42 (m,4H), 7.77-7.78 (dd,1H), 8.06-8.07 (d,1H), 13.2 (s,1H).



D16

4-[5-(5-Bromo-2-carboxymethoxy-phenyl)-[1,2,4]oxadiazol-3-yl]-4-phenyl-piperidine-1-carboxylic acid methyl ester. Title compound was prepared from intermediate **IM2** and Methyl chloroformate according to GP8 and GP5:LC/MS (tfa20p5.m) Rt 2.8 min, *m/z* 516 $[M+H]^-$; ^1H NMR (DMSO): δ 2.1 (m,2H), 2.65 (m,2H),

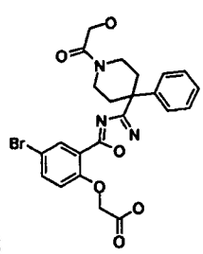
3.08 (m,2H), 3.6 (s,3H), 3.9 (m,2H), 4.9 (s,2H), 7.15-7.19 (d,1H), 7.21-7.28 (m,1H), 7.3-7.42 (m,4H), 7.76-7.81 (dd,1H), 8.30-8.50 (d,1H).



D17

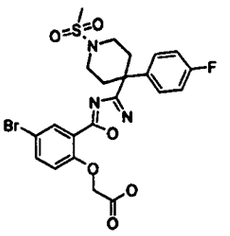
(2-{3-[1-(2-Acetoxy-acetyl)-4-phenyl-piperidin-4-yl]-[1,2,4]oxadiazol-5-yl}-4-bromo-phenoxy)-acetic acid. Title compound was prepared from **D5** and Acetoxyacetyl chloride as follows:

A mixture of D5 (230mg, 0.5 mmol), acetoxyacetyl chloride (120ul, 1.1 mmol) and triethylamine (160ul, 1.1 mmol) in tetrahydrofuran (10ml) was stirred at 0°C for 2 hours, under an argon atmosphere. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between dichloromethane and water. The phases were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified over silica gel chromatography (eluent: CH_2Cl_2/MeOH: 10/1) to give title compound (41mg, 0.07 mmol, 15%). LC/MS (tfa20p5.m) Rt 2.5 min, *m/z* 560[M+H]$^+$; ^{1}H NMR (DMSO): δ 2.0 (m,4H), 2.25 (m,1H), 2.65 (m2H), 2.9 (m,1H), 3.3 (m,1H), 3.7 (m,1H), 4.15 (m,1H), 4.42 (s,2H), 4.8 (d,2H), 6.95-6.99 (d,1H), 7.12-7.28 (m,1H), 7.31-7.41 (m,4H), 7.65-7.71 (dd,1H), 7.98-8.00 (d,1H).



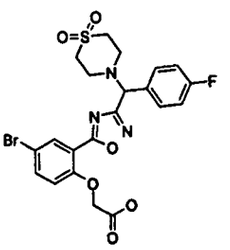
D18

(4-Bromo-2-{3-[1-(2-hydroxy-acetyl)-4-phenyl-piperidin-4-yl]-[1,2,4]oxadiazol-5-yl}-phenoxy)-acetic acid. Title compound was prepared from intermediate **IM2** and Acetoxyacetyl chloride according to GP8 and GP5:LC/MS (tfa20p5.m) Rt 2.4 min, *m/z* 516 [M+H]$^+$;



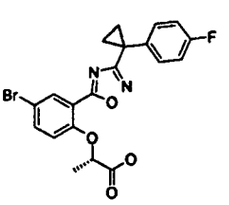
D19

(4-Bromo-2-{3-[4-(4-fluoro-phenyl)-1-methanesulfonyl-piperidin-4-yl]-[1,2,4]oxadiazol-5-yl}-phenoxy)-acetic acid. Title compound was prepared from intermediate **IM4** and Methanesulfonyl chloride according to GP8 and GP5: LC/MS (tfa20p5.m) Rt 2.8 min, *m/z* 556 $[M+H]^+$; ^1H NMR (DMSO): δ 2.35 (m,2H), 2.7-3.0 (m7H), 3.55 (m,2H), 4.9 (s,2H), 7.14-7.22 (m,3H), 7.42-7.50 (m,2H), 7.77-7.82 (dd,1H), 8.08-8.09 (d,1H).



D20

(4-Bromo-2-{3-[(1,1-dioxo-1lambda*6*-thiomorpholin-4-yl)-(4-fluoro-phenyl)-methyl]-[1,2,4]oxadiazol-5-yl}-phenoxy)-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and intermediate **IM5** according to GP1, GP3, GP4 and GP5: LC/MS (tfa20p5.m) Rt 2.62 min, *m/z* 540 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 3.12 (m, 8H), 4.78 (s, 2H), 5.14 (s, 1H), 6.97 (d, 1H), 7.10 (t, 2H), 7.48 (dd, 2H), 7.74 (dd, 1H), 8.23 (s, 1H).



D21

(S)-2-(4-Bromo-2-{3-[1-(4-fluoro-phenyl)-cyclopropyl]-[1,2,4]oxadiazol-5-yl}-phenoxy)-propionic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester , 1-(4-Fluoro-phenyl)-cyclopropanecarbonitrile and ethyl (R)-2-(trifluoromethylsulfonyl)propionate according to GP6, GP2, GP3, GP4 and GP5: LC/MS (tfa20p5.m) Rt 3.20 min, *m/z* 447$[M+H]^+$; ^1H NMR ($CDCl_3$): δ ,1.36-1.38 (m,2H), 1.61-1.65 (m,2H),1.69-1.72 (d,3H), 3.65-3.67 (m,1H), 6.88-6.91 (d,1H), 6.96-7.01 (m,2H), 7.37-7.41 (m,2H), 7.60-7.63 (dd,1H), 8.06-8.07 (d,1H).

Biological Assays

Materials and Methods

Generation/origin of the cDNA Constructs. The coding sequence of the human CRTH2 receptor (genbank accession no NM_004778) was amplified by PCR from a human hippocampus cDNA library and inserted into the pcDNA3.1(+) expression vector (invitrogen) via 5' Hind*III* and 3' EcoR*I*. To generate a CRTH2-Renilla luciferase (CRTH2-Rluc) fusion protein, the CRTH2 coding sequence without a STOP codon and Rluc were amplified, fused in frame by PCR and subcloned into the pcDNA3.1(+)Zeo expression vector (invitrogen). Human β-arrestin2 (β-arr2) N-terminally tagged with GFP^2 (βarr2-GFP^2) and Renilla luciferase were purchased from BioSignal Packard Inc, (Montreal, Canada). The sequence identity of the construct was verified by restriction endonuclease digests and sequencing in both directions on an ABI Prism (Applied Biosystems, Foster City, CA).

Cell Culture and Transfection. COS-7 cells were grown in Dulbecco's modified Eagle's medium (DMEM) 1885 supplemented with 10% fetal bovine serum, 100 units/ml penicillin, 1000 µg/ml streptomycin, and kept at 37°C in a 10% CO_2 atmosphere. HEK293 cells were maintained in Minimum Essential medium (MEM) supplemented with 10% (v/v) heat inactivated fetal calf serum (HIFCS), 2mM Glutamax™-I, 1% non essential amino acids (NEAA), 1% sodium pyruvate and 10 µg/ml gentamicin. For binding experiments, COS7 cells were transiently transfected with the CRTH2 receptor using a calcium phosphate-DNA coprecipitation method with the addition of chloroquine (as described by Holst et al., 2001). To perform the functional Bioluminescence Resonance Energy Transfer (BRET) assays, a HEK293 cell clone stably expressing βarr2-GFP^2 and CRTH2-Rluc was generated (CRTH2-HEK293 cells).

Binding assay. 24h after transfection COS-7 cells were seeded into 96well plates at a density of 30.000 cells/well. Competition binding experiments on whole cells were then performed about 18-24 h later using 0.1 nM [^{3}H]PGD2 (NEN, 172 Ci/mmol) in a binding buffer consisting of HBSS (GIBCO) and 10 mM HEPES. Competing ligands were diluted in DMSO which was kept constant at 1% (v/v) of the final incubation volume. Total and nonspecific binding were determined in the absence and presence of 10 µM PGD2. Binding reactions were routinely conducted for 3 h at 4°C and terminated by 2 washes (100 µl each) with ice cold binding buffer. Radioactivity was determined by liquid scintillation counting in a TOPCOUNTER (Packard) following

over night incubation in Microscint 20. Stable HEK293 cells were seeded at a density of 30.000 cells/well 18-24 h prior to the binding assay which was performed essentially as described for COS7 cells above. Determinations were made in duplicates.

BRET assay. Functional BRET assays were performed on HEK293 cells stably expressing human CRTH2-Rluc and GFP^2-β-arr2. Prior to their use in the BRET assay cells were detached and re-suspended in D-PBS with 1000 mg/L L-Glucose at a density of $2x10^6$ cells/mL. DeepBlueC™ was diluted to 50 µM in D-PBS with 1000 mg/L L-Glucose (light sensitive). 100 µL of cell suspension was transferred to wells in a 96-well microplate (white OptiPlate) and placed in the Mithras LB 940 instrument (BERTHOLD TECHNOLOGIES, Bad Wildbad, Germany). 12 µL/well agonist was then injected by injector 1 and 10 µL/well DeepBlueC™ was injected simultaneously by injector 2. Five seconds after the injections the light output from the well was measured sequentially at 400 nm and 515 nm, and the BRET signal (mBRET ratio) was calculated by the ratio of the fluorescence emitted by GFP^2-β-arr2 (515 nm) over the light emitted by the receptor-Rluc (400 nm). Antagonists were added before placing the microplates into the Mithras LB 940 and allowed to incubate for 15 minutes prior to the addition of agonist and DeepBlueC™. Compounds were dissolved in DMSO and the final DMSO concentration was kept constant at 1% in the assay.

Human eosinophil shape change assay. Blood was sampled from healthy volunteers according to a protocol approved by the Ethics Committee of the University of Graz and processed as described previously (Bohm et al., 2004). Preparations of polymorphonuclear leukocytes (containing eosinophils and neutrophils) were prepared by dextran sedimentation of citrated whole blood and Histopaque gradients. The resulting cells were washed and resuspended in assay buffer (comprising PBS with Ca^{2+}/Mg^{2+} supplemented with 0.1% BSA, 10 mM HEPES and 10 mM glucose, pH 7.4) at 5 x 10^6 cells/mL. Cells were incubated with the antagonists or vehicle (PBS or DMSO) for 10 min at 37°C and then stimulated with various concentration of the agonists (PGD2 or eotaxin) for 4 min at 37°C. To stop the reaction, samples were transferred to ice and fixed with 250 µL of fixative solution. Samples were immediately analyzed on a FACSCalibur flow cytometer (Becton Dickinson) and eosinophils were identified according to their autofluorescence in the FL-1 and FL-2 channels. Shape change responses were

quantified as percentage of the maximal response to PGD2 or eotaxin in the absence of an antagonist.

Materials

Tissue culture media and reagents were purchased from the Gibco invitrogen corporation (Breda, Netherlands). PGD2 was obtained from Cayman and [3H]PGD2 from NEN.

Data analysis

Curve analysis was performed with the GraphPadPrism software 3.0 (Graphpad Prism Inc., San Diego, USA) and IC_{50} values were calculated as a measure of the antagonistic potencies.

References

Holst B, Hastrup H, Raffetseder U, Martini L, Schwartz TW. Two active molecular phenotypes of the tachykinin NK1 receptor revealed by G-protein fusions and mutagenesis. J Biol Chem. 2001 Jun 8;276(23):19793-9. Epub 2001 Feb 22.

Biological data:

Compounds were tested in the receptor binding assay and the functional antagonist assay described below, and their IC_{50} values were assessed. The compounds are grouped in three classes:

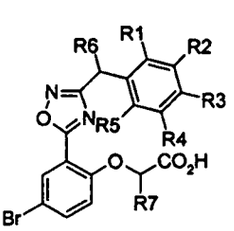
A: IC_{50} value lower than 0.5 µM

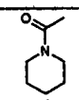
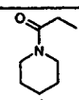
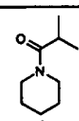
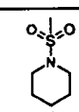
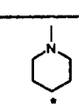
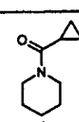
B: IC_{50} value between 0.5 µM and 5 µM

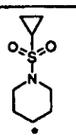
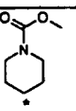
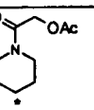
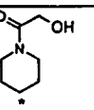
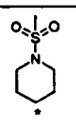
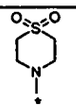
C: IC_{50} value higher than 5 µM

Table 1 gives the biological test results for the compounds synthesised above

Table 1

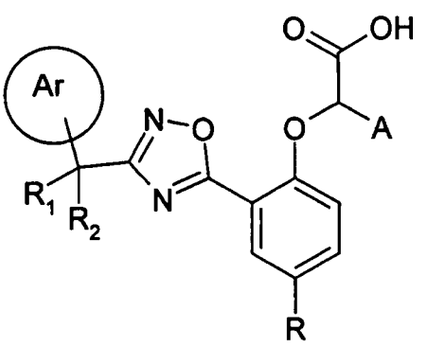


	R1	R2	R3	R4	R5	R6	R7	Binding IC_{50}	Antag. IC_{50}
D1	H	H	H	H	H		H	A	A
D2	H	H	H	H	H		H	A	A
D3	H	H	H	H	H		H	A	A
D4	H	H	H	H	H		H	A	A
D5	H	H	H	H	H		H	A	B
D6	H	H	F	H	H		H	A	A
D7	H	H	H	H	H		H	A	A
D8	H	H	H	H	H		H	A	A
D9	Cl	H	Cl	H	H		H	A	A
D10	H	H	H	H	H		H	A	A
D11	H	H	H	H	H		H	A	A
D12	H	H	H	H	H		H	A	A
D13	Cl	H	H	H	Cl		H	A	A
D14	H	H	H	H	H		H	A	A

D15	H	H	H	H	H		H	A	A
D16	H	H	H	H	H		H	A	A
D17	H	H	H	H	H		H	A	A
D18	H	H	H	H	H		H	A	A
D19	H	H	F	H	H		H	A	A
D20	H	H	F	H	H		H	A	A
D21	H	H	F	H	H		(S) CH_3	A	A

Claims:

1. A compound of formula (I) or a salt, hydrate or solvate thereof other than {4-bromo-2-[3-(1-phenylcyclopropyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid or a salt, hydrate or solvate thereof::



(I)

wherein

R_1 is hydrogen or methyl and R_2 is optionally substituted cycloalkyl, or optionally substituted non-aromatic heterocyclyl having 4 to 6 ring atoms; or **R_1 and R_2**, taken together with the carbon atom to which they are attached form an optionally substituted cycloalkyl, or optionally substituted non-aromatic heterocyclyl ring having 4 to 6 ring atoms;

R is hydrogen or an optional substituent;

the phenyl ring containing the substituent R is optionally substituted by 1, 2 or 3 optional substituents;

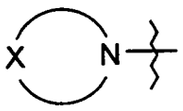
A is hydrogen or C_1-C_3 alkyl;

ring Ar is an optionally substituted phenyl or 5- or 6-membered monocyclic heteroaryl ring.

2. A compound as claimed in claim 1 wherein R_1 is hydrogen or methyl, and R_2 is optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

3. A compound as claimed in claim 1 wherein R_1 is hydrogen or methyl, and R_2 is cyclopropyl.

4. A compound as claimed in claim 1 wherein R_1 is hydrogen or methyl, and R_2 is a radical of formula



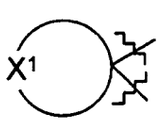
wherein the ring contains 4 to 6 ring atoms, and X is selected from $-CH_2-$, $-CH(C_1-C_3alkyl)-$, $-C(C_1-C_3alkyl)_2-$, -CH(cycloalkyl), $-CH(NH_2)-$, $-C(CH_3)(NH_2)-$, $-CH(NH(C_1-C_3alkyl))-$, $-CH(N(C_1-C_3alkyl)_2)-$, -CH(NH(cycloalkyl))-, $-CH(NHCO(C_1-C_3alkyl))-$, -CH(NHCO(cycloalkyl))-, $-CH(NHSO_2(C_1-C_3alkyl))-$, $-CH(NHSO_2(cycloalkyl))-$, -CH(OH)-, $-CH(C_1-C_3alkoxy)-$, -CH(cycloalkyloxy)-, -CO-, $-SO_2-$, -O-, -NH-, $-N(C_1-C_3alkyl)-$, -N(cycloalkyl)-, -CONH-, $-CON(C_1-C_3alkyl)-$, -CON(cycloalkyl)-, $-N(CO(OC_1-C_3alkyl))-$, -N(CO(O-cycloalkyl))-, $-N(CO(CH_2OH))-$, $-SO_2NH-$, $-SO_2N(C_1-C_6alkyl)-$, $-SO_2N(cycloalkyl)-$, $-N(SO_2(C_1-C_3alkyl))-$, $-N(SO_2(cycloalkyl))-$, $-N(CO(C_1-C_3alkyl))-$, or -N(CO(cycloalkyl))-.

5. A compound as claimed in claim 4 wherein X is–CH_2-, $-SO_2-$, -CO- (when adjacent to N), -O-, $-N(SO_2(C_1-C_3alkyl))-$, $-N(SO_2(cycloalkyl))-$, $-N(CO(C_1-C_3alkyl))-$ -N(CO(cycloalkyl))-, -CONH-, $-CON(C_1-C_3alkyl)-$, or -CON(cycloalkyl)-.

6. A compound as claimed in claim 1 wherein R_1 and R_2, taken together with the carbon atom to which they are attached form an optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl ring.

7. A compound as claimed in claim 6 wherein R_1 and R_2, taken together with the carbon atom to which they are attached form cyclopropyl ring.

8. A compound as claimed in claim 1 wherein R_1 and R_2, taken together with the carbon atom to which they are attached form a divalent ring of formula



wherein the ring contains 4 to 6 ring atoms and X^1 is selected from $-CH_2-$, $-CH(C_1-C_3alkyl)-$, $-C(C_1-C_3alky])_2-$, -CH(cycloalkyl), $-CH(NH_2)-$, $-CMe(NH_2)-$, $-CH(NH(C_1-C_3alkyl))-$, $-CH(N(C_1-C_3alkyl)_2)-$, -CH(NH(cycloalkyl))-,

-CH(NHCO(C_1-C_3alkyl))-, -CH(NHCO(cycloalkyl))-, -CH(NHSO$_2$(C_1-C_3alkyl))-, -CH(NHSO$_2$(cycloalkyl))-, -CH(OH)-, -CH(C_1-C_3alkoxy)-, -CH(cycloalkyloxy])-, -SO$_2$-, -O-, -NH-, -N(C_1-C_3alkyl)-, -N(cycloalkyl)-, -CONH-, -CON(C_1-C_3alkyl)-, -CON(cycloalkyl)-, -SO$_2$NH-, -SO$_2$N(C_1-C_6alkyl)-, -SO$_2$N(cycloalkyl)-, -N(SO$_2$(C_1-C_3alkyl))-, -N(SO$_2$(cycloalkyl))-, -N(CO(OC_1-C_3alkyl))-, -N(CO(O-cycloalkyl))-,-N(CO(CH$_2$OH))-, -N(CO(C_1-C_3alkyl))-, or -N(CO(cycloalkyl))-.

9. A compound as claimed in claim 8 wherein X^1 is -CH$_2$-, -SO$_2$-, -O-, -CONH-, -CON(C_1-C_3alkyl)-, -CON(cycloalkyl)-, -N(SO$_2$(C_1-C_3alkyl))-, -N(SO$_2$(cycloalkyl))-, -N(CO(C_1-C_3alkyl))-, or -N(CO(cycloalkyl))-.

10. A compound as claimed in any of the preceding claims wherein A is hydrogen or methyl.

11. A compound as claimed in any of the preceding claims wherein R is fluoro, chloro, bromo, (C_1-C_3)alkyl, cycloalkyl, trifluoromethyl, (C_1-C_3)alkoxy, (C_1-C_3)alkylmercapto, trifluoromethoxy, trifluoromethylthio, cyano, (C_1-C_3alkyl)SO$_2$-, NH$_2$SO$_2$-, (C_1-C_3alkyl)NHSO$_2$-, (C_1-C_3alkyl)$_2$NSO$_2$-, (cycloalkyl)NHSO$_2$-, NH$_2$CO-, (C_1-C_3alkyl)NHCO-, (C_1-C_3alkyl)$_2$NHCO-, or (cycloalkyl)NHCO-.

12. A compound as claimed in any of the preceding claims wherein ring Ar is optionally substituted phenyl, pyridyl, pyrimidyl, diazolyl, oxazolyl, triazinyl, quinolinyl, pyrrollyl, furanyl, or thiazolyl.

13. A compound as claimed in any of the preceding claims wherein optional substituents in Ar are selected from fluoro, chloro, bromo, (C_1-C_3)alkyl, cycloalkyl, trifluoromethyl, (C_1-C_3)alkoxy, trifluoromethoxy, trifluoromethylthio, cyano, NH$_2$CO-, (C_1-C_3alkyl)NHCO-, (C_1-C_3alkyl)$_2$NHCO-, (cycloalkyl)NHCO-, (C_1-C_3alkyl)SO$_2$-, NH$_2$SO$_2$-, (C_1-C_3alkyl)NHSO$_2$-, (cycloalkyl)NHSO$_2$-, and (C_1-C_3alkyl)$_2$NSO$_2$-.

14. A compound as claimed in any of claims 1 to 11 wherein Ar is a pyridone ring or a pyridine N-oxide ring.

15. A compound as claimed in any of the preceding claims wherein any optional substituents in the phenyl ring containing R are selected from fluoro, chloro, bromo, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, (C_1-C_3alkyl)SO$_2$-, NH$_2$SO$_2$-, (C_1-C_3alkyl)NHSO$_2$-, (C_1-C_3alkyl)$_2$NSO$_2$-, C_1-C_3alkyl, fluoroC_1-C_2alkyl,

difluoroC_1-C_2alkyl, C_1-C_3alkoxy, cycloalkyl, aryl, aryloxy, aryl(C_1-C_3)- or aryl(C_1-C_3alkoxy)-.

16. A pharmaceutical composition comprising a compound as claimed in any of the preceding claims, together with a pharmaceutically acceptable carrier.

17. Use of a compound as claimed in any of the preceding claims in the manufacture of a composition for the treatment of disease responsive to modulation of CRTH2 receptor activity.

18. A method of treatment of disease responsive to modulation of CRTH2 receptor activity comprising administering to a subject suffering such disease and effective amount of a compound as claimed in any of the preceding claims.

19. The use as claimed in claim 17 or a method as claimed in claim 18, wherein the disease is one associated with elevated levels of prostaglandin D2 (PGD2) or one or more active metabolites thereof.

20. The use as claimed in claim 17 or a method as claimed in claim 18, wherein the disease is an inflammatory, autoimmune, respiratory or allergy disease.

21. The use as claimed in claim 17 or a method as claimed in claim 18, wherein the disease is selected from asthma, rhinitis, allergic airway syndrome, allergic rhinobronchitis, bronchitis, chronic obstructive pulmonary disease (COPD), nasal polyposis, sarcoidosis, farmer's lung, fibroid lung, cystic fibrosis, chronic cough, conjunctivitis, atopic dermatitis, Alzheimer's disease, amyotrophic lateral sclerosis, AIDS dementia complex, Huntington's disease, frontotemporal dementia, Lewy body dementia, vascular dementia, Guillain-Barre syndrome, chronic demyelinating polyradiculoneurophathy, multifocal motor neuropathy, plexopathy, multiple sclerosis, encephalomyelitis, panencephalitis, cerebellar degeneration and encephalomyelitis, CNS trauma, migraine, stroke, rheumatoid arthritis, ankylosing spondylitis, Behçet's Disease, bursitis, carpal tunnel syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, dermatomyositis, Ehlers-Danlos Syndrome (EDS), fibromyalgia, myofascial pain, osteoarthritis (OA), osteonecrosis, psoriatic arthritis, Reiter's syndrome (reactive arthritis), sarcoidosis, scleroderma, Sjogren's Syndrome, soft tissue disease, Still's Disease, tendinitis, polyarteritis Nodossa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis,

lupus erythematosus, systemic lupus erythematosus (SLE), type I diabetes, nephritic syndrome, glomerulonephritis, acute and chronic renal failure, eosinophilia fascitis, hyper IgE syndrome, sepsis, septic shock, ischemic reperfusion injury in the heart, allograft rejection after transplantations, and graft versus host disease.

22. The use as claimed in claim 17 or a method as claimed in claim 18, wherein the disease is selected from asthma, rhinitis, allergic airway syndrome, and allergic rhinobronchitis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/011216

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D271/06 C07D413/04 A61K31/4245 A61P11/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/089885 A (ASTRAZENECA AB [SE]; BONNERT ROGER [GB]; BROUGH STEPHEN [GB]; DAVIES A) 21 October 2004 (2004-10-21) cited in the application claim 1	1-22
P,X	WO 2005/115382 A (7TM PHARMA AS [DK]; ULVEN TROND [DK]; FRIMURER THOMAS [DK]; RIST OEYST) 8 December 2005 (2005-12-08) cited in the application example D131	1-22

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2007	20/02/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	De Jong, Bart

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/011216

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/011216

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004089885 A	21-10-2004	AU 2004228599 A1	21-10-2004
		BR PI0409109 A	28-03-2006
		CA 2521425 A1	21-10-2004
		CN 1791572 A	21-06-2006
		EP 1611091 A1	04-01-2006
		JP 2006522118 T	28-09-2006
		KR 20050112123 A	29-11-2005
		MX PA05010682 A	12-12-2005
		US 2006264435 A1	23-11-2006
WO 2005115382 A	08-12-2005	AU 2005247110 A1	08-12-2005
		CA 2568766 A1	08-12-2005

DERIVADOS DE OXADIAZOL

Esta invención se refiere al uso de una clase de compuestos que son ligandos del receptor CRTH2 (Chemoattractant Receptor-homologous molecule expressed on T Helper cells type 2, molécula homóloga de receptor quimiotáctico expresada en células T cooperadoras de tipo 2), en el tratamiento de enfermedades sensibles a la modulación de la actividad del receptor CRTH2, principalmente enfermedades que tienen un componente inflamatorio significativo. La invención también se refiere a miembros novedosos de esta clase de ligandos y a composiciones farmacéuticas que los contienen.

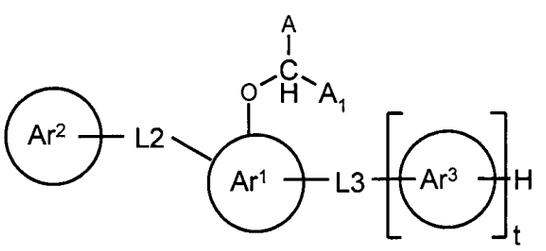
Se conocen muchas clases de agentes antiinflamatorios, incluyendo los compuestos antiinflamatorios no esteroideos conocidos como AINE y los inhibidores de la ciclooxigenasa (COX-1 y COX-2). Se han identificado como agentes antiinflamatorios el ácido benzoilfenilacético y algunos derivados de benzofenona con sustituyentes de carboximetoxilo en uno de los anillos (véase, por ejemplo, Khanum *et al.* Bioorganic Chemistry Vol 32, número 4, 2004, páginas 211-222 y la referencias citadas en el mismo). Se han notificado algunos ácidos o-fenilcarbamoil-fenoxiacéticos y o-benzamido-fenoximetiltetrazoles como potenciales agentes antiinflamatorios, véase por ejemplo Drain *et al.* J. Pharm. Pharmac., 1971, 23, 857-864, y *ibíd* 1970, 22, 684-693. El documento WO 99/15520 da a conocer algunos derivados de benzofenona con sustituyentes de carboximetoxilo o tetrazolilmetoxilo en uno de los anillos, sintetizados como miembros de un grupo de compuestos de los que se dice que tienen actividad como inhibidores del receptor activado por el proliferador de peroxisomas (PPAR), y utilidad en una variedad de estados de enfermedad incluyendo diabetes, enfermedad cardiaca, y enfermedad circulatoria.

El ligando natural del receptor CRTH2 asociado a proteínas G es la prostaglandina D2. Como su nombre implica, CRTH2 se expresa en células T cooperadoras de tipo 2 (células Th2) pero también se sabe que se expresan en células eosinófilas y basófilas. La activación celular como resultado de la unión de PGD2 al receptor CRTH2 da como resultado una respuesta biológica compleja, incluyendo la liberación de mediadores inflamatorios. Por consiguiente, niveles elevados de PGD2 están asociados con muchas enfermedades que tienen un fuerte componente inflamatorio, tales como asma, rinitis y alergias. Por consiguiente, bloquear la unión de PGD2 al receptor CRTH2 es una estrategia terapéutica útil para el tratamiento de tales enfermedades.

Se conocen algunos ligandos de molécula pequeña de CRTH2, que actúan aparentemente como antagonistas de PGD2, por ejemplo tal como se propone en las siguientes publicaciones de patente: WO 03/097042, WO 03/097598, WO 03/066046, WO 03/066047, WO 03/101961, WO 03/101981, GB 2388540, WO 04/089885 y WO 05/018529.

Las estructuras de los compuestos antagonistas de PGD2 mencionados en algunas de las publicaciones anteriores tienen un sistema de anillo con núcleo bicíclico o tricíclico relacionado con el núcleo indol de indometacina, un conocido agente antiinflamatorio, que ahora se sabe que se une a CRTH2. La presente invención surge de la identificación de una clase de compuestos que tienen un núcleo monocíclico cuyos restos de sustituyentes se seleccionan y se orientan por el núcleo monocíclico para interactuar con y unirse a CRTH2. Por tanto la clase de compuestos a la que se refiere esta invención puede modular la actividad de CRTH2 y es útil en el tratamiento de enfermedades que se benefician de tal modulación, por ejemplo asma, alergia y rinitis.

La solicitud internacional de patente en tramitación junto con la presente PCT/EP2005/005884 se refiere al uso de un compuesto de fórmula (IA) o una sal, hidrato o solvato del mismo en la fabricación de una composición para el tratamiento de una enfermedad sensible a la modulación de la actividad del receptor CRTH2:



(IA)

en la que

A representa un grupo carboxilo (–COOH) o un bioisóstero de carboxilo;

A_1 es hidrógeno o metilo;

el anillo Ar^1 es un anillo de heteroarilo monocíclico con 5 ó 6 miembros o anillo de fenilo opcionalmente sustituidos, en el que AA_1CHO- y L2 están unidos a los átomos adyacentes del anillo;

los anillos Ar^2, Ar^3 representan cada uno independientemente un anillo de heteroarilo monocíclico con 5 ó 6 miembros o de fenilo, o un sistema de anillo bicíclico que consiste en un anillo heterocíclico o carboxílico con 5 ó 6 miembros que es benzocondensado o condensado con el anillo de heteroarilo monocíclico con 5 ó 6 miembros, estando dicho anillo o sistema de anillo opcionalmente sustituido;

t es 0 ó 1;

L2 y L3 representan cada uno independientemente un radical divalente de fórmula $-(Alq^1)_m-(Z)_n-(Alq^2)_p$ en la que

m, n y p son independientemente 0 ó 1,

Alq^1 y Alq^2 son independientemente radicales alquenileno C_2-C_3 o alquileno C_1-C_3 de cadena lineal o ramificada opcionalmente sustituidos que pueden contener una unión -O-, -S- o -NR- compatible en la que R es hidrógeno o alquilo C_1-C_3, y

Z es -O-; -S-; -C(=O)-; $-SO_2-$; -SO-; -NR-, $-NRSO_2-$, $-SO_2NR-$, -C(=O)NR-, -NRC(=O)-, -NRCONH-, -NHCONR-, -NRC(=NR)NH-, -NHC(=NR)NR-, –C(R)=N-NR- o –NR-N=C(R)- en las que R es hidrógeno o alquilo C_1-C_3; o un radical heterocíclico o carboxílico monocíclico con 5 ó 6 miembros divalente,

Siempre que

(A) la longitud total de L2 y L3 no supere la de una cadena saturada no ramificada de 10 átomos de carbono; y

(B) L2 no sea –C(=O)-, -C(=O)NR- o -NRC(=O)- cuando Ar^2 es fenilo opcionalmente sustituido; y

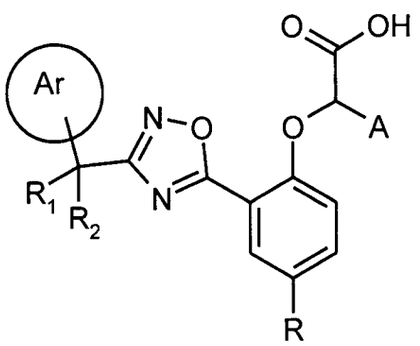
(C) (a) L2 no sea un enlace y (b) p en L2 no sea 0 cuando n es 1 y Z es arilo o heteroarilo, y

(D) (a) L2 no sea –O-, $-SO_2-$, -NR-, $-CHR^XR^Y-$ o $-CH(R^X)(OR^Y)-$, en las que R^X y R^Y son independientemente hidrógeno, halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6 o cicloalquilo C_3-C_7, o juntos forman un anillo, y (b) cuando p es 1 y n es 1 y Z es arilo o heteroarilo entonces Alq^2 no sea $-CHR^XR^Y-$ o $-CH(R^X)(OR^Y)-$, en las que R^X y R^Y son independientemente hidrógeno, halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, o cicloalquilo C_3-C_7, o juntos forman un anillo.

Dado que aún no se ha publicado, se adjunta una copia de la parte de descripción del documento anteriormente mencionado PCT/EP2005/005884 como apéndice.

La presente invención se refiere a compuestos relacionados con los del documento PCT/EP2005/005884, que tienen un radical arilmetiloxadiazolilo unido a un anillo de fenilo correspondiente al anillo Ar^1 de los compuestos del documento PCT/EP2005/005884, teniendo dicho radical una sustitución específica tal como se describe más adelante, en el átomo de carbono entre los anillos de arilo y oxadiazol.

Según la presente invención, se proporciona un compuesto de fórmula (I) o una sal, hidrato o solvato del mismo diferente del ácido {4-bromo-2-[3-(1-fenilciclopropil)-[1,2,4]oxadiazol-5-il]fenoxi}-acético o una sal, hidrato o solvato del mismo:



(I)

en la que

R_1 es hidrógeno o metilo y R_2 es cicloalquilo opcionalmente sustituido, o heterociclilo no aromático opcionalmente sustituido que tiene de 4 a 6 átomos en el anillo; o R_1 y R_2, tomados junto con el átomo de carbono al que están unidos forman un cicloalquilo opcionalmente sustituido, o anillo de heterociclilo no aromático opcionalmente sustituido que tiene de 4 a 6 átomos en el anillo;

R es hidrógeno o un sustituyente opcional;

el anillo de fenilo que contiene el sustituyente R está opcionalmente sustituido por 1, 2 ó 3 sustituyentes opcionales;

A es hidrógeno o alquilo C_1-C_3;

el anillo Ar es un anillo de heteroarilo monocíclico con 5 ó 6 miembros o de fenilo opcionalmente sustituidos.

El compuesto ácido {4-bromo-2-[3-(1-fenilciclopropil)-[1,2,4]oxadiazol-5-il]fenoxi}-acético (y sus sales, hidratos y solvatos) tiene la fórmula (I) anterior en la que A es hidrógeno, Ar es fenilo, R es bromo, y R_1 y R_2 tomados junto con el átomo de carbono al que están unidos forman un anillo de ciclopropilo. Este compuesto está excluido de todos los aspectos de la presente invención porque se da a conocer específicamente en el documento PCT/EP2005/005884.

En otro aspecto, la invención proporciona un método de tratamiento de un sujeto que padece una enfermedad sensible a la modulación de la actividad del receptor CRTH2, que comprende administrar al sujeto una cantidad de un compuesto (I) tal como se definió y se describió anteriormente eficaz para mejorar la enfermedad.

En particular, los compuestos a los que se refiere la invención son útiles en el tratamiento de una enfermedad asociada con niveles elevados de prostaglandina D2 (PGD2) o uno o más metabolitos activos de la misma.

Ejemplos de tales enfermedades incluyen asma, rinitis, síndrome alérgico de las vías respiratorias, rinobronquitis alérgica, bronquitis, enfermedad pulmonar obstructiva crónica (EPOC), poliposis nasal, sarcoidosis, pulmón de granjero, fibrosis pulmonar, fibrosis cística, tos crónica, conjuntivitis, dermatitis atópica, enfermedad de Alzheimer, esclerosis lateral amiotrófica, complejo demencia-SIDA, enfermedad de Huntington, demencia frontotemporal, demencia con cuerpos de Lewy, demencia vascular, síndrome de Guillain-Barre, polirradiculoneuropatía desmielinizante crónica, neuropatía motora multifocal, plexopatía, esclerosis múltiple, encefalomielitis, panencefalitis, degeneración cerebelosa y encefalomielitis, traumatismo del SNC, migraña, accidente cerebrovascular, artritis reumatoide, espondiloartritis anquilosante, enfermedad de Behçet, bursitis, síndrome de túnel carpiano, enfermedad inflamatoria intestinal, enfermedad de Crohn, colitis ulcerosa, dermatomiositis, síndrome de Ehlers-Danlos (SED), fibromialgia, dolor miofascial, osteoartritis (OA), osteonecrosis, artritis psoriásica, síndrome de Reiter (artritis reactiva), sarcoidosis, esclerodermia, síndrome de Sjogren, enfermedad de las partes blandas, enfermedad de Still, tendinitis, panarteritis nudosa, granulomatosis de Wegener, miositis (polimiositis - dermatomiositis), gota, aterosclerosis, lupus eritematoso, lupus eritematoso sistémico (LES), diabetes tipo I, síndrome nefrítico, glomerulonefritis, insuficiencia renal aguda y crónica, fascitis eosinofílica, síndrome de hiper-IgE, septicemia, choque septicémico, lesión por reperfusión isquémica en el corazón, rechazo de aloinjerto tras trasplantes, y enfermedad de injerto contra huésped.

Sin embargo, los compuestos a los que se refiere la invención son principalmente valiosos para el tratamiento de asma, rinitis, síndrome alérgico de las vías respiratorias y rinobronquitis alérgica.

Tal como se usa en el presente documento, el término "alquilo (C_a-C_b)" en el que a y b son números enteros se refiere a un radical alquilo de cadena lineal o ramificada que tiene desde a hasta b átomos de carbono. Por tanto, cuando a es 1 y b es 6, por ejemplo, el término incluye metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, t-butilo, n-pentilo y n-hexilo.

Tal como se usa en el presente documento, el término "cicloalquilo" se refiere a un radical carbocíclico saturado monocíclico que tiene desde 3-8 átomos de carbono e

incluye, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y ciclooctilo.

Tal como se usa en el presente documento, el término sin restricciones "arilo" se refiere a un radical aromático carbocíclico mono, bi o tricíclico, e incluye radicales que tienen dos anillos aromáticos carbocíclicos monocíclicos que están unidos directamente mediante un enlace covalente. Son ilustrativos de tales radicales, fenilo, bifenilo y naftilo.

Tal como se usa en el presente documento, el término sin restricciones "heteroarilo" se refiere a un radical aromático mono, bi o tricíclico que contiene uno o más heteroátomos seleccionados de S, N y O, e incluye radicales que tiene dos anillos monocíclico de este tipo, o un anillo monocíclico de este tipo y un anillo arilo monocíclico, que están unidos directamente mediante un enlace covalente. Son ilustrativos de tales radicales tienilo, benzotienilo, furilo, benzofurilo, pirrolilo, imidazolilo, bencimidazolilo, tiazolilo, benzotiazolilo, isotiazolilo, benzoisotiazolilo, pirazolilo, oxazolilo, benzoxazolilo, isoxazolilo, bencisoxazolilo, isotiazolilo, triazolilo, benzotriazolilo, tiadiazolilo, oxadiazolilo, pirinidilo, piridazinilo, pirimidilo, piridazinilo, triazinilo, indolilo y indazolilo.

Tal como se usa en el presente documento, el término sin restricciones "heterociclilo" o "heterocíclico" incluye "heteroarilo" tal como se definió anteriormente, y además significa un radical no aromático mono, bi o tricíclico que contiene uno o más heteroátomos seleccionados de S, N y O, y a grupos que consisten en un radical no aromático monocíclico que contiene uno o más heteroátomos de este tipo que está unido covalentemente a otro radical de este tipo o a un radical carbocíclico monocíclico. Son ilustrativos de tales radicales los grupos pirrolilo, furanilo, tienilo, piperidinilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, pirazolilo, pirinidilo, pirrolidinilo, pirimidilo, morfolinilo, piperazinilo, indolilo, morfolinilo, benzofuranilo, piranilo, isoxazolilo, bencimidazolilo, metilendioxifenilo, etilendioxifenilo, maleimido y succinimido.

A menos que se especifique lo contrario en el contexto en que se produce, el término "sustituido" tal como se aplica a cualquier resto en el presente documento significa sustituido con hasta cuatro sustituyentes compatibles, cada uno de los cuales puede ser independientemente, por ejemplo, alquilo (C_1-C_6), cicloalquilo, alcoxilo (C_1-C_6), hidroxilo, hidroxialquilo (C_1-C_6), mercapto, mercaptoalquilo (C_1-C_6), alquiltio (C_1-C_6), halógeno (incluyendo flúor, bromo y cloro), alquilo (C_1-C_3), alcoxilo (C_1-C_3) o alquiltio (C_1-C_3) total o parcialmente fluorados tales como trifluorometilo,

trifluorometoxilo y trifluorometiltio, nitro, nitrilo (-CN), oxo, fenilo, fenoxilo, -$COOR^A$, -COR^A, -$OCOR^A$, -SO_2R^A, -$CONR^AR^B$, -$SO_2NR^AR^B$, -NR^AR^B, $OCONR^AR^B$, -NR^BCOR^A, -NR^BCOOR^A, -$NR^BSO_2OR^A$ o -$NR^ACONR^AR^B$ en las que R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1-C_6) o, en el caso en el que R^A y R^B están unidos al mismo átomo de N, R^A y R^B tomados junto con este nitrógeno pueden formar un anillo amino cíclico. Cuando el sustituyente es fenilo o fenoxilo, el anillo de fenilo del mismo puede estar sustituido por sí mismo por cualquiera de los sustituyentes anteriores excepto fenilo o fenoxilo. Un "sustituyente opcional" puede ser uno de los grupos sustituyentes anteriores.

Tal como se usa en el presente documento, el término "sal" incluye sales de adición de bases, de adición de ácidos y cuaternarias. Los compuestos de la invención que son ácidos pueden formar sales, incluyendo sales farmacéuticamente aceptables, con bases tales como hidróxido de amonio; hidróxidos de metales alcalinos, por ejemplo hidróxidos de sodio y potasio; hidróxidos de metales alcalinotérreos, por ejemplo hidróxidos de calcio, bario y magnesio; con bases orgánicas por ejemplo N-metil-D-glucamina, colina, tris(hidroximetil)amino-metano, L-arginina, L-lisina, N-etilpiperidina, dibencilamina y similares. Los compuestos (I) que son básicos pueden formar sales, incluyendo sales farmacéuticamente aceptables con ácidos inorgánicos, por ejemplo con ácidos hidrácidos halogenados tales como ácidos clorhídrico o bromhídrico, ácido sulfúrico, ácido nítrico o ácido fosfórico y similares, y con ácidos orgánicos por ejemplo con los ácidos acético, tartárico, succínico, fumárico, maleico, málico, salicílico, cítrico, metanosulfónico, p-toluenosulfónico, benzoico, bencenosulfónico, glutámico, láctico y mandélico y similares.

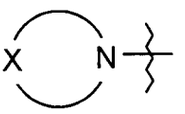
Los compuestos a los que se refiere la invención que pueden existir en una o más formas estereoisoméricas, debido a la presencia de átomos asimétricos o restricciones rotacionales, pueden existir como varios estereoisómeros con estereoquímica R o S en cada centro quiral o como atropisómeros con estereoquímica R o S en cada eje quiral. La invención incluye todos los enantiómeros y diastereoisómeros de este tipo y mezclas de los mismos.

También es parte de la invención el uso de profármacos, tales como ésteres, de los compuestos (I) a los que se refiere la invención.

Para el uso según los aspectos anteriores de la invención pueden estar presentes las siguientes características estructurales, en cualquier combinación compatible, en los compuestos (I):

En el caso en el que R_1 es hidrógeno o metilo, y R_2 es cicloalquilo opcionalmente sustituido, R_2 puede ser, por ejemplo, ciclohexilo, ciclopentilo, ciclobutilo o ciclopropilo opcionalmente sustituidos;

En el caso en el que R_1 es hidrógeno o metilo, y R_2 es heterociclilo no aromático opcionalmente sustituido que tiene de 4 a 6 átomos en el anillo, el radical de anillo R_2 puede ser, por ejemplo, de fórmula



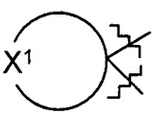
en la que el anillo contiene de 4 a 6 átomos en el anillo, y X se selecciona de -CH_2-, -CH(alquil C_1-C_3)-, -C(alquil C_1-C_3)$_2$-, -CH(cicloalquilo), -$CH(NH_2)$-, -$C(CH_3)(NH_2)$-, -CH(NH(alquil C_1-C_3))-, -CH(N(alquil C_1-C_3)$_2$)-, -CH(NH(cicloalquil))-, -CH(NHCO(alquil C_1-C_3))-, -CH(NHCO(cicloalquil))-, -$CH(NHSO_2$(alquil C_1-C_3))-, -$CH(NHSO_2$(cicloalquil))-, -CH(OH)-, -CH(alcoxi C_1-C_3)-, -CH(cicloalquiloxi)-, -CO-, -SO_2-, -O-, -NH-, -N(alquil C_1-C_3)-, -N(cicloalquil)-, -CONH-, -CON(alquil C_1-C_3)-, -CON(cicloalquil)-, -N(CO(O-alquil C_1-C_3))-, -N(CO(O-cicloalquil))-, -$N(CO(CH_2OH))$-, -SO_2NH-, -SO_2N(alquil C_1-C_6)-, -SO_2N(cicloalquil)-, -$N(SO_2$(alquil C_1-C_3))-, -$N(SO_2$(cicloalquil))-, -N(CO(alquil C_1-C_3))- o -N(CO(cicloalquil))-. De las opciones anteriores para X, se prefieren actualmente las siguientes: -CH_2-, -SO_2-, -CO-, -O-, -$N(SO_2$(alquil C_1-C_3))-, -$N(SO_2$(cicloalquil))-, -N(CO(alquil C_1-C_3))-, -N(CO(cicloalquil))-, -CONH-, -CON(alquil C_1-C_3)- y -CON(cicloalquil)-. Cuando, en las opciones anteriores para X, está presente un grupo alquilo C_1-C_3, se prefiere a menudo metilo, y cuando está presente un grupo cicloalquilo, se prefiere a menudo ciclopropilo.

En compuestos de la invención, cuando R_1 es hidrógeno o metilo, ejemplos específicos de grupos R_2 incluyen los presentes en los compuestos de los ejemplos en el presente documento.

En el caso en el que R_1 y R_2, tomados junto con el átomo de carbono al que están unidos forman un anillo cicloalquilo opcionalmente sustituido, este anillo puede ser, por ejemplo, ciclohexilo, ciclopentilo, ciclobutilo o ciclopropilo opcionalmente sustituidos.

En el caso en el que R_1 y R_2, tomados junto con el átomo de carbono al que están unidos forman un anillo de heterociclilo no aromático opcionalmente

sustituido que tiene de 4 a 6 átomos en el anillo, este anillo puede ser, por ejemplo, de fórmula



en la que el anillo contiene de 4 a 6 átomos en el anillo y X^1 se selecciona de -CH_2-, -CH(alquil C_1-C_3)-, -C(alquil C_1-C_3)$_2$-, -CH(cicloalquilo), -CH(NH_2)-, -CMe(NH_2)-, -CH(NH(alquil C_1-C_3))-, -CH(N(alquil C_1-C_3)$_2$)-, -CH(NH(cicloalquil))-, -CH(NHCO(alquil C_1-C_3))-, -CH(NHCO(cicloalquil))-, -CH(NHSO_2(alquil C_1-C_3))-, -CH(NHSO_2(cicloalquil))-, -CH(OH)-, -CH(alcoxi C_1-C_3)-, -CH(cicloalquiloxi])-, -SO_2-, -O-, -NH-, -N(alquil C_1-C_3)-, -N(cicloalquil)-, -CONH-, -CON(alquil C_1-C_3)-, -CON(cicloalquil)-, -SO_2NH-, -SO_2N(alquil C_1-C_6)-, -SO_2N(cicloalquil)-, -N(SO_2(alquil C_1-C_3))-, -N(SO_2(cicloalquil))-, -N(CO(O alquil C_1-C_3))-, -N(CO(O-cicloalquil))-, -N(CO(CH_2OH))-, -N(CO(alquil C_1-C_3))- o -N(CO(cicloalquil))-. De las opciones anteriores para X^1, se prefieren actualmente las siguientes: -CH_2-, -SO_2-, -O-, -CONH-, -CON(alquil C_1-C_3)-, -CON(cicloalquil)-, -N(SO_2(alquil C_1-C_3))-, -N(SO_2(cicloalquil))-, -N(CO(alquil C_1-C_3))- y -N(CO(cicloalquil))-. Cuando, en las opciones anteriores para X^1, está presente un grupo alquilo C_1-C_3, se prefiere a menudo metilo, y cuando está presente un grupo cicloalquilo, se prefiere a menudo ciclopropilo.

En compuestos de la invención, cuando R_1 y R_2, tomados junto con el átomo de carbono al que están unidos forman un anillo, ejemplos específicos de anillos de este tipo incluyen los presentes en los compuestos de los ejemplos en el presente documento.

A puede ser hidrógeno, metilo, etilo, n- o iso-propilo. Actualmente se prefieren los compuestos en los que A es hidrógeno o metilo.

R puede ser, por ejemplo, un sustituyente seleccionado de flúor, cloro, bromo, alquilo (C_1-C_3), cicloalquilo, trifluorometilo, alcoxilo (C_1-C_3), alquilmercapto (C_1-C_3), trifluorometoxilo, trifluorometiltio, ciano, (alquilo C_1-C_3)SO_2-, NH_2SO_2-, (alquil C_1-C_3)$NHSO_2$-, (alquil C_1-C_3)$_2NSO_2$-, (cicloalquil)$NHSO_2$-, NH_2CO-, (alquil C_1-C_3)NHCO-, (alquil C_1-C_3)$_2$NHCO- y (cicloalquil)NHCO-.

El anillo Ar corresponde al anillo Ar^2 de los compuestos del apéndice 1, y puede ser, por ejemplo, cualquiera de los grupos de Ar^2 mencionados en el

mismo o presentes en los compuestos facilitados a modo de ejemplo del apéndice 1. Por tanto, el grupo Ar presente puede ser, por ejemplo, tiazolilo, furanilo, pirrolilo, quinolinilo, triazinilo, oxazolilo, diazolilo, pirimidilo, piridilo, o fenilo opcionalmente sustituidos.

Asimismo, los sustituyentes opcionales en Ar pueden ser, por ejemplo, cualquiera de los sustituyentes de Ar^2 opcionales mencionados en, o presentes en los compuestos facilitados a modo de ejemplo del apéndice 1. Por tanto, los sustituyentes opcionales en el anillo Ar presente pueden seleccionarse de flúor, cloro, bromo, alquilo (C_1-C_3), trifluorometilo, alcoxilo (C_1-C_3), trifluorometoxilo, trifluorometiltio, dimetilamino, ciano, (alquil C_1-C_3)SO_2-, NH_2SO_2-, (alquil C_1-C_3)$NHSO_2$- y (alquil C_1-C_3)$_2NSO_2$-,

El anillo de fenilo que contiene R en los presentes compuestos de fórmula (I) corresponde al anillo Ar^1 de los compuestos del apéndice 1, por lo que cualquiera de los sustituyentes de Ar^1 opcionales mencionados en, o presentes en los compuestos facilitados a modo de ejemplo del apéndice 1 también pueden estar presentes en el anillo de fenilo que contiene R de los compuestos de esta invención. Por tanto, los sustituyentes opcionales de este tipo pueden seleccionarse de flúor, cloro, bromo, ciano, trifluorometilo, trifluorometoxilo, trifluorometiltio, (alquil C_1-C_3)SO_2-, NH_2SO_2-, (alquil C_1-C_3)$NHSO_2$-, (alquil C_1-C_3)$_2NSO_2$-, NH_2CO-, (alquil C_1-C_3)NHCO-, (alquil C_1-C_3)$_2$NHCO-, (cicloalquil)NHCO-, alquilo C_1-C_6, alcoxilo C_1-C_6, cicloalquilo, arilo, ariloxilo, aril (C_1-C_6)- o aril (C_1-C_6 alcoxi)-.

La invención también incluye composiciones farmacéuticas que comprenden un compuesto que pertenece a los compuestos de fórmula (I) descritos anteriormente junto con un vehículo farmacéuticamente aceptable.

Composiciones

Tal como se mencionó anteriormente, los compuestos a los que se refiere la invención pueden modular la actividad de CRTH2 y son útiles en el tratamiento de enfermedades que se benefician de tal modulación. Ejemplos de tales enfermedades se mencionaron anteriormente, e incluyen asma, alergia y rinitis.

Se entenderá que el nivel de dosis específico para cualquier paciente particular dependerá de una variedad de factores incluyendo la actividad del compuesto específico empleado, la edad, peso corporal, salud general, sexo, dieta, tiempo de administración, vía de administración, tasa de excreción, combinación de fármaco y la

gravedad de la enfermedad particular que se somete a tratamiento. Los niveles de dosis y la frecuencia de administración óptimos se determinarán mediante ensayos clínicos, tal como se requiere en la técnica farmacéutica.

Los compuestos a los que se refiere la invención pueden prepararse para su administración mediante cualquier vía compatible con sus propiedades farmacocinéticas. Las composiciones administrables por vía oral pueden estar en la forma de comprimidos, cápsulas, polvos, gránulos, pastillas para chupar, preparaciones líquidas o en gel, tales como suspensiones o disoluciones parenterales estériles, tópicas u orales. Los comprimidos y cápsulas para la administración oral pueden estar en forma de presentación de dosis unitaria, y pueden contener excipientes convencionales tales como agentes de unión, por ejemplo jarabe, goma arábiga, gelatina, sorbitol, tragacanto o polivinilpirrolidona; cargas por ejemplo lactosa, azúcar, almidón de maíz, fosfato de calcio, sorbitol o glicina; lubricante para la preparación de comprimidos, por ejemplo estearato de magnesio, talco, polietilenglicol o sílice; disgregantes por ejemplo almidón de patata, o agentes humectantes aceptables tales como laurilsulfato de sodio. Los comprimidos pueden recubrirse según los métodos bien conocidos en la práctica farmacéutica normal. Las preparaciones líquidas orales pueden estar en la forma de, por ejemplo, elixires, jarabes, emulsiones, disoluciones o suspensiones acuosas o aceitosas, o pueden presentarse como un producto seco para su reconstitución con agua u otro vehículo adecuado antes de su uso. Las preparaciones líquidas de este tipo pueden contener aditivos convencionales tales como agentes de suspensión, por ejemplo sorbitol, jarabe, metilcelulosa, jarabe de glucosa, grasas comestibles hidrogenadas de gelatina; agentes emulsionantes, por ejemplo lecitina, monooleato de sorbitano, o goma arábiga; vehículos no acuosos (que pueden incluir aceites comestibles), por ejemplo aceite de almendra, aceite de coco fraccionado, ésteres aceitosos tales como glicerina, propilenglicol o alcohol etílico; conservantes, por ejemplo p-hidroxibenzoato de propilo o metilo o ácido sórbico, y si se desea agentes aromatizantes o colorantes convencionales.

Para la aplicación tópica a la piel, el fármaco puede prepararse como una crema, loción o pomada. Las formulaciones de crema o pomada que pueden usarse para el fármaco son formulaciones convencionales bien conocidas en la técnica, por ejemplo tal como se describe en libros de texto convencionales de productos farmacéuticos tales como la Farmacopea Británica.

Para la aplicación tópica a los ojos, el fármaco puede prepararse como una disolución o suspensión en un vehículo acuoso o no acuoso estéril adecuado. También pueden incluirse aditivos, por ejemplo tampones tales como metabisulfito sódico o edetato disódico; conservantes incluyendo agentes bactericidas y fungicidas tales como nitrato o acetato mercúrico de fenilo, cloruro de benzalconio o clorhexidina, y agentes espesantes tales como hipromelosa.

El fármaco también puede formularse para inhalación, por ejemplo como un pulverizador nasal, o polvo seco o inhaladores en aerosol.

El principio activo también puede administrarse por vía parenteral en un medio estéril. Dependiendo del vehículo y de la concentración usada, el fármaco puede o bien suspenderse o bien disolverse en el vehículo. Ventajosamente, pueden disolverse en el vehículo adyuvantes tales como un anestésico local, un conservante y agentes de tamponamiento.

Los compuestos a los que se refiere la invención pueden administrarse solos, o como parte de una terapia de combinación con otros fármacos usados para el tratamiento de enfermedades con un componente inflamatorio principal. En el caso del asma, la rinitis y el síndrome alérgico de las vías respiratorias, tales fármacos incluyen corticosteroides, beta-agonistas inhalados de acción prolongada, cromolino, nedocromilo, teofilina, antagonistas del receptor de leucotrieno, antihistamínicos y anticolinérgicos (por ejemplo ipratropio), y a menudo se administran como pulverizadores nasales, polvo seco o inhaladores en aerosol.

En el caso de la artritis y las enfermedades inflamatorias relacionadas, otros fármacos conocidos incluyen glucocorticoides, AINE (fármacos antiinflamatorios no esteroideos, inhibidores convencionales de la síntesis de prostaglandina, inhibidores de COX-2, salicilatos), y FARME (fármacos antirreumáticos modificadores de enfermedad, tales como metotrexato, sulfasalazina, oro, ciclosporina).

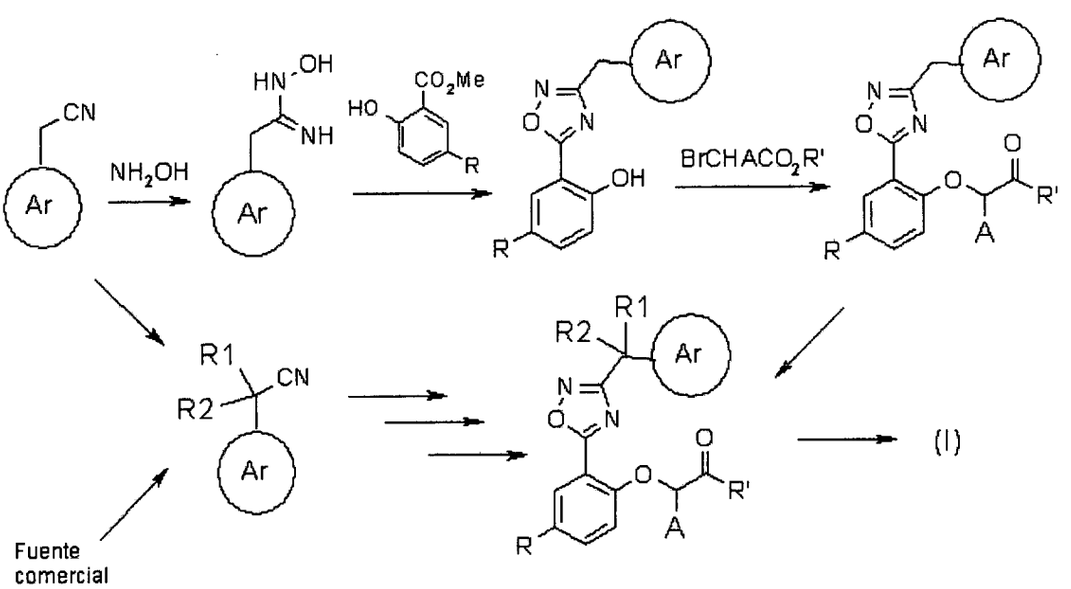
Rutas sintéticas

Existen múltiples estrategias sintéticas para la síntesis de los compuestos (I) a los que se refiere la presente invención, pero todas se basan en química conocida, conocida para el experto en química orgánica sintética. Por tanto, los compuestos según la fórmula I pueden sintetizarse según procedimientos descritos en la bibliografía convencional y el experto en la técnica los conoce bien. Fuentes bibliográficas típicas son "Advanced organic chemistry", 4ª Edición (Wiley), J March, "Comprehensive Organic Transformation", 2ª Edición (Wiley), R.C. Larock , "Handbook

of Heterocyclic Chemistry", 2ª Edición (Pergamon), A.R. Katritzky), artículos de revisión tales como los encontrados en "Synthesis", "Acc. Chem. Res.", "Chem. Rev", o fuentes bibliográficas principales identificadas mediante búsquedas on-line convencionales o a partir de fuentes secundarias tales como "Chemical Abstracts" o "Beilstein".

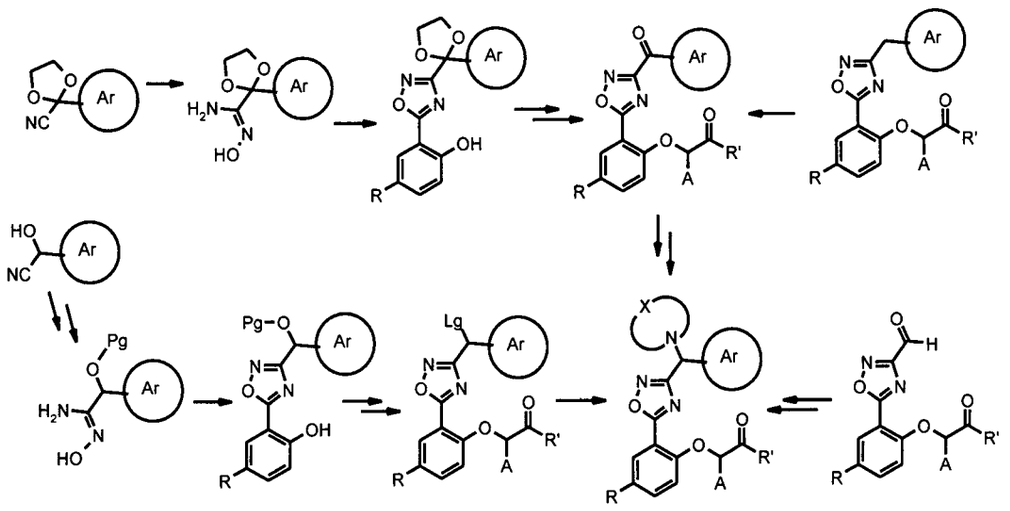
En particular, los compuestos de la presente invención pueden sintetizarse mediante el método descrito en las rutas generales resumidas en los tres párrafos siguientes, y en los ejemplos posteriores, o mediante métodos generalmente descritos en relación con los compuestos del apéndice 1.

El oxadiazol del núcleo de fórmula I normalmente se forma mediante condensación de amidoximas y benzoatos de metilo opcionalmente sustituidos. Las cadenas laterales ácidas se introducen mediante la sustitución catalizada por base del fenol, por ejemplo con ésteres de bromoacetato o 2-bromoproprionato seguido por la hidrólisis alcalina del éster. Los grupos R1 y R2 o bien están disponibles en materiales de partida comerciales o bien se introducen en la fase de nitrilo utilizando sustituciones nucleófilas catalizadas por base o R_1 y R_2 se introducen tras la reunión del sistema de oxadiazol.

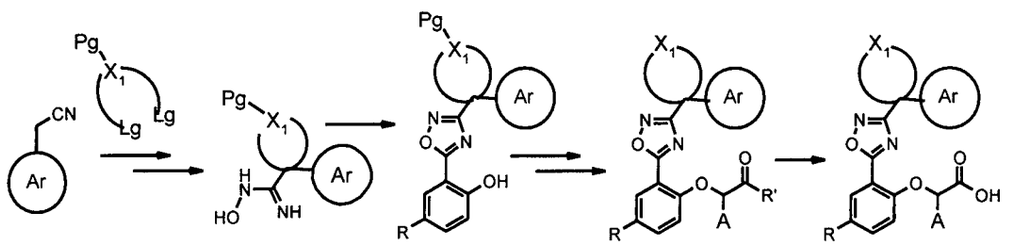


El grupo R_2 que contiene un anillo de nitrógeno cíclico puede introducirse a partir de la cetona correspondiente, obtenida mediante condiciones de oxidación convencionales, mediante por ejemplo alquilación reductora. Opcionalmente, la cetona puede introducirse en una forma protegida tal como cetal en una fase temprana de la síntesis. Alternativamente, el grupo R_2 puede introducirse mediante desplazamiento

nucleófilo de un compuesto correspondiente que contiene un grupo saliente Lg tal como cloro, bromo, mesilo o tosilo tal como se ilustra. Opcionalmente, el grupo saliente puede introducirse en una forma protegida en una fase temprana de la síntesis, por ejemplo a partir de una cianhidrina que se protege como acetal antes de la transformación del nitrilo en oxadiazol. Otro enfoque utiliza un función de aldehído en el oxadiazol que se funcionaliza mediante una especie metalorgánica adecuada que contiene el resto Ar seguido por la conversión del grupo hidroxilo resultante en el anillo que contiene nitrógeno.



Los compuestos que tienen R_1 y R_2 contiguos en un anillo común pueden introducirse, por ejemplo, mediante la siguiente estrategia en la que Lg indica un grupo saliente tal como cloro, bromo, mesilo o tosilo y Pg indica un grupo protector cuando sea necesario, tal como t-Boc para nitrógeno. Tras la desprotección, el grupo X_1 puede manipularse adicionalmente mediante reacciones convencionales, por ejemplo cuando X_1 es una amina secundaria, alquilación o acilación con cloruros de sulfonilo o cloruros de acilo para producir aminas alquiladas, sulfonamidas o carboxamidas, respectivamente.

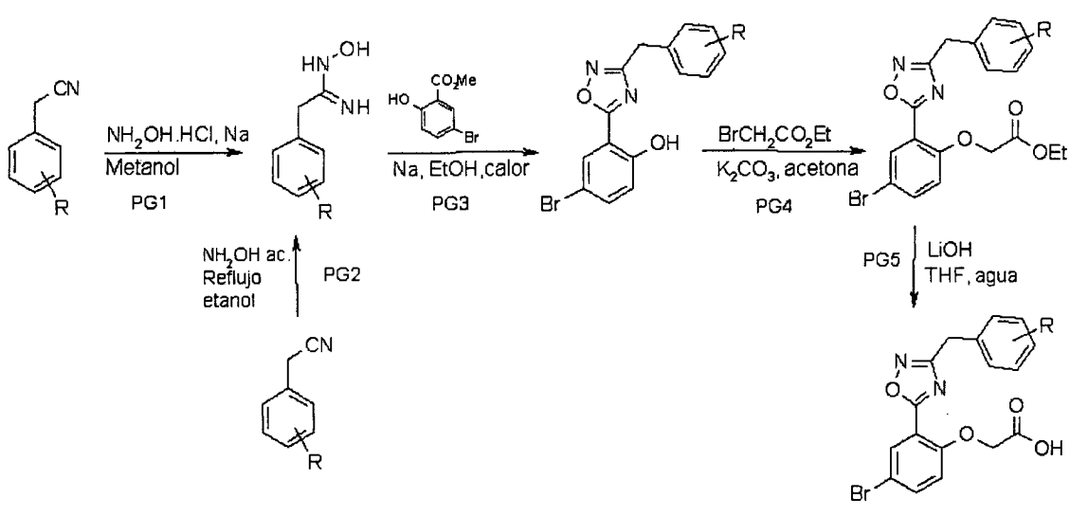


Los ejemplos siguientes ilustran la preparación de los compuestos a los que se refiere esta invención.

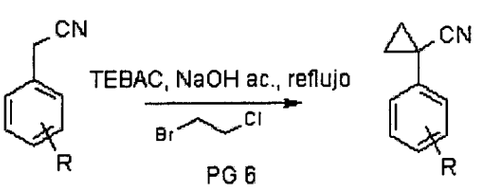
Comentarios generales:

Se realizó la química de microondas en un optimizador Emrys de Personal Chemistry. Se obtuvieron los espectros de RMN en un instrumento Avance AMX 300 MHz de Bruker. Se realizó LC/EM en un instrumento Agilent serie 1100. Los métodos de LC/EM son tal como sigue: An10p8: Columna: XTerra MS C18; Flujo: 1,0 ml/min; Gradiente: 0-5 min: 15-100% de MeCN en agua, 5-7½ min: 100% de MeCN; Modificador: formiato de amonio 5 mM; modo de ionización de EM: API-ES (pos.). An10n8: Columna: XTerra MS C18; Flujo: 1,0 ml/min; Gradiente: 0-5 min: 15-100% de MeCN en agua, 5-7½ min: 100% de MeCN; Modificador: formiato de amonio 5 mM; modo de ionización de EM: API-ES (neg.). TFA20p5: Columna: Gemini 5 µ C18 50x2,00 mm; Flujo: 1,2 ml/min; Gradiente: 0-3½ min: 10-95% de MeCN en agua, 3½-4½ min: 95% de MeCN; Modificador: TFA al 0,1%; modo de ionización de EM: API-ES (pos.).

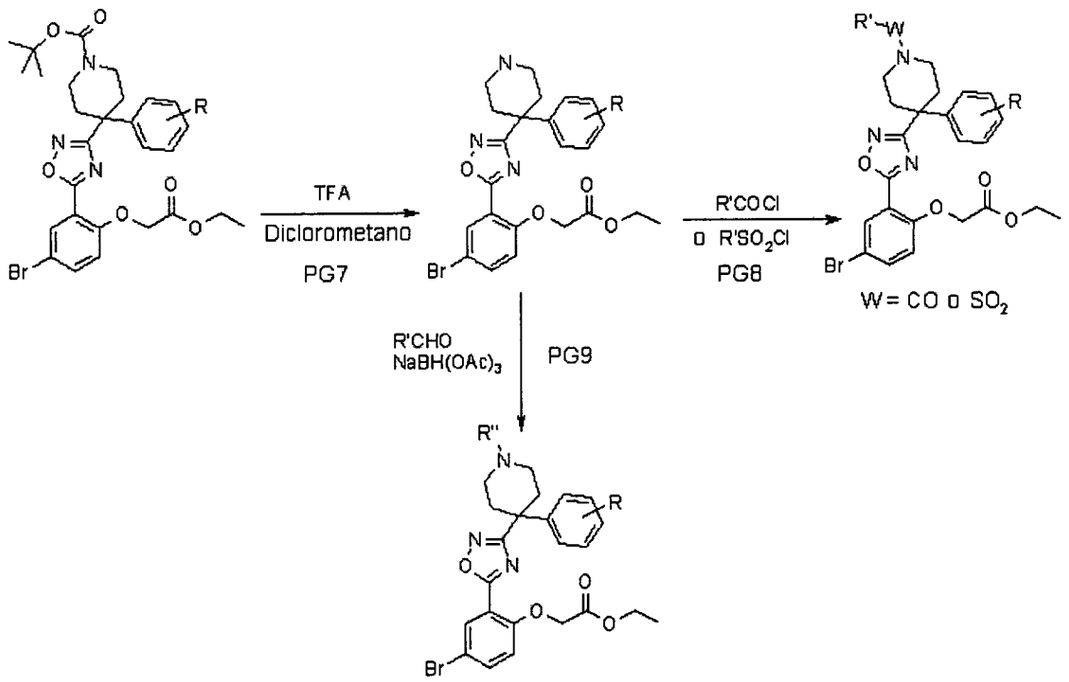
Ruta sintética general I



Ruta sintética general II



Ruta sintética general III



Procedimiento general 1 (PG1)

Síntesis de amidoximas

Se añadió sodio (1,25 mmol) a metanol seco (1 ml) para dar la disolución A. Se disolvió clorhidrato de hidroxilamina (1,2 mmol) en metanol seco (1 ml) para dar la disolución B. Se mezclaron las disoluciones A y B, se enfriaron en un baño de hielo y se filtraron. Entonces al filtrado se le añadió el nitrilo (1 mmol) y se agitó la mezcla de reacción durante la noche a temperatura ambiente. Se eliminó el disolvente a vacío para dar la amidoxima correspondiente. Se purificó el compuesto sobre cromatografía en gel de sílice (EtOAc/Heptano: 1/2) o se usó sin purificación adicional.

Procedimiento general 2 (PG2)

Síntesis de amidoximas

A 50 ml de etanol al 96% se le añadió el nitrilo (10 mmol) e hidroxilamina al 50% (40 mmol) en agua. Se calentó la mezcla hasta reflujo durante 2 horas. Tras el enfriamiento, se eliminó el disolvente a vacío y se añadió agua y se agitó la mezcla hasta que se produjo la precipitación. Se filtró el precipitado y se secó a vacío.

Procedimiento general 3 (PG3)

Síntesis de oxadiazoles

A una disolución de sodio (3,3 mmol) en etanol seco (10 ml) se le añadieron sucesivamente la amidoxima (1,15 mmol), tamices moleculares (1 g) y benzoato de metilo (1 mmol). Tras agitar durante 12 h a reflujo, se enfrió la mezcla de reacción y se filtró a través de un lecho de Celite. Se lavó el lecho de Celite con metanol y CH_2Cl_2. Se eliminó el disolvente a vacío y se agitó el residuo con agua. Se eliminó por filtración el precipitado y se secó para dar el oxadiazol correspondiente. Se purificó el compuesto sobre cromatografía en gel de sílice (EtOAc:Heptano, 1:2) o se usó sin purificación adicional.

Procedimiento general 4 (PG4):

Alquilación de fenol

Se añadió el fenol (0,5 mmol) en acetona (1 ml) a bromoacetato de etilo (85 mg, 0,5 mmol) o 2-bromopropionato de etilo (91 mg, 0,5 mmol) o 2-(trifluorometilsulfonil)propionato de etilo (125 mg, 0,5 mmol) y K_2CO_3 (75 mg, 0,54 mmol), y se agitó la mezcla de reacción a temperatura ambiente durante 12 h. Entonces se concentró la mezcla de reacción a vacío y se repartió el residuo entre agua y acetato de etilo. Se lavó la fase orgánica con salmuera, se secó ($MgSO_4$) y se concentró. Se usó el producto directamente o se purificó mediante recristalización en MeOH o mediante cromatografía ultrarrápida.

Procedimiento general 5 (PG5):

Hidrólisis de éster

Al éster (0,10 mmol) en THF (0,5 ml) se le añadió $LiOH·H_2O$ (6,3 mg, 0,15 mmol) en agua (0,5 ml). Se agitó la reacción a temperatura ambiente durante >2 h, se añadió HCl al 3% hasta pH <1, y se extrajo la mezcla con CH_2Cl_2. Se secó la fase orgánica ($MgSO_4$) y se concentró para dar el producto.

Procedimiento general 6 (PG6):

Síntesis de ciclopropilo

A una mezcla de fenilacetonitrilo (20 mmol) y cloruro de trietilbencilamonio (2 mmol) en hidróxido de sodio acuoso al 50% (10 ml), se le añadió lentamente 1-bromo-2-cloroetano (30 mmol). Se sometió a reflujo la mezcla durante 12 horas. Tras el enfriamiento, se repartió la mezcla entre agua y acetato de etilo. Se secó la fase

orgánica (Na_2SO_4), se redujo a vacío y se purificó mediante cromatografía ultrarrápida (EtOAc:Heptano, 1:4).

Procedimiento general 7 (PG7):

Eliminación del grupo protector Boc

Se agitó el compuesto protegido con Boc (2,6 mmol) en TFA al 10% en diclorometano (15 ml) a temperatura ambiente durante 12 horas. Se añadió carbonato de sodio acuoso sat. y se eliminó el diclorometano a vacío. Se repartió el residuo entre agua y acetato de etilo. Se secó la fase orgánica (Na_2SO_4), se redujo a vacío y se purificó mediante cromatografía ultrarrápida (EtOAc, entonces EtOAc:MeOH, 1:1).

Procedimiento general 8 (PG8):

Alquilación de nitrógeno de piperidina con RCOCl o RSO2Cl

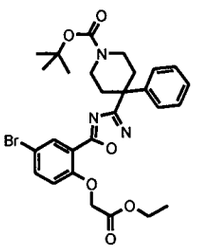
A una mezcla enfriada (0°C) de la "piperidina" (0,3 mmol) y trietilamina (0,33 mmol) en diclorometano (5 ml) se le añadió el cloruro ácido o cloruro de sulfonilo (0,33 mmol). Se agitó la mezcla de reacción a temperatura ambiente durante 2 horas. Se eliminó el disolvente a vacío. Se repartió el residuo entre agua y diclorometano. Se secó la fase orgánica (Na_2SO_4), se redujo a vacío y se purificó mediante cromatografía ultrarrápida (EtOAc:Heptano, 1:1) o se usó sin purificación adicional.

Procedimiento general 9 (PG9):

Alquilación reductora de nitrógeno de piperidina

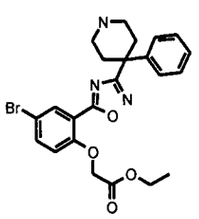
A una mezcla de la "piperidina" (0,2 mmol) y triacetoxiborohidruro de sodio (0,9 mmol) en diclorometano (8 ml) se le añadió formaldehído al 37% (0,9 mmol). Se agitó la mezcla de reacción a temperatura ambiente durante la noche. Se añadió hidrogenocarbonato de sodio acuoso sat. y se extrajo el compuesto con diclorometano. Se secó la fase orgánica (Na_2SO_4), se redujo a vacío y se usó sin purificación adicional.

Preparación de los productos intermedios



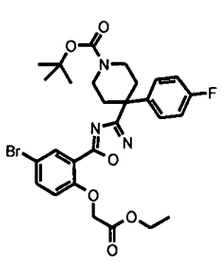
IM1

Éster terc-butílico del ácido 4-[5-(5-bromo-2-etoxicarbonilmetoxi-fenil)-[1,2,4]oxadiazol-3-il]-4-fenil-piperidin-1-carboxílico. Se preparó el compuesto del título a partir de éster metílico del ácido 5-bromo-2-hidroxibenzoico y éster terc-butílico del ácido 4-ciano-4-fenil-piperidin-1-carboxílico según PG2, PG3 y PG4: LC/EM (tfa20p5.m) Tr 3,22 min, *m/z* 566 $[M+H]^+$;



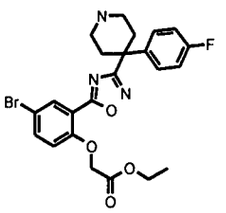
IM2

Éster etílico del ácido {4-bromo-2-[3-(4-fenil-piperidin-4-il)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se preparó el compuesto del título a partir del producto intermedio **IM1** según PG7: LC/EM (tfa20p5.m) Tr 2,194 min, *m/z* 502 $[M+H]^+$;



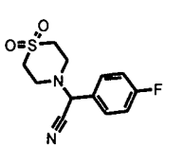
IM3

Éster terc-butílico del ácido 4-[5-(5-bromo-2-etoxicarbonilmetoxi-fenil)-[1,2,4]oxadiazol-3-il]-4-(4-fluoro-fenil)-piperidin-1-carboxílico. Se preparó el compuesto del título a partir de éster metílico del ácido 5-bromo-2-hidroxibenzoico y éster terc-butílico del ácido 4-ciano-4-(4-fluoro-fenil)-piperidin-1-carboxílico según PG2, PG3 y PG4: LC/EM (tfa20p5.m) Tr 3,75 min, *m/z* 628[M+Na].



IM4

Éster etílico del ácido (4-bromo-2-{3-[4-(4-fluoro-fenil)-piperidin-4-il]-[1,2,4]oxadiazol-5-il}-fenoxi)-acético. Se preparó el compuesto del título a partir del producto intermedio **IM3** según PG7: LC/EM (tfa20p5.m) Tr 2,3 min, *m/z* 506 $[M+H]^-$;

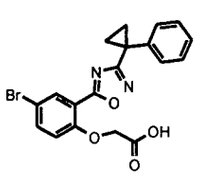


IM5

(1,1-Dioxo-1lambda*6*-tiomorfolin-4-il)-(4-fluoro-fenil)-acetonitrilo. Se preparó el compuesto del título a partir de 4-fluoro-benzaldehído y 1,1-dióxido de tiomorfolina tal como sigue:

A una disolución de 1,1-dióxido de tiomorfolina (2,52 g, 18,64 mmol) en HCl acuoso 1 N (18,64 ml, 18,64 mmol) se le añadió cianuro de sodio (0,822 g, 16,78 mmol). Tras la disolución del cianuro de sodio, se añadió gota a gota una disolución de 4-fluoro-benzaldehído (1 ml, 9,32 mmol) en acetonitrilo (38 ml). Se agitó la mezcla de reacción a temperatura ambiente durante 3 días. Se eliminó el disolvente a vacío y se añadió agua. Se agitó la mezcla durante ~10 minutos y se eliminó por filtración el precipitado blanco, se lavó con agua y se secó a vacío para dar el compuesto del título (1,74 g, 6,48 mmol, 70%). LC/EM (tfa20p5.m) Tr 2,01 min, *m/z* 269 $[M+H]^-$; ^{1}H RMN ($CDCl_3$): δ 3,12 (m, 8H), 4,94 (s, 1H), 7,16 (t, 2H), 7,53 (dd, 2H).

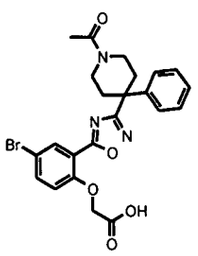
Ejemplos



D1

Ácido {4-bromo-2-[3-(1-fenilciclopropil)-[1,2,4]oxadiazol-5-il]fenoxi}-acético. Se preparó el compuesto del título a partir de éster metílico del ácido 5-bromo-2-hidroxi-benzoico y 1-fenil-1-ciclopropanocarbonitrilo según PG1, PG3, PG4 y PG5: LC/EM (an10n8) Tr,2,756 *m/z* 413,4 $[M-H]^-$; ^{1}H RMN (DMSO-d_6): δ 0,92 (m, 2H),

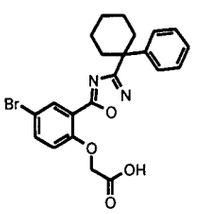
1,11 (m, 2H), 4,38 (s, 2H), 6,63-6,66 (d, 1H), 6,79-6,88 (m, 3H), 6,93-6,95 (m, 2H), 7,25-7,29 (dd, 1H), 7,50-7,51 (d, 1H).



D2

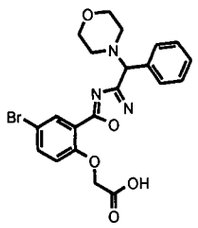
Ácido {2-[3-(1-acetil-4-fenil-piperidin-4-il)-[1,2,4]oxadiazol-5-il]-4-bromo-fenoxi}-acético. Se preparó el compuesto del título a partir del ejemplo **D5** y anhídrido acético tal como sigue:

Se calentó una suspensión del ejemplo D5 (0,04 mmol) en anhídrido acético (0,5 ml) hasta 50ºC durante 1 hora. Se eliminó el disolvente a vacío para dar una goma incolora. Se añadió agua y se agitó vigorosamente la mezcla hasta que se formó precipitado fino. Se eliminó por filtración el precipitado, se lavó con agua y se secó a vacío para dar el compuesto del título: LC/EM (an10p8.n) Tr 2,507 min, *m/z* 500 [M – H]$^-$; ^{1}H RMN (DMSO): δ 2,0 (s, 3H), 1,95-2,3 (m, 2H), 2,6-2,7 (m, 2H), 2,8-2,9 (m, 1H), 3,2-3,3 (m, 1H), 3,75-3,85 (m, 1H), 4,15-4,3 (m, 1H), 4,9 (s, 3H), 7,15-7,19 (d, 1H), 7,21-7,28 (1H), 7,31-7,43 (m, 4H), 7,75-7,81 (dd, 1H), 8,05-8,07 (d, 1H).



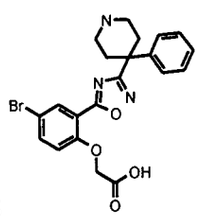
D3

Ácido {4-bromo-2-[3-(1-fenil-ciclohexil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se preparó el compuesto del título a partir de éster metílico del ácido 5-bromo-2-hidroxibenzoico y 1-fenil-ciclohexanocarbonitrilo según PG1, PG3, PG4 y PG5: LC/EM (an10p8.m) Tr 3,21 min, *m/z* 457 [M+H]$^-$; ^{1}H RMN (DMSO): δ 1,3-1,7 (m, 6H), 2,0-2,1 (m, 2H), 2,5-2,6 (m, 2H), 4,9 (m, 2H), 7,13-7,25 (m, 2H), 7,28-7,41(m, 4H) , 7,74-7,80 (dd, 1H), 8,00-8,03 (d, 1H)



D4

Ácido {4-bromo-2-[3-(morfolin-4-il-fenil-metil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se preparó el compuesto del título a partir de éster metílico del ácido 5-bromo-2-hidroxibenzoico y morfolin-4-il-fenil-acetonitrilo según PG1, PG3, PG4 y PG5: LC/EM (an10n8.m) Tr 2,39 min, *m/z* 474 $[M-H]^-$; ^1H RMN (DMSO): δ 1,9 (s, 1H), 2,3-2,5 (m, 3H), 3,6 (s, 4H), 4,85 (s, 1H), 4,9 (s, 2H), 7,13-7,2 (d, 1H), 7,27-7,45 (m, 4H), 7,5-7,6 (m, 2H), 7,75-7,83 (d, 1H), 8,05-8,1 (s, 1H).

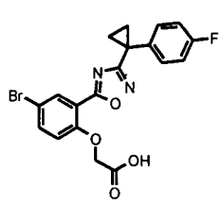


D5

Ácido {4-bromo-2-[3-(4-fenil-piperidin-4-il)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se preparó el compuesto del título a partir del producto intermedio IM2 e hidróxido de litio tal como sigue:

Al éster (0,10 mmol) en THF (0,5 ml) se le añadió $LiOH \cdot H_2O$ (6,3 mg, 0,15 mmol) en agua (0,5 ml). Se agitó la reacción a temperatura ambiente durante >2 h, se añadió HCl ac. hasta que se produjo la precipitación. Se eliminó por filtración el precipitado y se secó a vacío para dar el compuesto del título.

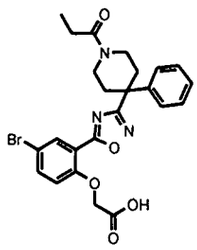
LC/EM (an10n8.m) Tr 2,33 min, *m/z* 458 $[M-H]^-$; ^1H RMN (DMSO): δ 2,3 (m, 2H), 2,8 (m, 2H), 2,95 (m, 2H), 3,2 (m, 2H), 4,4 (s, 2H), 6,9 (s, 1H), 7,3 (m, 1H), 7,4 (m, 4H), 7,65 (d, 1H), 8,0(s, 1H),



D6

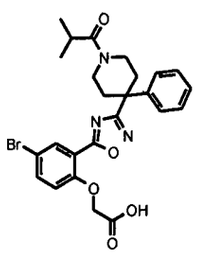
Ácido (4-bromo-2-{3-[1-(4-fluoro-fenil)-ciclopropil]-[1,2,4]oxadiazol-5-il}-fenoxi)-acético. Se preparó el compuesto del título a partir de éster metílico del ácido

5-bromo-2-hidroxibenzoico y 1-(4-fluoro-fenil)-ciclopropanocarbonitrilo según PG6, PG2, PG3, PG4 y PG5 LC/EM (tfa20p5.m) Tr 3,09 min, *m/z* 436 $[M+H]^-$; ^1H RMN (DMSO): δ 1,45 (m, 2H), 1,65 (m, 2H), 4,9 (s, 2H), 7,1-7,2 (m, 3H), 7,4-7,55 (m, 2H), 7,8 (dd, 1H), 8,0 (d, 1H).



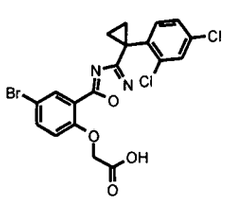
D7

Ácido {4-bromo-2-[3-(4-fenil-1-propionil-piperidin-4-il)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se preparó el compuesto del título a partir del producto intermedio IM2 y cloruro de propionilo según PG8 y PG5: LC/EM (tfa20p5.m) Tr 2,78 min, *m/z* 514 $[M+H]^-$; ^1H RMN (DMSO): δ 0,95-1,0 (t, 3H), 2,0-2,2 (m, 2H), 2,3-2,4 (m, 2H), 2,55-2,70 (m, 2H), 2,8-2,95 (m, 1H),3,15-3,3 (m, 1H), 3,75-3,9 (m, 1H), 4,15-4,3 (m, 1H), 4,85 (s, 2H), 7,13-7,18 (d, 1H), 7,2-7,28 (m, 1H), 7,31-7,43 (m, 4H), 7,74-7,80 (dd, 1H), 8,03-8,06 (d, 1H).



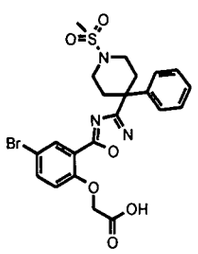
D8

Ácido {4-bromo-2-[3-(1-isobutiril-4-fenil-piperidin-4-il)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se preparó el compuesto del título a partir del producto intermedio IM2 y cloruro de isobutirilo según PG8 y PG5: LC/EM (tfa20p5.m) Tr 2,947 min, *m/z* 528 $[M+H]^-$; ^1H RMN (DMSO): δ 0,95 1,05 (m, 6H), 1,95-2,02 (m, 2H), 2,6-2,75 (m, 2H), 2,8-2,95 (m, 2H), 3,2-3,3 (m, 1H), 3,85-3,95 (m, 1H), 4,2-4,3 (m, 1H), 4,85 (s, 2H), 7,1-7,17 (d, 1H), 7,2-7,28 (m, 1H), 7,31-7,44 (m, 4H), 7,73-7,78 (dd, 1H), 8,5(d, 1H).



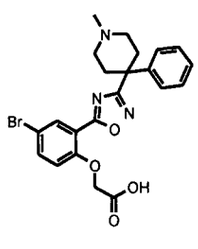
D9

Ácido (4-bromo-2-{3-[1-(2,4-dicloro-fenil)-ciclopropil]-[1,2,4]oxadiazol-5-il}-fenoxi)-acético. Se preparó el compuesto del título a partir de éster metílico del ácido 5-bromo-2-hidroxibenzoico y 1-(2,4-dicloro-fenil)-ciclopropanocarbonitrilo según PG6, PG2, PG3, PG4 y PG5: LC/EM (tfa20p5.m) Tr 3,483 min, *m/z* 485 $[M+H]^-$; ^1H RMN (DMSO): δ 1,4-1,5 (m, 2H), 1,7-1,8 (m, 2H), 4,6 (s, 2H), 7,0-7,04 (d, 1H), 7,44-7,49 (dd, 1H), 7,58-7,62 (d, 1H), 7,66-7,68 (d, 1H), 7,69-7,75 (dd, 1H), 7,96-7,99 (d, 1H).



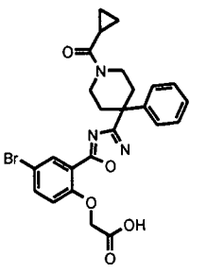
D10

Ácido {4-bromo-2-[3-(1-metanosulfonil-4-fenil-piperidin-4-il)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se preparó el compuesto del título a partir del producto intermedio IM2 y cloruro de metanosulfonilo según PG8 y PG5: LC/EM (tfa20p5.m) Tr 2,725 min, *m/z* 538 $[M+H]^-$; ^1H RMN (DMSO): δ 2,2-2,3 (m, 2H), 2,7-3,0 (m, 7H), 3,5-3,6 (m, 2H), 4,9 (s, 2H), 7,14-7,19 (d, 1H), 7,21-7,29 (m, 1H), 7,32-7,44 (m, 4H), 7,75-7,80 (dd, 1H), 8,05-8,08 (d, 1H).



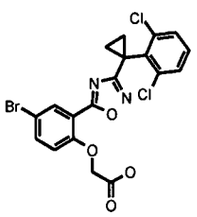
D11

Ácido {4-bromo-2-[3-(1-metil-4-fenil-piperidin-4-il)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se preparó el compuesto del título a partir del producto intermedio IM2 y formaldehído según PG9 y PG5: LC/EM (tfa20p5.m) Tr 1,849 min, *m/z* 474$[M+H]^-$; ^1H RMN (DMSO): δ 2,25-2,4 (m, 5H), 2,5 (m, 2H), 2,65-2,75 (m, 2H), 2,95-3,05 (m, 2H), 4,7 (s, 2H), 7,03-7,1 (d, 1H), 7,2-7,29 (m, 1H), 7,3-7,45 (m, 4H), 7,67-7,73 (dd, 1H), 8,01-8,04 (d, 1H).



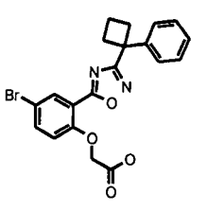
D12

Ácido {4-bromo-2-[3-(1-ciclopropanocarbonil-4-fenil-piperidin-4-il)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se preparó el compuesto del título a partir del producto intermedio IM2 y cloruro de ciclopropanocarbonilo según PG8 y PG5: LC/EM (tfa20p5.m) Tr 2,82 min, *m/z* 528 $[M+H]^-$; ^{1}H RMN (DMSO): δ 0,68-0,70 (m, 4H), 2,00-2,27 (m, 2H), 2,72 (m, 2H), 3,1 (m, 1H), 4,08 (m, 1H), 4,18 (m, 2H), 4,91 (s, 2H), 7,15-7,18 (d, 1H), 7,25-7,27(m, 1H), 7,32-7,42 (m, 4H), X (7,76-7,80) (dd, 1H), 8,05-8,06 (d, 1H),



D13

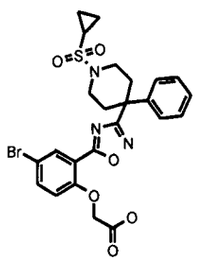
Ácido (4-bromo-2-{3-[1-(2,6-dicloro-fenil)-ciclopropil]-[1,2,4]oxadiazol-5-il}-fenoxi)-acético. Se preparó el compuesto del título a partir de éster metílico del ácido 5-bromo-2-hidroxibenzoico y 1-(2,6-dicloro-fenil)-ciclopropanocarbonitrilo según PG6, PG2, PG3, PG4 y PG5: LC/EM (tfa20p5.m) Tr 3,313 min, *m/z* 485 $[M+H]^-$; ^{1}H RMN (DMSO): δ 1,54-1,58 (m, 2H), 1,93-1,98 (m, 2H), 4,89 (s, 2H), 7,15-7,19 (d, 1H), 7,39-7,55 (m, 2H), 7,77-7,81 (dd, 1H), 8,04-8,05 (d, 1H).



D14

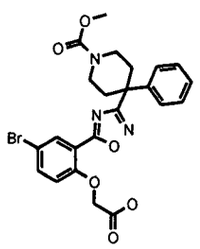
Ácido {4-bromo-2-[3-(1-fenil-ciclobutil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se preparó el compuesto del título a partir de éster metílico del ácido 5-bromo-2-hidroxibenzoico y 1-fenil-ciclobutanocarbonitrilo según PG6, PG2, PG3, PG4 y PG5: LC/EM (an10p,8.m) Tr 2,90 min, *m/z* 429 $[M+H]^-$; ^{1}H RMN (DMSO): δ 1,97 (m, 1H), 2,08 (m, 1H), 2,68-2,72 (m, 2H), 2,87 (m, 2H), 4,90 (s, 2H), 7,14-7,17 (d, 1H),

7,22-7,26 (m, 1H), 7,35-7,36 (m, 4H), 7,75-7,79 (dd, 1H), 8,00-8,02 (d, 1H), 13,17 (s, 1H).



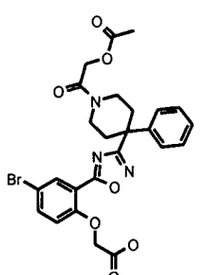
D15

Ácido {4-bromo-2-[3-(1-ciclopropanosulfonil-4-fenil-piperidin-4-il)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se preparó el compuesto del título a partir del producto intermedio IM2 y cloruro de ciclopropanosulfonilo según PG8 y PG5: LC/EM (tfa20p5.m) Tr 2,9 min, *m/z* 564 $[M+H]^-$; ^1H RMN (DMSO): δ 0,98 (m, 4H) , 2,2 (m, 2H), 2,56 (m, 1H), 2,75 (m, 2H), 3,04 (m, 2H), 3,58 (m, 2H), 4,9 (s, 2H), 7,15-7,18 (d, 1H), 7,25-7,28 (m, 1H), 7,33-7,42 (m, 4H), 7,77-7,78 (dd, 1H), 8,06-8,07 (d, 1H), 13,2 (s, 1H).



D16

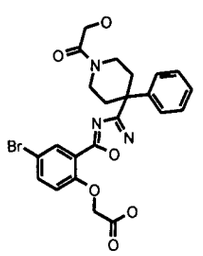
Éster metílico del ácido 4-[5-(5-bromo-2-carboximetoxi-fenil)-[1,2,4]oxadiazol-3-il]-4-fenil-piperidin-1-carboxílico. Se preparó el compuesto del título a partir del producto intermedio IM2 y cloroformiato de metilo según PG8 y PG5: LC/EM (tfa20p5.m) Tr 2,8 min, *m/z* 516 $[M+H]^-$; ^1H RMN (DMSO): δ 2,1 (m, 2H), 2,65 (m, 2H), 3,08 (m, 2H), 3,6 (s, 3H), 3,9 (m, 2H), 4,9 (s, 2H), 7,15-7,19 (d, 1H), 7,21-7,28 (m, 1H), 7,3-7,42 (m, 4H), 7,76-7,81 (dd, 1H), 8,30-8,50 (d, 1H).



D17

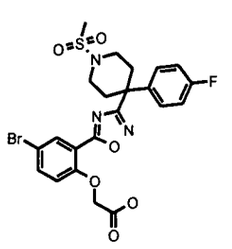
Ácido (2-{3-[1-(2-acetoxi-acetil)-4-fenil-piperidin-4-il]-[1,2,4]oxadiazol-5-il}-4-bromo-fenoxi)-acético. Se preparó el compuesto del título a partir de D5 y cloruro de acetoxiacetilo tal como sigue:

Se agitó una mezcla de D5 (230 mg, 0,5 mmol), cloruro de acetoxiacetilo (120 µl, 1,1 mmol) y trietilamina (160 µl, 1,1 mmol) en tetrahidrofurano (10 ml) a 0ºC durante 2 horas, bajo una atmósfera de argón. Se concentró la mezcla de reacción a vacío. Se repartió el residuo entre diclorometano y agua. Se separaron las fases y se secó la fase orgánica sobre $MgSO_4$ y se concentró a vacío. Se purificó el residuo sobre cromatografía en gel de sílice (eluyente: CH_2Cl_2/MeOH: 10/1) para dar el compuesto del título (41 mg, 0,07 mmol, 15%). LC/EM (tfa20p5.m) Tr 2,5 min, *m/z* 560 $[M+H]^-$; ^1H RMN (DMSO): δ 2,0 (m, 4H), 2,25 (m, 1H), 2,65 (m, 2H), 2,9 (m, 1H), 3,3 (m, 1H), 3,7 (m, 1H), 4,15 (m, 1H), 4,42 (s, 2H), 4,8 (d, 2H), 6,95-6,99 (d, 1H), 7,12-7,28 (m, 1H), 7,31-7,41 (m, 4H), 7,65-7,71 (dd, 1H), 7,98-8,00 (d, 1H).



D18

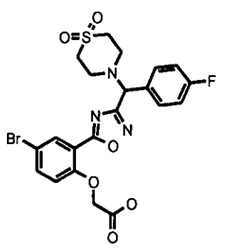
Ácido (4-bromo-2-{3-[1-(2-hidroxi-acetil)-4-fenil-piperidin-4-il]-[1,2,4]oxadiazol-5-il}-fenoxi)-acético. Se preparó el compuesto del título a partir del producto intermedio IM2 y cloruro de acetoxiacetilo según PG8 y PG5: LC/EM (tfa20p5.m) Tr 2,4 min, *m/z* 516 $[M+H]^-$;



D19

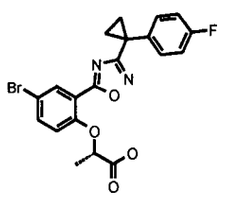
Ácido (4-bromo-2-{3-[4-(4-fluoro-fenil)-1-metanosulfonil-piperidin-4-il]-[1,2,4]oxadiazol-5-il}-fenoxi)-acético. Se preparó el compuesto del título a partir del producto intermedio IM4 y cloruro de metanosulfonilo según PG8 y PG5: LC/EM

(tfa20p5.m) Tr 2,8 min, *m/z* 556 $[M+H]^-$; ^1H RMN (DMSO): δ 2,35 (m, 2H), 2,7-3,0 (m, 7H), 3,55 (m, 2H), 4,9 (s, 2H), 7,14-7,22 (m, 3H), 7,42-7,50 (m, 2H), 7,77-7,82 (dd, 1H), 8,08-8,09 (d, 1H).



D20

Ácido (4-bromo-2-{3-[(1,1-dioxo-1lambda*6*-tiomorfolin-4-il)-(4-fluoro-fenil)-metil]-[1,2,4]oxadiazol-5-il}-fenoxi)-acético. Se preparó el compuesto del título a partir de éster metílico del ácido 5-bromo-2-hidroxibenzoico y el producto intermedio IM5 según PG1, PG3, PG4 y PG5: LC/EM (tfa20p5.m) Tr 2,62 min, *m/z* 540 $[M+H]^-$; ^1H RMN ($CDCl_3$): δ 3,12 (m, 8H), 4,78 (s, 2H), 5,14 (s, 1H), 6,97 (d, 1H), 7,10 (t, 2H), 7,48 (dd, 2H), 7,74 (dd, 1H), 8,23 (s, 1H).



D21

Ácido (S)-2-(4-bromo-2-{3-[1-(4-fluoro-fenil)-ciclopropil]-[1,2,4]oxadiazol-5-il}-fenoxi)-propiónico. Se preparó el compuesto del título a partir de éster metílico del ácido 5-bromo-2-hidroxibenzoico, 1-(4-fluoro-fenil)-ciclopropanocarbonitrilo y (R)-2-(trifluorometilsulfonil)propionato de etilo según PG6, PG2, PG3, PG4 y PG5: LC/EM (tfa20p5.m) Tr 3,20 min, *m/z* 447$[M+H]^-$; ^1H RMN ($CDCl_3$): δ ,1,36-1,38 (m, 2H), 1,61-1,65 (m, 2H),1,69-1,72 (d, 3H), 3,65-3,67 (m, 1H), 6,88-6,91 (d, 1H), 6,96-7,01 (m, 2H), 7,37-7,41 (m, 2H), 7,60-7,63 (dd, 1H), 8,06-8,07 (d, 1H).

Ensayos Biológicos

Materiales y Métodos

Generación/origen de los constructos de ADNc. Se amplificó la secuencia codificante del receptor humano CRTH2 (número de registro en el banco de genes NM_004778) mediante PCR a partir de un biblioteca de ADNc de hipocampo humano

y se insertó en el vector de expresión pADNc3.1(+) (invitrogen) mediante 5' HindIII y 3' EcoRI. Para generar una proteína de fusión de CRTH2-luciferasa de *Renilla* (CRTH2-Rluc), se amplificaron la secuencia codificante de CRTH2 sin un codón de terminación y Rluc, se fusionaron en marco mediante PCR y se subclonaron en el vector de expresión pADNc3.1(+)Zeo (invitrogen). Se adquirieron β-arrestina2 humana (β-arr2) marcada en el extremo N-terminal con GFP^2 (βarr2-GFP^2) y la luciferasa de *Renilla* de BioSignal Packard Inc, (Montreal, Canadá). Se verificó la identidad de la secuencia del constructo mediante los digestos de la endonucleasa de restricción y la secuenciación en ambas direcciones en un ABI Prism (Applied Biosystems, Foster City, CA).

Cultivo celular y transfección. Se hicieron crecer células COS-7 en medio Eagle modificado por Dulbecco (DMEM) 1885 complementado con un 10% de suero bovino fetal, 100 unidades/ml de penicilina, 1000 µg/ml de estreptomicina, y se mantuvieron a 37ºC en una atmósfera de CO_2 al 10%. Se mantuvieron células HEK293 en medio mínimo esencial (MEM) complementado con un 10% (v/v) de suero de ternero fetal inactivado por calor (HIFCS), Glutamax™-I 2 mM, un 1% de aminoácidos no esenciales (NEAA), un 1% de piruvato de sodio y 10 µg/ml de gentamicina. Para los experimentos de unión, se transfectaron transitoriamente células COS7 con el receptor CRTH2 usando un método de coprecipitación con fosfato de calcio-ADN con la adición de cloroquina (tal como se describió por Holst *et al.*, 2001). Para realizar los ensayos de transferencia de energía por resonancia en bioluminiscencia (BRET) funcional, se generó un clon de células HEK293 que expresaba de manera estable βarr2-GFP^2 y CRTH2-Rluc (CRTH2-células HEK293).

Ensayo de unión. 24 h tras la transfección, se sembraron células COS-7 en placas de 96 pocillos en una densidad de 30.000 células/pocillo. Entonces se realizaron los experimentos de unión por competencia de células enteras aproximadamente 18-24 h más tarde usando [^{3}H]PGD2 0,1 nM (NEN, 172 Ci/mmol) en un tampón de unión que consistía en HBSS (GIBCO) y HEPES 10 mM. Se diluyeron los ligandos de competencia en DMSO que se mantuvo constante en el 1% (v/v) del volumen de incubación final. Se determinaron la unión total y la no específica en ausencia y presencia de PGD2 10 µM. Se realizaron rutinariamente reacciones de unión durante 3 h a 4ºC y se terminaron mediante 2 lavados (100 µl cada uno) con tampón de unión helado. Se determinó la radiactividad mediante recuento de centelleo líquido en un TOPCOUNTER (Packard) seguido por incubación durante la noche en Microscint 20. Se sembraron células HEK293 estables en una densidad de 30.000

células/pocillo 18-24 h antes al ensayo de unión que se realizó esencialmente tal como se describió anteriormente para las células COS7. Se realizaron las determinaciones por duplicados.

Ensayo de BRET. Se realizaron los ensayos de BRET funcionales en células HEK293 que expresaban de manera estable GFP^2-β-arr2 y CRTH2-Rluc humano. Antes de su uso en el ensayo de BRET se separaron las células y se resuspendieron en D-PBS con 1000 mg/L de L-glucosa en una densidad de $2x10^6$ células/ml. Se diluyó DeepBlueC™ hasta 50 μM en D-PBS con 1000 mg/L de L-glucosa (sensible a la luz). Se transfirieron 100 μL de suspensión de células a pocillos en una microplaca de 96 pocillos (white OptiPlate) y se colocaron en el instrumento Mithras LB 940 (BERTHOLD TECHNOLOGIES, Bad Wildbad, Alemania). Entonces se inyectaron 12 μl/pocillo de agonista mediante el inyector 1 y se inyectaron simultáneamente 10 μl/pocillo de DeepBlueC™ mediante el inyector 2. Cinco segundos tras las inyecciones se medió la salida de luz del pocillo secuencialmente a 400 nm y 515 nm, y se calculó la señal de BRET (razón de mBRET) mediante la razón de la fluorescencia emitida mediante GFP^2-β-arr2 (515 nm) con respecto a la luz emitida por el receptor-Rluc (400 nm). Se añadieron los antagonistas antes de colocar las microplacas en el Mithras LB 940 y se las dejó incubar durante 15 minutos antes de la adición del agonista y DeepBlueC™. Se disolvieron los compuestos en DMSO y se mantuvo constante la concentración de DMSO final en el 1% en el ensayo.

Ensayo de cambio de forma de eosinófilos humanos. Se recogieron muestras de sangre de voluntarios sanos según un protocolo aprobado por el Comité Ético de la Universidad de Graz y se procesaron tal como se describió anteriormente (Bohm *et al.*, 2004). Se prepararon preparaciones de leucocitos polimorfonucleares (que contienen eosinófilos y neutrófilos) mediante sedimentación de dextrano de la sangre completa tratada con citrato y gradientes de Histopaque. Se lavaron las células resultantes y se resuspendieron en tampón de ensayo (que comprende PBS con Ca^{2+}/Mg^{2+} complementado con BSA al 0,1%, HEPES 10 mM y glucosa 10 mM, pH 7,4) en $5x10^6$ células/ml. Se incubaron las células con los antagonistas o vehículo (PBS o DMSO) durante 10 min a 37°C y entonces se estimularon con diversas concentraciones de los agonistas (PGD2 o eotaxina) durante 4 min a 37°C. Para parar la reacción, se trasfirieron las muestras a hielo y se fijaron con 250 μL de disolución de fijación. Se analizaron inmediatamente las muestras en un citómetro de flujo

FACSCalibur (Becton Dickinson) y se identificaron los eosinófilos según su autofluorescencia en los canales FL-1 y FL-2. Se cuantificaron las respuestas de cambios de formas como el porcentaje de la respuesta máxima a PGD2 o eotaxina en ausencia de un antagonista.

Materiales

Se adquirieron los medios de cultivo tisulares y los reactivos de Gibco invitrogen corporation (Breda, Países Bajos). Se obtuvo PGD2 de Cayman y [3H]PGD2 de NEN.

Análisis de los datos

Se realizó el análisis de curva con el software GraphPadPrism 3.0 (Graphpad Prism Inc., San Diego, EE.UU.) y se calcularon los valores de CI_{50} como una medida de las potencias antagonistas.

Bibliografía

Holst B, Hastrup H, Raffetseder U, Martini L, Schwartz TW. Two active molecular phenotypes of the tachykinin NK1 receptor revealed by G-protein fusions and mutagenesis. J Biol Chem. 8 de junio de 2001; 276(23):19793-9. Epub 22 de febrero de 2001.

Datos biológicos:

Se sometieron los compuestos a prueba en el ensayo de unión del receptor y el ensayo del antagonista funcional descrito más adelante, y se evaluaron sus valores de CI_{50}. Se agruparon los compuestos en tres clases:

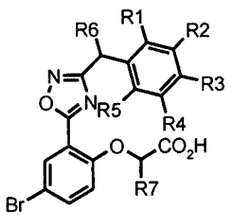
A: Valor de CI_{50} inferior a 0,5 μM

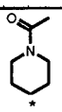
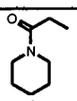
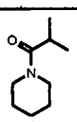
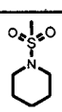
B: Valor de CI_{50} entre 0,5 μM y 5 μM

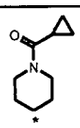
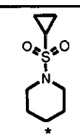
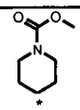
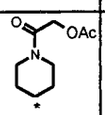
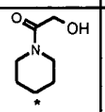
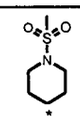
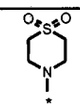
C: Valor de CI_{50} superior a 5 μM

La tabla 1 facilita los resultados de las pruebas biológicas para los compuestos sintetizados anteriormente.

Tabla 1

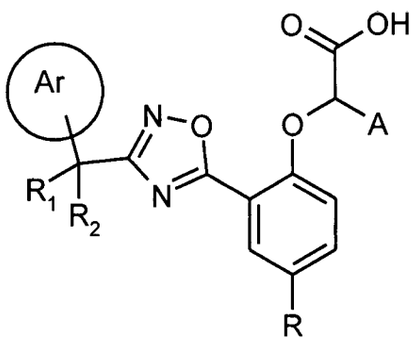


	R1	R2	R3	R4	R5	R6	R7	Unión CI_{50}	Antag. CI_{50}
D1	H	H	H	H	H		H	A	A
D2	H	H	H	H	H		H	A	A
D3	H	H	H	H	H		H	A	A
D4	H	H	H	H	H		H	A	A
D5	H	H	H	H	H		H	A	B
D6	H	H	F	H	H		H	A	A
D7	H	H	H	H	H		H	A	A
D8	H	H	H	H	H		H	A	A
D9	Cl	H	Cl	H	H		H	A	A
D10	H	H	H	H	H		H	A	A
D11	H	H	H	H	H		H	A	A

D12	H	H	H	H	H		H	A	A
D13	Cl	H	H	H	Cl		H	A	A
D14	H	H	H	H	H		H	A	A
D15	H	H	H	H	H		H	A	A
D16	H	H	H	H	H		H	A	A
D17	H	H	H	H	H		H	A	A
D18	H	H	H	H	H		H	A	A
D19	H	H	F	H	H		H	A	A
D20	H	H	F	H	H		H	A	A
D21	H	H	F	H	H		(S)CH_3	A	A

REIVINDICACIONES

1. Compuesto de fórmula (I) o una sal, hidrato o solvato del mismo diferente del ácido {4-bromo-2-[3-(1-fenilciclopropil)-[1,2,4]oxadiazol-5-il]fenoxi}acético o una sal, hidrato o solvato del mismo:



(I)

en la que

R_1 es hidrógeno o metilo y R_2 es cicloalquilo opcionalmente sustituido, o heterociclilo no aromático opcionalmente sustituido que tiene de 4 a 6 átomos en el anillo; o R_1 y R_2, tomados junto con el átomo de carbono al que están unidos forman un cicloalquilo opcionalmente sustituido, o anillo de heterociclilo no aromático opcionalmente sustituido que tiene de 4 a 6 átomos en el anillo;

R es hidrógeno o un sustituyente opcional;

el anillo de fenilo que contiene el sustituyente R está opcionalmente sustituido por 1, 2 ó 3 sustituyentes opcionales;

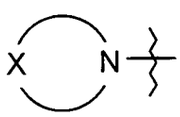
A es hidrógeno o alquilo C_1-C_3;

el anillo Ar es un anillo de heteroarilo monocíclico con 5 ó 6 miembros o de fenilo opcionalmente sustituidos .

2. Compuesto según la reivindicación 1, en el que R_1 es hidrógeno o metilo y R_2 es ciclohexilo, ciclopentilo, ciclobutilo, o ciclopropilo opcionalmente sustituidos.

3. Compuesto según la reivindicación 1, en el que R_1 es hidrógeno o metilo y R_2 es ciclopropilo.

4. Compuesto según la reivindicación 1, en el que R_1 es hidrógeno o metilo y R_2 es un radical de fórmula



en la que el anillo contiene de 4 a 6 átomos en el anillo, y X se selecciona de

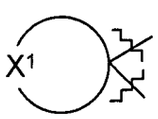
$-CH_2-$, -CH(alquil C_1-C_3)-, -C(alquil C_1-C_3)$_2$-, -CH(cicloalquilo), $-CH(NH_2)-$, $-C(CH_3)(NH_2)-$, -CH(NH(alquil C_1-C_3))-, -CH(N(alquil C_1-C_3)$_2$)-, -CH(NH(cicloalquil))-, -CH(NHCO(alquil C_1-C_3))-, -CH(NHCO(cicloalquil))-, $-CH(NHSO_2$(alquil C_1-C_3))-, $-CH(NHSO_2$(cicloalquil))-, -CH(OH)-, -CH(alcoxi C_1-C_3)-, -CH(cicloalquiloxi)-, -CO-, $-SO_2-$, -O-, -NH-, -N(alquil C_1-C_3)-, -N(cicloalquil)-, -CONH-, -CON(alquil C_1-C_3)-, -CON(cicloalquil)-, -N(CO(O-alquil C_1-C_3))-, -N(CO(O-cicloalquil))-, $-N(CO(CH_2OH))-$, $-SO_2NH-$, $-SO_2N$(alquil C_1-C_6)-, $-SO_2N$(cicloalquil)-, $-N(SO_2$(alquilo C_1-C_3))-, $-N(SO_2$(cicloalquil))-, -N(CO(alquil C_1-C_3))- o -N(CO(cicloalquil))-.

5. Compuesto según la reivindicación 4, en el que X es $-CH_2-$, $-SO_2-$, -CO- (cuando está adyacente a N), -O-, $-N(SO_2$(alquil C_1-C_3))-, $-N(SO_2$(cicloalquil))-, -N(CO(alquil C_1-C_3))-, -N(CO(cicloalquil))-, -CONH-, -CON(alquil C_1-C_3)- o -CON(cicloalquil)-.

6. Compuesto según la reivindicación 1, en el que R_1 y R_2, tomados junto con el átomo de carbono al que están unidos forman un anillo de ciclohexilo, ciclopentilo, ciclobutilo o ciclopropilo opcionalmente sustituidos.

7. Compuesto según la reivindicación 6, en el que R_1 y R_2, tomados junto con el átomo de carbono al que están unidos forman un anillo de ciclopropilo.

8. Compuesto según la reivindicación 1, en el que R_1 y R_2, tomados junto con el átomo de carbono al que están unidos forman un anillo divalente de fórmula



en la que el anillo contiene de 4 a 6 átomos en el anillo y X^1 se selecciona de $-CH_2-$, -CH(alquil C_1-C_3)-, -C(alquil C_1-C_3)$_2$-, -CH(cicloalquilo), $-CH(NH_2)-$, $-CMe(NH_2)-$, -CH(NH(alquil C_1-C_3))-, -CH(N(alquil C_1-C_3)$_2$)-, -CH(NH(cicloalquil))-, -CH(NHCO(alquil C_1-C_3))-, -CH(NHCO(cicloalquil))-, $-CH(NHSO_2$(alquil C_1-C_3))-, $-CH(NHSO_2$(cicloalquil))-, -CH(OH)-, -CH(alcoxi C_1-C_3)-, -CH(cicloalquiloxi])-, $-SO_2-$, -O-, -NH-, -N(alquil C_1-C_3)-, -N(cicloalquil)-, -CONH-, -CON(alquil C_1-C_3)-, -CON(cicloalquil)-, $-SO_2NH-$, $-SO_2N$(alquil C_1-C_6)-, $-SO_2N$(cicloalquil)-, $-N(SO_2$(alquil C_1-C_3))-, $-N(SO_2$(cicloalquil))-, -N(CO(O alquil C_1-C_3))-,-N(CO(O-cicloalquil))-, $-N(CO(CH_2OH))-$, -N(CO(alquil C_1-C_3))- o -N(CO(cicloalquil))-.

9. Compuesto según la reivindicación 8, en el que X^1 es $-CH_2-$, $-SO_2-$, -O-,

-CONH-, -CON(alquil C_1-C_3)-, -CON(cicloalquil)-, -N(SO_2(alquilo C_1-C_3))-, -N(SO_2(cicloalquil))-, -N(CO(alquil C_1-C_3))- o -N(CO(cicloalquil))-.

10. Compuesto según cualquiera de las reivindicaciones anteriores, en el que A es hidrógeno o metilo.

11. Compuesto según cualquiera de las reivindicaciones anteriores, en el que R es flúor, cloro, bromo, alquilo (C_1-C_3), cicloalquilo, trifluorometilo, alcoxilo (C_1-C_3), alquilmercapto (C_1-C_3), trifluorometoxilo, trifluorometiltio, ciano, (alquil C_1-C_3)SO_2-, NH_2SO_2-, (alquil C_1-C_3)$NHSO_2$-, (alquil C_1-C_3)$_2NSO_2$-, (cicloalquil)$NHSO_2$-, NH_2CO-, (alquil C_1-C_3)NHCO-, (alquil C_1-C_3)$_2$NHCO- o (cicloalquil)NHCO-.

12. Compuesto según cualquiera de las reivindicaciones anteriores, en el que anillo Ar es tiazolilo, furanilo, pirrolilo, quinolinilo, triazinilo, oxazolilo, diazolilo, pirimidilo, piridilo o fenilo opcionalmente sustituidos.

13. Compuesto según cualquiera de las reivindicaciones anteriores, en el que los sustituyentes opcionales en Ar se seleccionan de flúor, cloro, bromo, alquilo (C_1-C_3), cicloalquilo, trifluorometilo, alcoxilo (C_1-C_3), trifluorometoxilo, trifluorometiltio, ciano, NH_2CO-, (alquil C_1-C_3)NHCO-, (alquil C_1-C_3)$_2$NHCO-, (cicloalquil)NHCO-, (alquil C_1-C_3)SO_2-, NH_2SO_2-, (alquil C_1-C_3)$NHSO_2$-, (cicloalquil)$NHSO_2$- y (alquil C_1-C_3)$_2NSO_2$-.

14. Compuesto según cualquiera de las reivindicaciones 1 a 11, en el que Ar es un anillo de piridona o un anillo de N-óxido de piridina.

15. Compuesto según cualquiera de las reivindicaciones anteriores, en el que cualquiera de los sustituyentes opcionales en el anillo de fenilo que contiene R se seleccionan de flúor, cloro, bromo, ciano, trifluorometilo, trifluorometoxilo, trifluorometiltio, (alquil C_1-C_3)SO_2-, NH_2SO_2-, (alquil C_1-C_3)$NHSO_2$-, (alquil C_1-C_3)$_2NSO_2$-, alquilo C_1-C_3, fluoroalquilo C_1-C_2, difluoroalquilo C_1-C_2, alcoxilo C_1-C_3, cicloalquilo, arilo, ariloxilo, aril (C_1-C_3)- o aril(alcoxi C_1-C_3)-.

16. Composición farmacéutica que comprende un compuesto según cualquiera de las reivindicaciones anteriores, junto con un vehículo farmacéuticamente aceptable.

17. Uso de un compuesto según cualquiera de las reivindicaciones anteriores, en la fabricación de una composición para el tratamiento de una enfermedad sensible a la modulación de la actividad del receptor CRTH2.

18. Método de tratamiento de una enfermedad sensible a la modulación de la actividad del receptor CRTH2 que comprende administrar a un sujeto que

padece tal enfermedad una cantidad eficaz de un compuesto según cualquiera de las reivindicaciones anteriores.

19. Uso según la reivindicación 17 o método según la reivindicación 18, en el que la enfermedad es una asociada con niveles elevados de prostaglandina D2 (PGD2) o uno o más metabolitos activos de la misma.

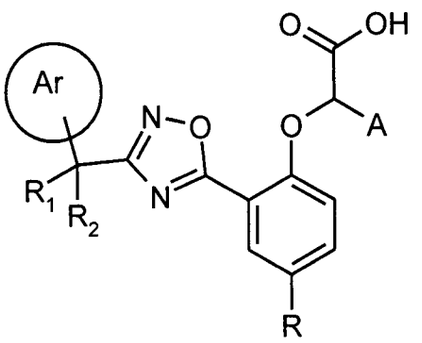
20. Uso según la reivindicación 17 o método según la reivindicación 18, en el que la enfermedad es una enfermedad inflamatoria, autoinmunitaria, respiratoria o alérgica.

21. Uso según la reivindicación 17 o método según la reivindicación 18, en el que la enfermedad se selecciona de asma, rinitis, síndrome alérgico de las vías respiratorias, rinobronquitis alérgica, bronquitis, enfermedad pulmonar obstructiva crónica (EPOC), poliposis nasal, sarcoidosis, pulmón de granjero, fibrosis pulmonar, fibrosis cística, tos crónica, conjuntivitis, dermatitis atópica, enfermedad de Alzheimer, esclerosis lateral amiotrófica, complejo demencia-SIDA, enfermedad de Huntington, demencia frontotemporal, demencia con cuerpos de Lewy, demencia vascular, síndrome de Guillain-Barre, polirradiculoneuropatía desmielinizante crónica, neuropatía motora multifocal, plexopatía, esclerosis múltiple, encefalomielitis, panencefalitis, degeneración cerebelosa y encefalomielitis, traumatismo del SNC, migraña, accidente cerebrovascular, artritis reumatoide, espondiloartritis anquilosante, enfermedad de Behçet, bursitis, síndrome del túnel carpiano, enfermedad inflamatoria intestinal, enfermedad de Crohn, colitis ulcerosa, dermatomiositis, síndrome de Ehlers-Danlos (SED), fibromialgia, dolor miofascial, osteoartritis (OA), osteonecrosis, artritis psoriásica, síndrome de Reiter (artritis reactiva), sarcoidosis, esclerodermia, síndrome de Sjogren, enfermedad de las partes blandas, enfermedad de Still, tendinitis, panarteritis nudosa, granulomatosis de Wegener, miositis (polimiositis - dermatomiositis), gota, aterosclerosis, lupus eritematoso, lupus eritematoso sistémico (LES), diabetes tipo I, síndrome nefrítico, glomerulonefritis, insuficiencia renal aguda y crónica, fascitis eosinofílica, síndrome de hiper-IgE, septicemia, choque septicémico, lesión por reperfusión isquémica en el corazón, rechazo de aloinjerto tras trasplantes y enfermedad de injerto contra huésped.

22. Uso según la reivindicación 17 o método según la reivindicación 18, en el que la enfermedad se selecciona de asma, rinitis, síndrome alérgico de las vías respiratorias y rinobronquitis alérgica.

RESUMEN

Los compuestos de fórmula (I) son ligandos de CRTH2, útiles para el tratamiento de una enfermedad inflamatoria, autoinmunitaria, respiratoria o alérgica:



(I)

en la que R_1 es hidrógeno o metilo y R_2 es cicloalquilo opcionalmente sustituido o heterociclilo no aromático opcionalmente sustituido que tiene de 4 a 6 átomos en el anillo; o R_1 y R_2, tomados junto con el átomo de carbono al que están unidos forman un cicloalquilo opcionalmente sustituido, o anillo de heterociclilo no aromático opcionalmente sustituido que tiene de 4 a 6 átomos en el anillo; R es hidrógeno o un sustituyente opcional; el anillo de fenilo que contiene el sustituyente R está opcionalmente sustituido por 1, 2 ó 3 sustituyentes opcionales; A es hidrógeno o alquilo C_1-C_3; y el anillo Ar es un anillo de heteroarilo monocíclico con 5 ó 6 miembros o de fenilo opcionalmente sustituidos.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/EP2006/011216

International Filing Date 22.11.2006 22 NOV 2006

Name of receiving Office and "PCT International Application" RO/EP

Applicant's or agent's file reference *(if desired) (12 characters maximum)* TM12

Box No. I TITLE OF INVENTION

Oxadiazole Derivatives

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

7TM PHARMA A/S
Fremtidsvej 3
DK-2970 Hoersholm
Denmark

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: DK

State *(that is, country)* of residence: DK

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RECEVEUR, Jean-Marie
7TM Pharma A/S
Fremtidsvej 3
DK-2970 Hoersholm
Denmark

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: DK

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WALLS, Alan James
PO Box 223
Tadworth,
Surrey KT20 ~~5BS~~ 5YF
GB

Telephone No. +44 (0)1737 813849

Facsimile No. +44 (0)1737 813063

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III **FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CHRISTENSEN, Ann
7TM Pharma A/S
Fremtidsvej 3
DK-2970 Hoersholm
Denmark

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: DK

State *(that is, country)* of residence: DK

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GRIMSTRUP, Marie
7TM Pharma A/S
Fremtidsvej 3
DK-2970 Hoersholm
Denmark

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: DK

State *(that is, country)* of residence: DK

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HOEGBERG, Thomas
7TM Pharma A/S
Fremtidsvej 3
DK-2970 Hoersholm
Denmark

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATIONS

The filing of this request **constitutes under Rule 4.9(a), the designation** of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.
However,

- ☐ DE Germany **is not designated** for any kind of national protection
- ☐ JP Japan **is not designated** for any kind of national protection
- ☐ KR Republic of Korea **is not designated** for any kind of national protection
- ☐ RU Russian Federation **is not designated** for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application. See the Notes to Box No. V as to the consequences of such national law provisions in these States).

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 2005* 30/11/~~2006~~* ~~30 November 2006~~ 2005*	0524428.0	GB		
item (2)				
item (3)				

*RO/EP

*RO/EP

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):*

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA / EP .....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

See Notes to the request form

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application **contains:**

(a) **on paper,** the following number of sheets:

request (including declaration sheets)	:	4
description (excluding sequence listing and/or tables related thereto)	:	32
claims	:	5
abstract	:	1
drawings	:	0
Sub-total number of sheets	:	42
sequence listing	:	
tables related thereto	:	
(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)		
Total number of sheets	:	42

(b) ☐ **only in electronic form** (Section 801(a)(i))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

(c) ☐ **also in electronic form** (Section 801(a)(ii))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listing: .....
- ☐ tables related thereto: .....

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is **accompanied** by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item):*

	Number of items
1. ☒ fee calculation sheet	:
2. ☐ original separate power of attorney	:
3. ☐ original general power of attorney	:
4. ☐ copy of general power of attorney; reference number, if any:	:
5. ☐ statement explaining lack of signature	:
6. ☐ priority document(s) identified in Box No. VI as item(s):	:
7. ☐ translation of international application into *(language)*:	:
8. ☐ separate indications concerning deposited microorganism or other biological material	:
9. ☐ sequence listing in electronic form *(indicate type and number of carriers)*	
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:
(ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column	:
10. ☐ tables in electronic form related to sequence listing *(indicate type and number of carriers)*	
(i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application)	:
(ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*)	:
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:
11. ☐ other *(specify)*:	:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: EN

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Alan J Walls
Agent

For receiving Office use only

1. Date of actual receipt of the purported international application: 22.11.2006 22 NOV 2006
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

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

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

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2006/011216	22.11.2006	30.11.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07D271/06 C07D413/04 A61K31/4245 A61P11/00

Applicant
7TM PHARMA A/S

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

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

2. **FURTHER ACTION**

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

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

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

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

Name and mailing address of the ISA:	Date of completion of this opinion	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	see form PCT/ISA/210	De Jong, Bart Telephone No. +31 70 340-2833

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2006/011216

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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

☐ the entire international application

☒ claims Nos. 18-22

because:

☒ the said international application, or the said claims Nos. 18-22 (with respect to industrial application) relate to the following subject matter which does not require an international search *(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 *(specify)*:

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

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

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

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

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

☐ See Supplemental Box for further details

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

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-22
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item III.

Claims 18-22 relate (at least partially) 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).

Re Item V.

Reference is made to the following document:

D1 : WO 2004/089885 A (ASTRAZENECA) 21 October 2004 cited in the application

The present application relates to novel oxadiazol-5-yl-phenoxyacetic acid derivatives of formula (I) having CRTH2 receptor activity. Document D1, which is considered to represent the most relevant state of the art, discloses phenoxyacetic acid in which the phenoxy group can be substituted by a 6-membered aromatic heteroring. The problem to be solved by the present invention may be regarded as the provision of alternative compounds having CRTH2 receptor activity. This problem has been solved by compounds of the present application (see tests on pages 30-32). Starting from D1 it was not obvious to come to the oxadiazol substituted compounds.

For the assessment of the present claims 18-22 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.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

WALLS, Alan, James
P.O. Box 223
Tadworth
Surrey KT20 5YF
ROYAUME-UNI

Date of mailing *(day/month/year)* 16 March 2007 (16.03.2007)	
Applicant's or agent's file reference TM12	**IMPORTANT NOTIFICATION**
International application No. PCT/EP2006/011216	International filing date *(day/month/year)* 22 November 2006 (22.11.2006)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 30 November 2005 (30.11.2005)
Applicant 7TM PHARMA A/S et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)***An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
30 November 2005 (30.11.2005)	0524428.0	GB	22 January 2007 (22.01.2007)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Ellen Moyse
Facsimile No. +41 22 338 82 70
Telephone No. +41 22 338 91 54

93

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-052891- -00000-0000

Fecha: 2008-05-23 15:11:09 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 92

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE

PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia