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División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No** 06-129530

54 **TÍTULO** Uso de ligandos de Receptor en terapia

51 **CLASIFICACIÓN INTERNACIONAL** C07D 277/30 417/06 417/09 A61K

71 **SOLICITANTE** 7TM Pharma A/S

DOMICILIO Hørsholm, Alemania

74 **APODERADO** D/a Nora Rodríguez D' Hemmer

22 **BOGOTÁ, D C,** Dc 27/06

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SUPERINTENDENCIA

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1) SOLICITUD DE

☒ Patente de invención ☐ Patente de Modelo de Utilidad

☒ Capitulo I ☐ Capitulo II

2) S LICITANTE (71)	**Nombre 7TM PHARMA A/S** **Direccion Fremtidsvej 3 DK 2970 Hoersholm Alemania** **Nacionalidad o domicilio Hoersholm Alemania** **Lugar de constitución Alemania**	**IDENTIFICACIÓN** **C C** ☐ **NIT** ☒ **C E** ☐ **OTRO** ☐ **Cual** _____ **NÚMERO** _____
	Telefono Fax **E Mail**	
3) REPRESENTANTE APODERADO	Nombre DILIA MARÍA RODRÍGUEZ D ALEMAN Dirección Carrera 11 N 86 53 Piso 6 Bogotá D C Teléfono 6181088 Fax 6350824 E Mail info@clarkemodet com co	**IDENTIFICACIÓN** **C C** ☒ **NIT** ☐ **C E** ☐ **OTRO** ☐ **NUMERO** 41 654 882 **TP** 20824 CSJ
4) INVENTOR (ES) (72)	**Nombre 1 ULVEN Trond; 2 FRIMURER Thomas; 3 RIST Øystein; 4 KOSTENIS Evi; 5 HÖGBERG Thomas, 6 RECEVEUR Jean Marie; 7 GRIMSTRUP Marie** **Dirección Todos los anteriores 7TM PHARMA A/S Fremtidsvej 3 DK 2970 Hoersholm Alemania** **Nacionalidad o Domicilio Todos los anteriores Hoersholm Alemania**	

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Instrucciones para el diligenciamiento del presente formulario Ver reverso de esta pagina

10) ANEX S

- [x] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Comprobante de pago por reivindicación de prioridad
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- [ ] Poderes si fuera el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud Internacional (Resumen descripción reivindicación Dibujos)
- [x] Traducción de la solicitud internacional al castellano (Resumen descripción reivindicación Dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA
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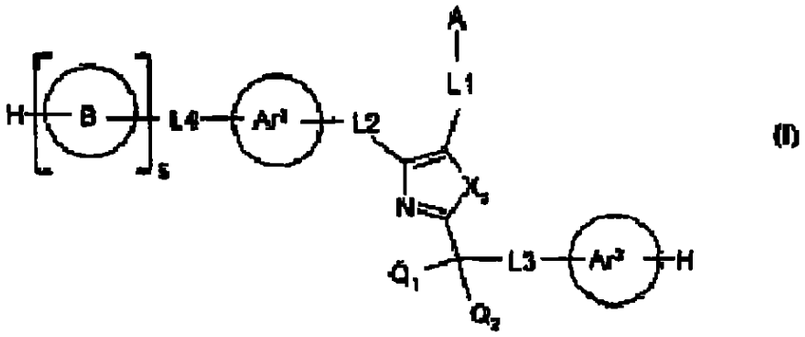
- [ ] De ser el caso documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso certificado de depósito del material biológico
- [ ] Arte final 12 x 12 y 6 x 6 cm
- [ ] De ser el caso información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante relacionados parcial o totalmente con la invención de esta solicitud
- [ ] Otros

11) FIGURA CARACTERÍSTICA



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12) Solicitud concesión de la patente

NOMBRE DILIA RODRÍGUEZ D-ALEMAN

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C C 41 654 882 de Bogota TP 20824 CSJ

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SUPERINTENDENC A DE INDUSTR A Y COMERC O

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(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)*: ULVEN, Trond [NO/DK] 7TM Pharma A/S, Fremtidsvej 3 DK-2970 Hoersholm (DK). FRIMURER, Thomas [DK/DK] 7TM Pharma A/S, Fremtidsvej 3, DK-2970 Hoersholm (DK). RIST Øystein [NO/DK] 7TM Pharma A/S, Fremtidsvej 3 DK-2970 Hoersholm (DK). KOSTENIS, Evi [DE/DK] 7TM Pharm A/S, Fremtidsvej 3 DK 2970 Hoersholm (DK). HÖGBERG Thomas [SE/SE] 7TM Pharma A/S, Fremtidsvej 3, DK 2970 Hoersholm (DK) RECEVEUR, Jean Marie [FR/DK] 7TM Pharma A/S, Fremtidsvej 3 DK-2970 Hoersholm (DK) GRIMSTRUP Marie [NO/DK] 7TM Pharma A/S, Fremtidsvej 3 DK-2970 Hoersholm (DK)

(74) Agent WALLS, Alan, James, P.O Box 223 Tadworth, Surrey KT20 5SS (GB).

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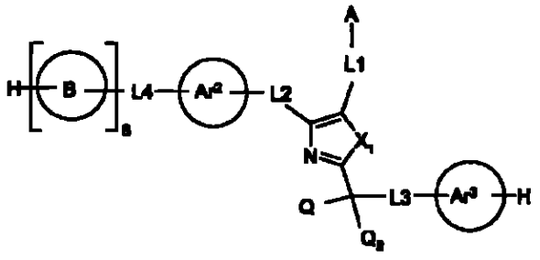
(54) Title: SUBSTITUTED THIAZOLEACETIC AS CRTH2 LIGANDS



(I)

(57) Abstract: Compounds of formula (I) are useful for the treatment of disease responsive to modulation of CRTH2 receptor activity such as asthma rhinitis, allergic airway syndrome and allergic rhinobronchitis wherein X is -S-, -O- N=N NR_7-, $-CR_7=CR_8$- $-CR_7=N-$, where R and R_8 are independently hydrogen or C -C_3 alkyl A is a carboxyl group -COOH or carboxyl bioisostere rings Ar^2 and Ar^3 each independently represent phenyl or 5 or 6-membered monocyclic heteroaryl ring, or 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 ring B is as defined for Ar^2 and Ar^3 or an optionally substituted N-pyrrolidinyl, N piperidinyl or N-azepinyl ring s is 0 or 1 L1 L... and L4 are linker radicals as defined in the description. Q and Q_2 represent substituents as defined in the description.

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SUBSTITUTED THIAZOLEACETIC ACIDS AS CRTH2 LIGANDS

This invention relates to a class of compounds which are ligands of the CRTH2 receptor (Chemoattractant Receptor-homologous molecule expressed on T Helper cells type 2) and their use 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

Background to the invention

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 03/101961 GB 2388540 WO 04/089885 and WO 05/018529

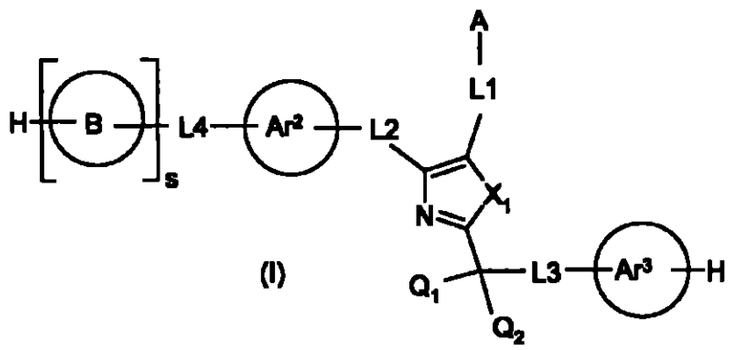
NSAIDs (non-steroidal anti-inflammatory drugs) constitute another class of anti-inflammatory agents One NSAID is 4-(4-chlorophenyl)-2-phenyl thiazole-5 acetic acid (fentiazac) Some other thiazole compounds have been investigate as anti-inflammatory agents (see for example Nagatomi et al Arzneimittel-Forschung (1984) 34(5) 599-603 Bonina et al Farmaco Edizione Scientifica (1987) 42(12 905-13 Greidanowski et al Archivum Immunologiae et Therapiae Experimentalis 1978 26, 921-929 Brown et al J Med Chem 1974 Vol 17 No 11 1177 1181 Attimarad et al Asian J Chem 2004 16(1) 179-182 Japanese Patent publications JP07149745 and 07149746 and International patent publications WO 9727190 WO 2003103657

Brief Description of the Invention

The structures of the PGD2 antagonist compounds referred to in 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 5- or 6-membered nitrogen-containing monocyclic core such as a thiazole ring whose substituent moieties are 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

Detailed Description of the Invention

According to the present invention there is provided a compound of formula (I) or a salt hydrate or solvate thereof



wherein

X_1 is S- -O- N=N –NR_7- -CR_7=CR_8- -CR_7=N- wherein R_7 and R_8 are independently hydrogen or C_1-C_3 alkyl

A is a carboxyl group –COOH or a carboxyl bioisostere;

rings Ar^2 and 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

ring B is as defined for Ar^2 and Ar^3 or an optionally substituted N-pyrrolidinyl N piperidinyl or N-azepinyl ring

s is 0 or 1

L1 represents a divalent radical of formula $-(Alk^1)_m-$ and L2 and L4 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 -$NRSO_2-$ -C(=O)NR- -NRCONH NRC(=NR)NH or =N-NR wherein R is hydrogen or C_1-C_3 alkyl or a divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical

L3 represents a divalent radical of formula $-(Alk^3)_m-(Z)_n-(Alk^2)_p-$ wherein m, n p Alk^2 and Z are as defined in relation to L2 and L4 and Alk3 is an optionally substituted straight or branched chain C_1-C_2 alkylene or C_1-C_2 alkenylene radical which may contain a compatible –O -S- or –NR- link wherein R is hydrogen or C_1 C_3 alkyl

Q_1 represents hydrogen or (C_1-C_6)alkyl

Q_2 represents
(i) (C_1-C_6)alkyl (C_1-C_6)alkoxy hydroxy hydroxy(C_1-C_6)alkyl nitrile (-CN) phenyl phenoxy monocyclic heteroaryl or heteroaryloxy with 5 or 6 ring atoms $-CONR^AR^B$ $-NR^BCOR^A$ $-NR^BSO_2R^A$ or $-NR^ACONR^AR^B$ wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring and when Q is phenyl phenoxy or monocyclic heteroaryl or heteroaryloxy with 5 or 6 ring atoms the phenyl or heteroaryl ring is optionally substituted by any of (C_1-C_6)alkyl (C_1-C_6)alkoxy hydroxy hydroxy(C_1-C_6)alkyl (C_1 C_3)alkylthio halo fully or partially fluorinated (C_1-C_3)alkyl (C_1-C_3)alkoxy or (C_1 C_3)alkylthio, trifluoromethylthio nitro nitrile (-CN) $-COOR^A$ $-COR^A$ $-OCOR^A$ SO_2R^A $CONR^AR^B$ $-SO_2NR^AR^B$ $-NR^AR^B$ NR^BCOR^A NR^BCOOR^A $-NR^BSO_2R^A$ or $NR^ACONR^AR^B$ wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring or

(ii) hydrogen but only when in L3 Z represents an optionally substituted divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical

or Q_1 and Q_2 taken together with the carbon atom to which they are attached form a C_3-C_6 cycloalkyl ring or a monocyclic non-aromatic heterocyclic ring with 4-6 ring atoms

and wherein the total length of L2 and L3 does not exceed that of an unbranched saturated chain of 10 carbon atoms

In a narrower definition of the compounds (I) (i) the length of each of L2 L3 and L4 does not exceed that of an unbranched saturated chain of 5 atoms and (ii) the total length of L2, L3 and L4 does not exceed that of an unbranched saturated chain of 7 atoms, and (iii) none of L1 L2 L3 and L4 includes more than two R substituents different from hydrogen

The compounds with which the invention is concerned are defined by reference to formula (I) as a result of studies towards elucidation of the ligand binding site of CRTH2 Such studies led to the overall conclusion that a general pharmacophore comprising one negatively charged moiety represented by AL1 and two aromatic and/or hydrophobic moieties represented by $H(B)_nL4Ar^2L2$ and either the ring containing X_1 or the ring containing X_1 together with the $H(Ar^2)L3C(Q_1)(Q_2)$- fragment, oriented in an approximate triangle would form an arrangement for interaction with the receptor binding site It was concluded that the substituent groupings AL1 $H(B)_nL4Ar^2L2$ should be on adjacent ring atoms of the ring containing X_1 The linkers L1 L2 L3 and L4 provide some flexibility to the molecule to facilitate optimum binding The restrictions on the lengths of and and substitutions in the linkers L2 L3 and L4 are in order to restrict the total molecular size and complexity of structures for use in accordance with the invention For the avoidance of doubt, the total length of L2 and L3 is for the purposes of this description and claims the sum n2+n3 where n2 is the number of connected atoms in the shortest chain of atoms from terminal atom to terminal atom of linker L2 and n3 is the number of connected atoms in the shortest chain of atoms from terminal atom to terminal atom of linker L2 Preferably the compounds with which the invention is concerned should have a molecular weight of no more than 600 Optional substituents in any element of the compounds (I) are permitted as in the definition of compounds (I) Such substituents can

modulate pharmacokinetic and solubility properties as well as picking up additional binding interactions with the receptor

In another aspect, the invention provides the use of a compound as defined and discussed herein in the manufacture of a composition for the treatment of disease responsive to modulation of CRTH2 receptor activity

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 discussed herein 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 polyradiculoneuropathy 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 fasciitis hyper IgE syndrome, sepsis, septic shock, ischemic reperfusion injury in the heart, allograft rejection after transplantations and graft versus host disease

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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 $(C_a\text{-}C_b)$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 divalent $(C_a\text{-}C_b)$alkylene radical" wherein a and b are integers refers to a saturated hydrocarbon chain having from a to b carbon atoms and two unsatisfied valences

As used herein the term $(C_a\text{-}C_b)$alkenyl" wherein a and b are integers refers to a straight or branched chain alkenyl moiety having from a to b carbon atoms having at least one double bond of either E or Z stereochemistry where applicable The term includes for example vinyl allyl 1 and 2-butenyl and 2-methyl-2-propenyl

As used herein the term "divalent $(C_a\text{-}C_b)$alkenylene radical means a hydrocarbon chain having from a to a carbon atoms at least one double bond and two unsatisfied valences

As used herein the term $C_a\text{-}C_b$ alkynyl" wherein a and b are integers refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond This term would include for example ethynyl 1 and 2-propynyl 1 2- and 3-butynyl 1 2- 3- and 4-pentynyl 1 2 3- 4- and 5-hexynyl 3-methyl-1 butynyl 1-methyl-2-pentynyl

As used herein the term divalent $(C_a\text{-}C_b)$alkynylene radical" wherein a and b are integers refers to a divalent hydrocarbon chain having from 2 to 6 carbon atoms at least one triple bond and two unsatisfied valences.

As used herein the term carbocyclic" refers to a mono- bi- or tricyclic radical having up to 16 ring atoms all of which are carbon and includes aryl and cycloalkyl

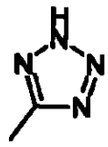
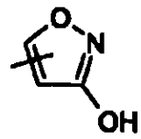
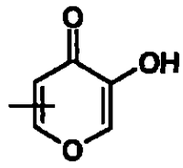
As used herein the term "cycloalkyl" refers to a monocyclic saturated carbocyclic radical having from 3-8 carbon atoms and includes for example, cyclopropyl cyclobutyl cyclopentyl cyclohexyl cycloheptyl and cyclooctyl

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 pyndazinyl 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

The term carboxyl bioisostere is a term familiar to medicinal chemists (see for example "The Organic Chemistry of Drug Design and Drug Action by Richard B Silverman pub Academic Press 1992) and refers to a group which has similar acid base characteristics to those of a carboxyl group Well known carboxyl bioisosteres include $-SO_2NHR$ or $-P(=O)(OH)(OR)$ wherein R is for example hydrogen methyl or ethyl $-SO_2OH$ $P(=O)(OH)(NH_2)$ $-C(=O)NHCN$ and groups of formulae

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-C_6)alkyl (C_1-C_6)alkoxy hydroxy hydroxy(C_1-C_6)alkyl mercapto mercapto(C_1-C_6)alkyl (C_1-C_6)alkylthio halo (including fluoro bromo and chloro) fully or partially fluorinated (C_1-C_3)alkyl (C_1-C_3)alkoxy or (C_1-C_3)alkylthio such as trifluoromethyl trifluoromethoxy and trifluoromethylthio nitro nitrile (-CN) oxo phenyl phenoxy monocyclic heteroaryl or heteroaryloxy with 5 or 6 ring atoms $-COOR^A$ $-COR^A$ $-OCOR^A$ $-SO_2R^A$ $-CONR^AR^B$ $-SO_2NR^AR^B$ 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-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 phenoxy or monocyclic heteroaryl or heteroaryloxy with 5 or 6 ring atoms, the phenyl or heteroaryl ring thereof may itself be substituted by any of the above substituents except phenyl phenoxy heteroaryl or heteroaryloxy 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 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, benzenesulfonic, 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 invention the following structural characteristics are currently preferred In any compatible combination in the compounds (I)

Q_1 is hydrogen and Q_2 is phenyl or monocyclic heteroaryl with 5 or 6 ring atoms optionally substituted by any of $(C_1$-$C_6)$alkyl $(C_1$-$C_6)$alkoxy hydroxy hydroxy$(C_1$-$C_6)$alkyl $(C_1$-$C_3)$alkylthio halo fully or partially fluorinated $(C_1$ $C_3)$alkyl $(C_1$-$C_3)$alkoxy or $(C_1$-$C_3)$alkylthio trifluoromethylthio, nitro nitrile (CN) $-COOR^A$ $-COR^A$ $-OCOR^A$ $-SO_2R^A$ $-CONR^AR^B$ $-SO_2NR^AR^B$ $-NR^AR^B$ 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 $(C_1$-$C_6)$alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring or

Q_1 is hydrogen and Q_2 is phenyl optionally substituted by any of 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$)NHSO_2$- $(C_1$-C_3alkyl$)_2NSO_2$- $-CONR^AR^B$ and $-NR^BCOR^A$ wherein R^A and R^B are independently hydrogen or a $(C_1$-$C_6)$alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

L3 is $-CH_2$- -O- -S- $-SO_2$- –NHC(=O)- -CH=CH- $-NR_{11}$ or $-NR_{11}CH_2$- wherein R_{11} is hydrogen or C_1-C_3 alkyl or

L3 represents a divalent radical of formula $–(Alk^3)_m$-$(Z)_n$-$(Alk^2)_p$- wherein m is 0 n is 1 and Z is a phenylene radical optionally substituted by one or more of 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$)NHSO_2$- $(C_1$-C_3alkyl$)_2NSO_2$- $-CONR^AR^B$ and

NR^BCOR^A wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring In these cases Z may be for example a 1 2-phenylene radical optionally substituted by one or more of fluoro chloro bromo (C_1-C_3)alkyl trifluoromethyl (C_1-C_3)alkoxy trifluoromethoxy trifluoromethylthio dimethylamino cyano $(C_1-C_3$alkyl$)SO_2$- NH_2SO_2- $(C_1-C_3$alkyl$)NHSO_2$- $(C_1-C_3$alkyl$)_2NSO_2$- $-CONR^AR^B$ and $-NR^BCOR^A$ wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

In particular Q_1 may be hydrogen X_1 may be –S- and A is may be carboxyl group –COOH

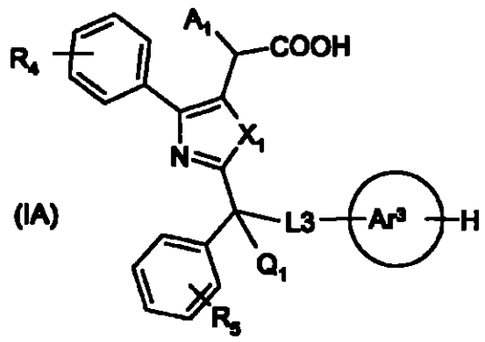
L1 is a bond $-CR_{11}R_{12}$- $-CH_2CR_{11}R_{12}$- $-OCR_{11}R_{12}$- $-SCR_{11}R_{12}$- $-NR_{11}CH_2$- or $-NR_{11}$ wherein R_{11} and R_{12} are independently hydrogen or C_1-C_3 alkyl the bond marked with an asterisk being the one connected to the ring containing X^1 For example L1 may be $-CH_2$- or $-CH(CH_3)$-

Ar^2 is phenyl thienyl naphthyl or 2 3- or 4-pyridyl any of which is optionally substituted for example by one or more substituents selected from fluoro chloro bromo (C_1-C_3)alkyl trifluoromethyl (C_1-C_3)alkoxy trifluoromethoxy trifluoromethylthio dimethylamino cyano $(C_1-C_3$alkyl$)SO_2$- NH_2SO_2- $(C_1-C_3$alkyl$)NHSO_2$- $(C_1-C_3$alkyl$)_2NSO_2$- $CONR^AR^B$ and NR^BCOR^A wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

L2 is a bond and Ar^2 is an optionally substituted phenyl thienyl furanyl pyrrolyl or pyridyl ring optional substituents being selected from fluoro, chloro bromo (C_1-C_3)alkyl trifluoromethyl (C_1-C_3)alkoxy trifluoromethoxy trifluoromethylthio dimethylamino cyano $(C_1-C_3$alkyl$)SO_2$- NH_2SO_2- $(C_1-C_3$alkyl$)NHSO_2$- $(C_1-C_3$alkyl$)_2NSO_2$- $-CONR^AR^B$ and $-NR^BCOR^A$ wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

s is 0

One preferred subclass of the compounds with which the invention is concerned consists of compounds of formula (IA), and salts hydrates and solvates thereof



wherein A_1 is hydrogen or methyl X_1 Q_1 Ar^3 and L3 are as defined and discussed above and R_4 and R_5 independently represent hydrogen or one or more optional substituents In this subclass it is currently preferd that

A_1 is hydrogen

Q_1 is hydrogen

X_1 is –S-

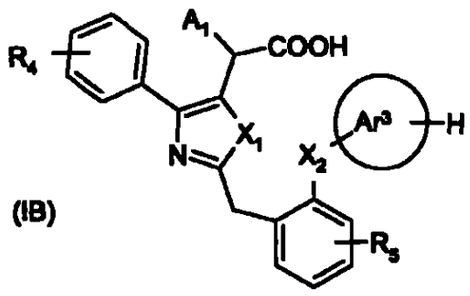
Ar^3 is optionally substituted phenyl

L3 is a bond -O- –S- or –NR wherein R is hydrogen or C_1-C_3 alkyl

Particularly preferred in this subclass are compounds (IA) wherein A_1 is hydrogen Q_1 is hydrogen X_1 is –S- Ar^3 is optionally substituted phenyl and L3 is a bond

In this subclass, optional substituents R_4 and R_5 and optional substituents in Ar^3 are preferably independently 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)$NHSO_2$- (C_1-C_3alkyl)$_2NSO_2$- $CONR^AR^B$ and -NR^BCOR^A wherein R^A and R^B are independently hydrogen or a (C_1 C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

One preferred subclass of the compounds with which the invention is concerned consists of compounds of formula (IA) and salts hydrates and solvates thereof



(IB)

wherein A_1 is hydrogen or methyl X_2 is a bond $-CH_2-$ -O- –S- or –NR wherein R is hydrogen or C_1-C_3 alkyl and X_1 and Ar^3 are as defined in claim 1 and R_4 and R_5 independently represent hydrogen or one or more optional substituents In this subclass It is currently preferrd that

A_1 is hydrogen

X_1 is –S-

Ar^3 is optionally substituted phenyl

X_2 is $-CH_2-$ or a bond

In this subclass optional substituents R_4 and R_5 and optional substituents in Ar^3 are independently 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)$NHSO_2$- (C_1 C_3alkyl)$_2NSO_2$- $-CONR^AR^B$ and NR^BCOR^A wherein R^A and R^B are independently hydrogen or a (C_1-C_3)alkyl group, or R^A and R^B are linked to the same N atom to form a cyclic amino ring

Specific examples of compounds with which the invention is concerned include

[2-benzhydryl-4-(4-chlorophenyl)-thiazol-5-yl]-acetic acid
[2-benzhydryl-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-[1-(4-chloro-phenyl)-2-phenyl-ethyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid
{4-(4-chloro-phenyl)-2-[(4-chloro-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid
[2-[(4-chloro-phenyl)-phenyl-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-[bis-(4-fluoro-phenyl)-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid
{4-(4-fluoro-phenyl)-2-[(4-methoxy-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid
{4-(4-chloro-phenyl)-2-[(4-methoxy-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid
[2-[(3 4-difluoro-phenyl)-phenyl-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-[bis-(4-methoxy-phenyl)-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid

[2-benzhydryl-4-(3-fluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-[bis-(4-fluoro-phenyl)-methyl]-4-(3,4-difluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-benzhydryl-4-(3,4-difluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-[bis-(4-fluoro-phenyl)-methyl]-4-(3-fluoro-phenyl)-thiazol-5-yl]-acetic acid

and salts hydrates and solvates thereof

The invention also includes pharmaceutical compositions comprising a compound formula (II) or (IIA) 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 rhinitis allergic airway syndrome and allergic rhinobronchitis

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 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

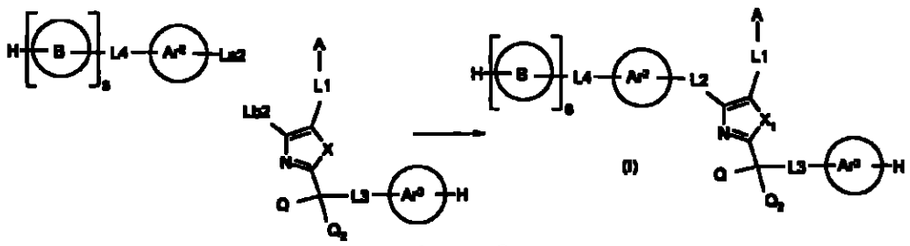
In the case of arthritis and related inflammatory diseases other known drugs include glucocorticoids NSAIDs (Non Steroidal Anti-Inflammatory Drugs – conventional prostaglandin synthesis inhibitors COX 2 inhibitors salicylates) and DMARDs (disease-modifying anti-rheumatic drugs such as methotrexate sulfasalazine 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 the following discussion of synthetic routes the ring Ar^1 is the ring shown in formula (I) containing X_1

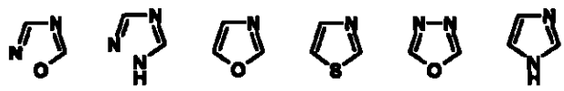
The linker L2 can be formed by joining two appropriately functionalised and if needed suitably protected fragments containing La2 and Lb2 as reactive moieties as outlined below La2 and Lb2 are defined as any moieties that can react by e g a nucleophilic substitution addition to multiple bonds or cyclisation reaction to form a given L2 linker as in



For example the linker L2 being –Alk^1-Z-(Alk^2)$_p$- can be formed by reacting HBL4Ar^2–Alk^1 "leaving group with a nucleophilic derivative H-Z-(Alk^2)$_p$-Ar^1(L1A)L3Ar^{3}H wherein Z could be O S or NR and Alk^1 could be an alkyl group The reactions can also be made by reversing the functionalisation of La2 and Lb2 to make the connection between Z and Alk^2 The linkers having Z being SO or SO_2 can be obtained by oxidations of the corresponding –(Alk^1)$_m$-S-(Alk^2)$_p$- derivatives during appropriate conditions.

Further representative examples –L2 being -Alk^1 Z-(Alk^2)$_p$- wherein Z is NH(CO) or $NHSO_2$ can be formed by reacting HBL4Ar^2–(Alk^1)-NH_2 with an acylating derivative leaving group"-CO-(Alk^2)$_p$-Ar^1(L1A)L3Ar^{3}H or leaving group -SO_2-(Alk^2)$_p$-Ar^1(L1A)L3Ar^{3}H respectively Alternatively the conversion can be made directly with the acids HO-CO-(Alk^2)$_p$-Ar^1(L1A)L3Ar^{3}H and HO-SO_2-(Alk^2)$_p$-Ar^1(L1A)L3Ar^{3}H respectively using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC) and promoters such as 1-hydroxybenzotriazole Analogously –L2 being –Alk^1 Z-(Alk^2)$_p$- wherein Z being NH(CO)NH can be formed by reacting HBL4Ar^2–(Alk^1)-NH_2 with an isocyanate derivative OCN-(Alk^2)$_p$-Ar^1(L1A)L3Ar^{3}H using suitable acid or base catalysis. The reactions can also be made by reversing the functionalisation of La2 and Lb2 to provide the "retro-bonds in the case of NH(CO) or $NHSO_2$. Analogously the connections can be made between Z and Alk^2

Likewise L2 being –(Alk^1)$_m$-Z (Alk^2)$_p$- wherein Z is a 5-membered heterocyclic system exemplified by

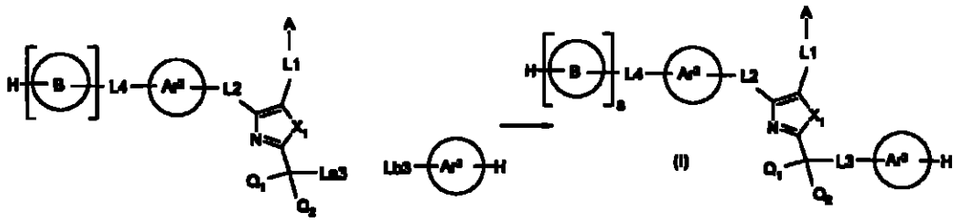


can be made according to standard cyclisation procedures using appropriate solvents catalysts and temperatures For example formation of 1 2 4-triazole can be made with La2 being acylhydrazide and Lb2 being amide or thioamide or the reverse orientation of La2 and Lb2 1 2,4-Oxadiazole can be formed from La2 being amidoxime and Lb2 being carboxylic ester or the reverse orientation of La2 and Lb2.

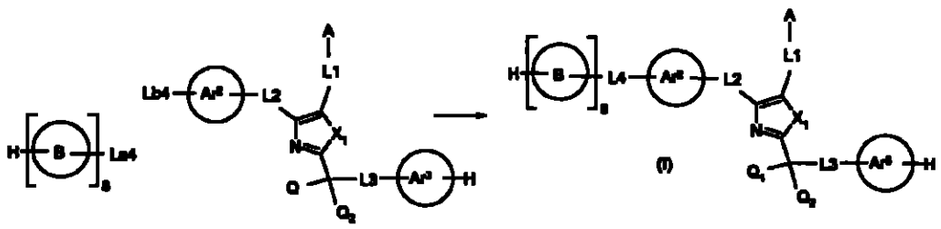
21

1 3 4-Oxadiazole can be formed from La2 being acylhydrazide and Lb2 being carboxylic ester or the reverse orientation of La2 and Lb2 The thiazole can be made from La2 being thioamide and Lb2 being an α-haloketone or the reverse orientation of La2 and Lb2

In an analogous manner the compounds of formula (I) can be made by forming the linkers L3 or L4 according to procedures outlined for L2 as depicted below Thus La and Lb are defined as any moieties that can react by e.g a nucleophilic substitution addition to multiple bonds or cyclisation reaction to form a given linker L as exemplified below

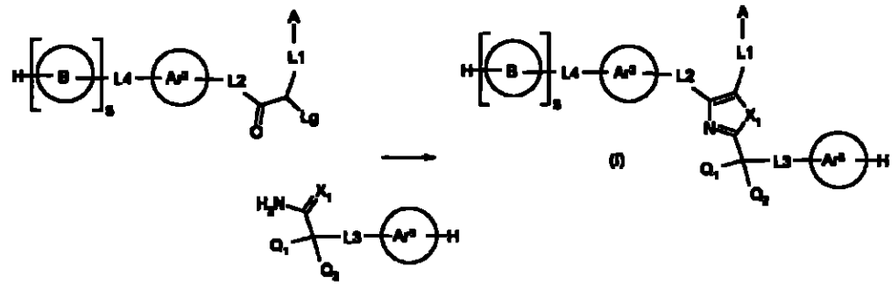


and

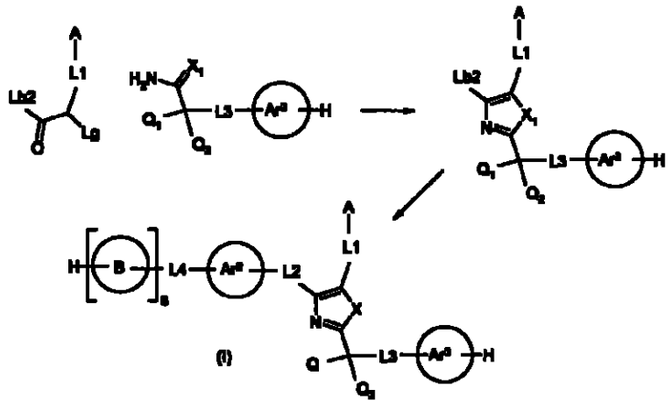


The Ar^1 moiety can also be the central scaffold that is used in connecting the L1 L2 and L3 parts in a stepwise fashion This can be done via aromatic substitutions of the Ar^1 core to attach L1 L2 and/or L3 which then can be further functionalised to give the final Formula I compounds

Furthermore the five-membered X_1-azole moiety can also be assembled via conventional ring cyclisation reactions with reactants containing the L1 L2 and L3 units either containing the full appendices as exemplified below wherein Lg is a leaving group such as halogen



or in forms that can be further functionalised into the final formula (I) structures as described previously One such illustration is given below



For example 1 2,4-triazoles can be made from acylhydrazides and amides or thioamides 1 2 4-oxadiazoles from amidoximes and carboxylic esters 1,3 4-oxadiazoles from acylhydrazides and carboxylic esters thiazoles from thioamides and α haloketones pyrazines pyrimidines and pyridines via various condensation and cycloaddition reactions

The building blocks used in the reactions are either commercially available or made according to standard procedures well-know to one skilled in the art as described in *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 or other suitable literature sources.

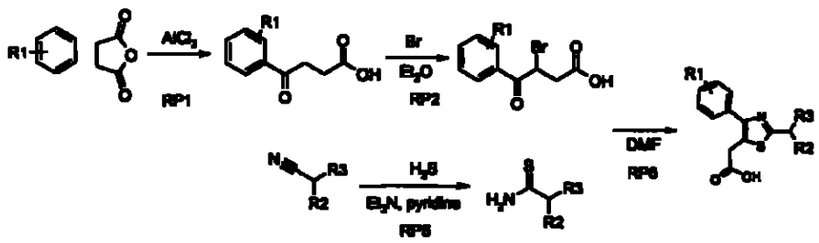
The Examples herein describe specific strategies for the synthesis of compounds (I) wherein X1 is S

The following Examples illustrate the preparation of compounds with which this invention is concerned Some compounds were synthesised and some were acquired from commercial sources In the Examples

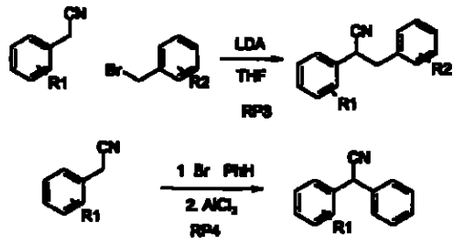
General comments

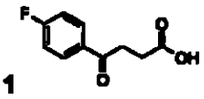
NMR spectra were obtained on a Bruker Avance AMX 300 MHz instrument. For some compounds only selected characteristic ^{1}H NMR signals are reported LC/MS was performed on an Agilent 1100-series instrument LC/MS methods are as follows An10p8 Column XTerra MS C18 Flow 1 0 mL/min Gradient 0-5 min 15-100% 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)

General synthetic route I



Synthetic routes to nitrile intermediates.





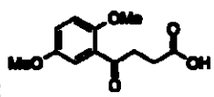
Intermediate 1

4-(4-Fluoro-phenyl)-4-oxo-butyric acid – Representative Procedure 1a (RP1a)

Succinic anhydride (1 0 g 10 mmol) was dissolved in 4-fluorobenzene (3 75 ml 40

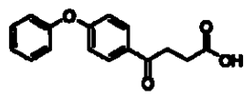
mmol) and cooled to -9 °C under nitrogen $AlCl_3$ (2 67 g 20 mmol) was added and the temperature was kept between -9 and 0 C for 4½ hours The reaction was allowed to warm to room temperature and stirred over night The reaction mixture was poured into aqueous 4 M HCl (10 ml) at 0 C and the precipitated was filtered and washed with water The solid was recrystallized from toluene to give 1 40 g (71 %) of a colorless solid LC/MS (an10n8) Rt 0 26 min *m/z* 195 [M – H] 413 [2M-2H+Na] ^{1}H NMR ($CDCl_3$) δ 2 84 (t, *J* = 6 5 Hz, 2H) 3 31 (t, *J* = 6 5 Hz, 2H) 7 16 (m 3H) 8.03 (m 2H)

In an analogous way the following compounds were made



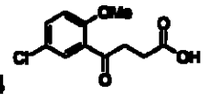
Intermediate-2

4-(2 5-Dimethoxy-phenyl)-4-oxo-butyric acid LC/MS (an10n8) Rt 0 50 min *m/z* 237 [M-H] 497 [2M-2H+Na] ^{1}H NMR (DMSO-d_6) δ 2 53 (t *J* = 6 0 Hz, 2H), 3 16 (t, *J* = 6 3 Hz, 2H) 3.73 (s 3H) 3 85 (s 3H) 7 12-7 14 (m 3H) ^{13}C NMR/APT (DMSO d_6) δ 29 1 (CH2), 39 2 (CH2) 56 4 (CH3) 57 2 (CH3) 114 5 (CH) 115 0 (CH) 120 4 (CH) 128 5 (C) 153 8 (C) 174 7 (CO) 200 2 (CO)



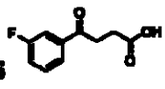
Intermediate-3

4-Oxo-4-(4-phenoxy-phenyl)-butyric acid ^{1}H NMR (DMSO-d6) δ 2 57 (t, *J* = 6 22, 2H) 3.21 (t, *J* = 6 22 2H), 7 05 (m 2H) 7 13 (m 2H) 7 25 (m 1H) 7 47 (m 2H), 8 01 (m, 2H) 12 13 (br s 1H (COOH))



Intermediate-4

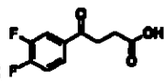
4-(5-Chloro-2-methoxy-phenyl)-4-oxo-butyric acid ^{1}H NMR (DMSO-d_6) δ 2.53 (t, *J* = 6 6 Hz 2H) 3.15 (t, *J* = 6 0 Hz, 2H) 3 90 (s 3H) 7 23 (d *J* = 8 9 Hz, 1H) 7 53 (d *J* = 2 6 Hz, 1H) 7 60 (dd *J* = 2.9 8 9 Hz, 1H) and 12 11 (br s 1H)



Intermediate-5

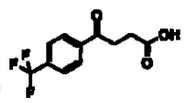
4-(3-Fluoro-phenyl)-4-oxo-butyric acid – Representative Procedure 1b (RP1b) In a flame dried flask under nitrogen succinic anhydride (471 mg 4 7 mmol) was dissolved in dry THF (5 mL) The mixture was cooled to 78 C 3-Fluorophenyl-magnesium bromide in THF (1N 5 mL 5 mmol) was added slowly The mixture was stirred at 78 C for 3 h then allowed to raise room temperature The mixture was transferred into 1N HCl (aq) then extracted with CH_2Cl_2. The organic layer was dried and evaporated The residue was purified by flash chromatography on SiO_2 to give 350 mg (38%) of the title compound ^{1}H NMR ($CDCl_3$) δ 2 84 (t *J* = 6 5 Hz 2H) 3 31 (t, *J* = 6 5 Hz, 2H) 7 30 (m 1H) 7 47 (td *J* = 8 1 5 7 1H) 7 68 (m, 1H) 7 79 (m 1H)

The following compounds were prepared by an analogous procedure



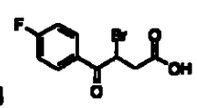
Intermediate-6

4-(3,4-Difluoro-phenyl)-4-oxo-butyric acid. ^{1}H NMR ($CDCl_3$) δ 2 57 (t *J* = 6.2 Hz 2H) 3 25 (t, *J* = 6 2 Hz, 2H) 7 60 (m 1H) 7 87 (m 1H) 8.02 (m 1H) 12 17 (br s 1H)



Intermediate-7

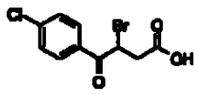
4-Oxo-4-(4-trifluoromethyl-phenyl)-butyric acid 4-Iodobenzotrifluoride (500 µL 3 4 mmol) was dissolved in dry diethylether (5 mL) in a flamedried flask under nitrogen Magnesium (83 mg 3.4 mmol) was added and the mixture was stirred at room temperature for 45 min Succinic anhydride was dissolved in THF (5 mL) in a flamedried flask under nitrogen then cooled to 78 C The freshly made Grignard reagent was added slowly The mixture was allowed to warm to room temperature over 3 h The mixture was transferred into NH_4Cl (aq) then extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) then evaporated The product was purified by flash chromatography on SiO_2 to give 250 mg (30%) ^{1}H NMR ($CDCl_3$) δ 2 86 (t, *J* = 6 4 Hz, 2H) 3 35 (t *J* = 6.4 Hz, 2H) 7 78 (d *J* = 8 3 Hz 2H) 8 10 (d *J* = 8 3 Hz 2H)



Intermediate-8

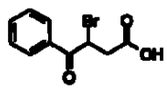
3-Bromo-4-(4-fluoro-phenyl)-4-oxo-butyric acid – Representative Procedure 2 (PR2) 4-(4-Fluoro-phenyl)-4-oxo-butyric acid (1 20 g 6 12 mmol) was suspended in ether (10 mL) at room temperature Bromine (0 34 ml 6 73 mmol) was added drop-wise After 4 hours the reaction was concentrated and the residue was recrystallized from ether/heptane to give 1 26 g (75 %) of pale orange crystals ^{1}H NMR ($CDCl_3$) δ 3 16 (dd J = 2.2 6 9 Hz 1H) 3 56 (dd J = 3.5 6 9 Hz, 1H) 5 41 (dd J = 2.2 3 5 Hz, 1H) 7 19 (m 2H) 8.08 (m, 2H) ^{13}C NMR/APT ($CDCl_3$) δ 190 9 175 6 168 3 164 9 132 3 132 1 116 6 116 3 38 8 38 3

In an analogous way the following compounds were made



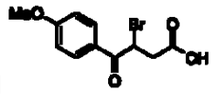
Intermediate-9

3-Bromo-4-(4-chloro-phenyl)-4-oxo-butyric acid ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3 18 (dd J = 5 7 17 5 Hz, 1H) 3 52 (dd J = 8 5 17 5 Hz 1H), 5 43 (dd J = 5 8 8.5 Hz, 1H) 6 99 (d J = 8 9 Hz, 2H) 8 10 (d J = 8 9 Hz, 2H)



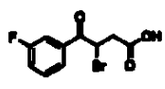
Intermediate-10

3-Bromo-4-oxo-4-phenyl-butyric acid. LC/MS (an10p8) Rt 2.69 min *m/z* 257/259 [M+H] 279/281 [M+Na] ^{1}H NMR ($CDCl_3$) δ 3 17 (dd J = 5 7 17 6 Hz, 1H) 3 56 (dd J = 8 7 17 6 Hz, 1H), 5 46 (dd J = 5 7 8 7 Hz 1H) 7 52 (m 2H) 7 64 (m 1 H) 8 05 (m 2 H)



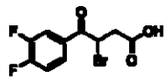
Intermediate-11

3-Bromo-4-(4-methoxy-phenyl)-4-oxo-butyric acid ^{1}H NMR ($CDCl_3$) δ 3 17 (dd J = 5 7 17 7 Hz 1H) 3 55 (dd J = 9 0 17 7 Hz, 1H) 3 91 (s 3H), 5 40 (dd J = 5 5 8 9 Hz, 1H), 7 51 (d J = 8 7 Hz 2H), 7 98 (d J = 8 7 Hz, 2H).

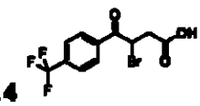


Intermediate-12

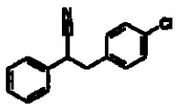
3-Bromo-4-(3-fluoro-phenyl)-4-oxo-butyric acid ^{1}H NMR ($CDCl_3$) δ 3 18 (m 1H) 3 54 (m 1H) 5 39 (m 1H) 7 34 (m 1H) 7 50 (m 1H) 7 83 (m 2H) and 10 11 (br s 1H)

Intermediate-13 

3-Bromo-4-(3,4-difluoro-phenyl)-4-oxo-butyric acid ^{1}H NMR ($CDCl_3$) δ 3 16 (dd *J* = 17 7 5 3 Hz, 1H) 3 55 (dd *J* = 17 7 9 0 Hz, 1H) 5 32 (dd J = 9 0 5 5 Hz, 1H) 7 31 (m 1H) 7 85 (m 2H)

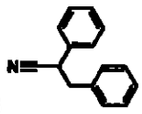
Intermediate-14 

3-Bromo-4-oxo-4-(4-trifluoromethyl-phenyl)-butyric acid ^{1}H NMR ($CDCl_3$) δ 3 19 (dd *J* = 17 7 5 5 Hz 1H) 3 59 (dd *J* = 17 5, 9 0 Hz, 1H) 5 44 (dd *J* = 9 0 5 5 Hz, 1H) 7 79 (d *J* = 2 8 Hz) and 8 16 (d *J* = 3 0 Hz)

Intermediate 15 

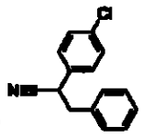
3-(4-Chloro-phenyl)-2-phenyl-propionitrile – Representative Procedure 3 (RP3) The reaction was preformed under N_2 in flame dried glassware Benzylcyanide (1 2 mL, 10 mmol) was added slowly (over a period of 40 min) to a solution of LDA (10 mmol) in THF (10 mL) at 78 C The mixture was stirred for 1 h at 78 C and then added slowly (over a period of 16 min) to a solution of 4-chlorobenzyl bromide in THF (10 mL) at 78 C The mixture was stirred for 1 h at 78 C and left over night to reach room temperature The reaction mixture was added saturated aq NH_4Cl and the aqueous mixture was extracted with EtOAc. The organic phase was washed with brine dried ($MgSO_4$) and concentrated and the residue was recrystallized from heptane to give 1 26 g (53%) of a light brown powder ^{1}H NMR ($CDCl_3$) δ 3 16 (m 2H) and 4 01 (t, *J* = 7 2 Hz 1H) 7 05 (d *J* = 8 3 Hz, 2H) 7 32 (m 7H)

In an analogous way the following compounds were made



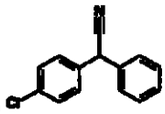
Intermediate 16

2,3-Diphenyl-propionitrile ^{1}H NMR ($CDCl_3$) δ 3.19 (m 2H) and 4 02 (t, J = 7 9 Hz, 1H)



Intermediate-17

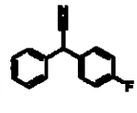
2-(4-Chloro-phenyl)-3-phenyl-propionitrile. ^{1}H NMR ($CDCl_3$) δ 3 16 (m 2H) and 4.14 (t, J = 7 2 Hz 1H).



Intermediate-18

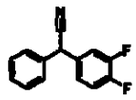
(4-Chloro-phenyl)-phenyl-acetonitrile – Representative Procedure 4 (RP4) The reaction was preformed under N_2 and flamedried glassware 4-Chlorobenzyl cyanide (1 mL 7 8 mmol) was dissolved in benzene (10 mL) and heated to reflux Bromide (442 µL 8 6 mmol) was added over 30 min The mixture was stirred 20 min at reflux, then cooled to approx 40°C and added over 30 min to a refluxing mixture of aluminum chloride (1 g 7 8 mmol) in benzene (10 mL) The mixture was stirred 1 h at reflux then cooled to r t. The mixture was transferred into ice and conc. HCl (50 mL) then extracted with diethyl ether The organic layer was dried ($MgSO_4$) and concentrated in vacuum to give brown oil The product was purified by flash chromatography on SiO_2 to give 523 mg (28%) yellow oil ^{1}H NMR ($CDCl_3$) δ 5.14 (s 1H) and 7 38 (m 9H) APT ($CDCl_3$) δ 42.42 (CH).

In an analogous way the following compounds were made



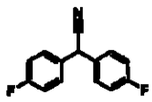
Intermediate-19

(4-Fluoro-phenyl)-phenyl-acetonitrile ^{1}H NMR ($CDCl_3$) δ 5 15 (s, 1H) 7 08 (m 2H) 7 36 (m 7H)



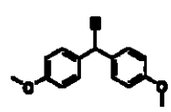
Intermediate-20

(3,4-Difluoro-phenyl)-phenyl-acetonitrile ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5 12 (s 1H) 7 15 (m 3H) 7 41 (m 5H).



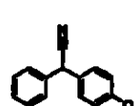
Intermediate-21

Bis-(4-fluoro-phenyl)-acetonitrile 4 4 -Difluorobenzhydrol (1 g 4 54 mmol) was dissolved in TFA (10 mL). Potassium cyanide (620 mg 9 53 mmol) was added and the mixture was cooled to 0 C Sulfuric acid (conc. 3 mL) was added slowly The mixture was stirred at room temperature for 5h then quenched with H_2O and ethyl acetate The organic phase was washed with water and brine dried ($MgSO_4$) and concentrated The residue was purified by flash chromatography on SiO_2 to give 450 mg (43%) of the title compound ^{1}H NMR ($CDCl_3$) δ 5 14 (s 1H) 7 09 (m 4H) and 7 32 (m 4H) ^{13}C NMR (APT $CDCl_3$). δ 41 53 (CH)



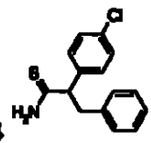
Intermediate-22

Bis-(4-methoxy-phenyl)-acetonitrile. 4 4 Dimethoxybenzhydrol (5 g 20 mmol) was dissolved in dry CH_2Cl_2 (50 mL) then cooled to 0 C Thionylchloride (1 5 mLl 20 mmol) was added slowly The mixture was stirred at room temperature for 4h The mixture was concentrated under vacuum The product was dissolved in dry CH_2Cl_2 (10 mL) and added to a mixture of potassium cyanide (2.6 g 40 mmol) and 18-crown-6 (500 mg) dissolved in dry CH_2Cl_2 (20 mL) The mixture was stirred over night at room temperature The mixture was transferred into water then extracted with CH_2Cl_2. The organic layer was washed with water and brine dried ($MgSO_4$) and concentrated The residue was recrystallized from ethyl acetate to give 2 54 g (50%) of the title compound ^{1}H NMR ($CDCl_3$)· δ 3 82 (s 6H) 5 07 (s 1H) 6 90 (m, 4H) 7 25 (m 4H)



Intermediate-23

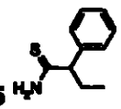
(4-Methoxy-phenyl)-phenyl-acetonitrile (4-Methoxyphenyl)acetonitrile (5 mL, 37 mmol) was dissolved in dry benzene (10 mL) in a flamedried flask under nitrogen The mixture was heated to reflux and bromine (1 9 mL, 37 mmol) was added in small portions over 2 h The mixture was stirred at reflux for 30 min then added to a refluxing mixture of $AlCl_3$ (4 9 g 37 mmol) in benzene (30 mL) over 80 min The mixture was stirred at reflux for 1 h then cooled to room temperature The mixture was transferred into 1N HCl and ice then extracted with diethylether The organic layer was dried ($MgSO_4$) and concentrated The product was purified by flash chromatography on SiO_2 to give 1 3 g (16%) of the title compound ^{1}H NMR ($CDCl_3$) δ 3 82 (s 3H) 5 12 (s 1H) 6 90 (m 2H) 7 27 (m 2H), 7 37 (m 5H)



Intermediate-24

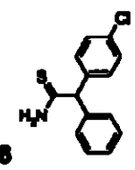
2-(4-Chloro-phenyl)-3-phenyl-thiopropionamide – Representative Procedure 5 (RP5) 2-(4-Chloro-phenyl)-3-phenyl-propionitrile (200 mg 0 8 mmol) was dissolved in pyridine (5 mL) and triethylamine (1 mL) The mixture was saturated with hydrogen sulfide and stirred under an atmosphere of hydrogen sulfide room temperature for 3 days The mixture was extracted with EtOAc. The extract was washed with brine dried ($MgSO_4$) and concentrated to give 250 mg of crude product which was used directly in the next step ^{1}H NMR (DMSO-d6) δ 3 17 (dd *J* = 8 1 13 8 Hz 1H) 3 75 (dd *J* = 7 0 13 8 Hz 1H) 4 03 (t, *J* = 7 5 Hz, 1H) and 7 20 (m 9H)

In an analogous way the following compounds were made



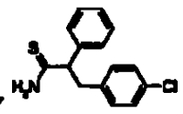
Intermediate-25

2-Phenyl-thiobutyramide. LC/MS (an10p8) Rt 2.9 min *m/z* 180 [M + 1] ^{1}H NMR ($CDCl_3$): δ 0 93 (t 3H); 2 01 (m 1H); 2.41 (m 1H) 3 75 (dd 1H); 6 75 (br s 1H); 7 36 (m 5H) 7 58 (br s 1H)

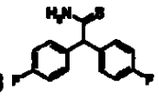


Intermediate-26

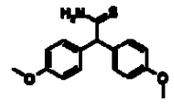
2-(4-Chloro-phenyl)-2-phenyl-thioacetamide ^{1}H NMR ($CDCl_3$) δ 5 59 (s 1H)

Intermediate-27 

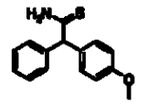
3-(4-Chloro-phenyl)-2-phenyl-thiopropionamide ^{1}H NMR (DMSO-d_6) δ 3 14 (m 1H) 3.77 (dd *J* = 6 6 13 9 Hz, 1H) 4 00 (t, *J* = 7 73 Hz, 1H)

Intermediate-28 

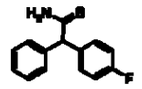
2,2-Bis-(4-fluoro-phenyl)-thioacetamide ^{1}H NMR ($CDCl_3$) δ 5.57 (s, 1H) 6 76 (br s, 1H (NH)) 7 08 (m 4H) and 7.23 (m 4H) and 7 68 (br s 1H (NH)).

Intermediate-29 

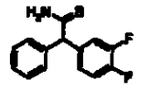
2,2-Bis-(4-methoxy-phenyl)-thioacetamide LC/MS (an10p6)· Rt 2.96 min *m/z* 288 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 81 (s 6H) 5 54 (s 1H) 6 83 (bs, 1H (NH)) 6 90 (m 4H) 7 18 (m 4H) 7 73 (br s 1H (NH))

Intermediate-30 

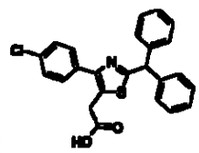
2-(4-Methoxy-phenyl)-2-phenyl-thioacetamide. ^{1}H NMR ($CDCl_3$): δ 3 82 (s 3H), 5 59 (s 1H) 6 83 (bs 1H (NH)) 6 90 (m 2H) 7 18 (m 2H), 7 35 (m 5H) 7 76 (bs 1H (NH)).

Intermediate-31 

2-(4-Fluoro-phenyl)-2-phenyl-thioacetamide ^{1}H NMR ($CDCl_3$) δ 5 61 (s 1H) 6 84 (br s 1H (NH)) 7 06 (m 2H) 7 26 (m 2H) 7 37 (m 5H), 7 86 (br s 1H (NH))

Intermediate-32 

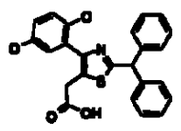
2-(3,4-Difluoro-phenyl)-2-phenyl-thioacetamide ^{1}H NMR ($CDCl_3$) δ 5 56 (s 1H) 6 81 (br s 1H (NH)) 7 04 (m 1H) 7 14 (m 2H) 7 25 (m, 2H) 7 38 (m 3H), 7 92 (br s 1H (NH))



A1

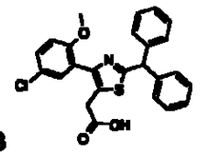
[2-Benzhydryl-4-(4-chloro-phenyl)-thiazol-5-yl]-acetic acid – Representative Procedure 6 (RP6) 3-Bromo-4-(4-chlorophenyl)-4-oxo-butyric acid (119 mg 0 4 mmol) and 2 2-diphenyl-thioacetamide (91 mg 0 4 mmol) was dissolved in DMF (1 mL) and heated to 100 °C for 10 minutes in a microwave oven The reaction mixture was poured into water at 0 °C The precipitation was filtered off and recrystallized from CH_2Cl_2 to give 77 mg (54%) yellow powder ^{1}H NMR (DMSO-d_6) δ 3.91 (s 2H) 5 96 (s, 1H) 7 37 (m 10H) 7 52 (d *J* = 8.48 Hz 2H) 7 60 (d *J* = 8 67 Hz, 2H) 12 82 (br s 1H (COOH)).

In an analogous way the following compounds were made



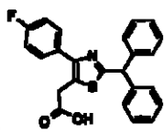
A2

[2-Benzhydryl-4-(2 5-dimethoxy-phenyl)-thiazol-5-yl]-acetic acid LC/MS (an10p8) Rt 3 18 min *m/z* 446 [M + 1] ^{1}H NMR (DMSO-d6) δ 3 59 (s 2H), 5 92 (s, 1H) 6 85 (d *J* = 3 0 Hz, 1H) 6 98 (dd *J* = 8 9 and 3.0 Hz) 7 04 (d *J* = 8 5 Hz) 7 22-7 45 (m 10H)



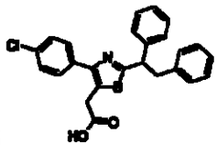
A3

[2-Benzhydryl-4-(5-chloro-2-methoxy-phenyl)-thiazol-5-yl]-acetic acid LC/MS (an10p8), Rt 3 70 min *m/z* 450 [M + 1] ^{1}H NMR (DMSO-d_6) δ 3 60 (s 2H) 3 73 (s 3H) 5 93 (s, 1H) 7 14 (d *J* = Hz, 1H) 7 26 (m 3H) 7 36 (m 8H) 7.44 (m, 1H)



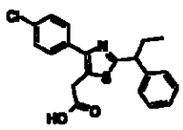
A4

[2-Benzhydryl-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid LC/MS (an10p8): Rt 2.93 min *m/z* 404 [M + 1] ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 2H) 5.88 (s 1H) 7.12 (m 2H) 7.25-7.38 (m 10H) 7.58 (m 2H)



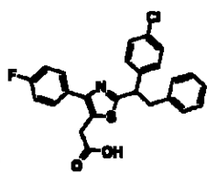
A5

[4-(4-Chloro-phenyl)-2-(1,2-diphenyl-ethyl)-thiazol-5-yl]-acetic acid. LC/MS (an10p8) Rt 4.74 min *m/z* 434 [M + 1] ^{1}H NMR (DMSO-d_6) δ 3.32 (m 1H) 3.61 (m, 1H) 3.85 (s 2H (CH_2)) 4.75 (m 1H (CH))



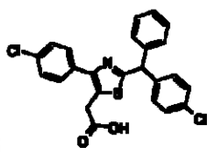
A6

[4-(4-Chloro-phenyl)-2-(1-phenyl-propyl)-thiazol-5-yl]-acetic acid LC/MS (an10p8): Rt 3.1 min *m/z* 372 [M+1]



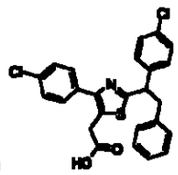
A7

[2-[1-(4-Chloro-phenyl)-2-phenyl-ethyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid ^{1}H NMR (DMSO-d_6) δ 3.32 (m 1H) 3.61 (m 1H), 3.84 (s, 2H (CH_2)), 4.80 (m 1H (CH)).



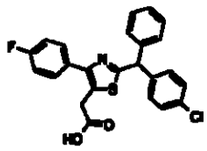
A8

{4-(4-Chloro-phenyl)-2-[(4-chloro-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid ^{1}H NMR (DMSO-d6) δ 3 91 (s 2H), 6 01 (s 1H), 7 37 (m 9H), 7 50 (d J = 8 10 Hz 2H) 7 60 (d J = 8.29 Hz 2H).



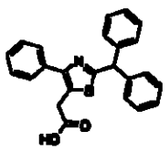
A9

{4-(4-Chloro-phenyl)-2-[1-(4-chloro-phenyl)-2-phenyl-ethyl]-thiazol-5-yl}-acetic acid LC/MS (an10p8) Rt 5 17 min m/z 469 [M+1] ^{1}H NMR (DMSO-d_6) δ 3 32 (m 1H) 3 61 (dd J = 6 90 and 13 94 1H) 3 86 (s 2H (CH_2)) and 4 81 (t J = 7 90 1H (CH))



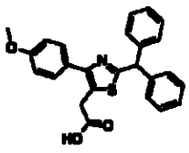
A10

[2-[(4-Chloro-phenyl)-phenyl-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid LC/MS (an10p8): Rt 5 04 min m/z 438 [M + 1] ^{1}H NMR (DMSO-d_6) δ 3 83 (s 2H) 5 86 (s 1H) 7 11 (m 2H) 7 20-7 40 (m 9H) 7 55 (m 2H)



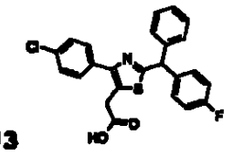
A11

(2-Benzhydryl-4-phenyl-thiazol-5-yl)-acetic acid. LC/MS (an10p8). Rt 3 95 min m/z 386 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 85 (s 2H) 6 01 (s 1H) 7 22 7 48 (m, 12H) and 7 80 (m, 2H)



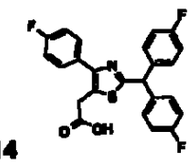
A12

[2-Benzhydryl-4-(4-methoxy-phenyl)-thiazol-5-yl]-acetic acid LC/MS (an10p8) Rt 3 52 min m/z 416 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 84 (s 3H) 3.85 (s 2H) 5.86 (s 1H) 6 97 (m, 2H) 7 26-7 37 (m 10H) and 7 54 (m 2H).



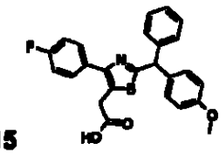
A13

{4-(4-Chloro-phenyl)-2-[(4-fluoro-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid. LC/MS (an10p8): Rt 0 98 min *m/z* 438 [M + H] ^{1}H NMR (DMSO-d_6) δ 3.91 (s 2H) 6 00 (s 1H) 7 19 (m 2H) 7 29 (m 1H) 7 36-7 43 (m 6H) 7 54 (m 2H) 7 59 (m 2H) 12 87 (br s 1H)



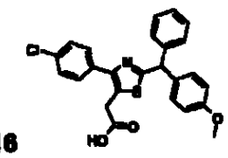
A14

[2-[Bis-(4-fluoro-phenyl)-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid. LC/MS (an10p8): Rt 4 81 min *m/z* 440 [M + H] ^{1}H NMR (DMSO-d_6) δ 3 89 (s 2H) 6 03 (s 1H) 7 19 (m 4H) 7 30 (m 2H) 7 41 (m 4H) 7 62 (m 2H).



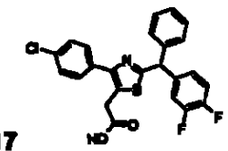
A15

{4-(4-Fluoro-phenyl)-2-[(4-methoxy-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid LC/MS (an10p8) Rt 3 45 min *m/z* 434 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 81 (s 3H) 3 84 (s 2H) 5 81 (s 1H), 6 89 (m 2H) 7 12 (m 2H) 7 24 (m 2H), 7 28-7 38 (m 5H) 7 56 (m, 2H) ^{13}C-APT ($CDCl_3$) δ 32 79 (CH_2) 54 62 55 65 (CH_3/CH)



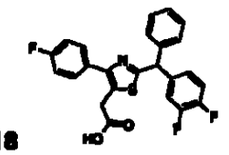
A16

{4-(4-Chloro-phenyl)-2-[(4-methoxy-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid. LC/MS (an10p8) Rt 3 71 min *m/z* 450 [M + H] ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H) 3 84 (s 2H) 5.84 (s 1H) 6 87 (m 2H) 7 21 (m 2H), 7 24-7 36 (m 5H), 7.41 (m 2H) 7 55 (m 2H) ^{13}C-APT ($CDCl_3$) δ 32 83 (CH_2) 54 57 55 66 (CH_3 / CH)



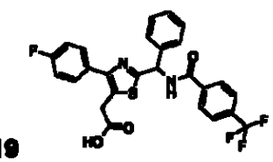
A17

{4-(4-Chloro-phenyl)-2-[(3,4-difluoro-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid LC/MS (an10p8): Rt 3 98 min *m/z* 456 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 89 (s 2H) 5 79 (s 1H), 7 04 (m 1H) 7 15 (m 2H) 7 25-7 40 (m 5H) 7 44 (m 2H) 7 53 (m 2H). ^{13}C-APT ($CDCl_3$) δ 32 60 (CH_2) 54.54 (CH)



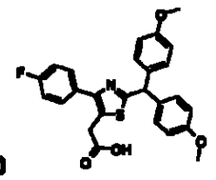
A18

[2-[(3,4-Difluoro-phenyl)-phenyl-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid. LC/MS (an10p8): Rt 3 76 min *m/z* 440 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 88 (s 2H) 5 83 (s 1H) 7 03 (m 1H), 7 14 (m 4H) 7 28-7 44 (m 5H), 7 58 (m 2H) ^{13}C-APT ($CDCl_3$) δ 32.65 (CH_2) 54 46 (CH)



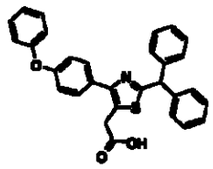
A19

{4-(4-Fluoro-phenyl)-2-[phenyl-(4-trifluoromethyl-benzoylamino)-methyl] thiazol-5-yl}-acetic acid LC/MS (an10p8) Rt 2.88 min *m/z* 515 [M + H] ^{1}H NMR (DMSO-d_6) δ 3 90 (s 2H) 6 64 (d *J* = 8 2 Hz, 1H) 7 30 (m 2H) 7 36-7 45 (m 3H) 7 54-7 65 (m 4H) 7 87 (d *J* = 8.2 Hz 2H) 8 16 (d *J* = 8 2 Hz 2H) 9 87 (m 1H (NH)) and 12 82 (s 1H (OH))



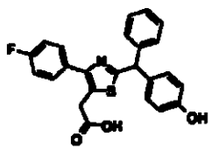
A20

[2-[Bis-(4-methoxy-phenyl)-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid LC/MS (an10p8)· Rt 2.17 min *m/z* 484 [M + H] ^{1}H NMR ($CDCl_3$) δ 3.81 (s 6H) 3 83 (s 2H) 5 77 (s 1H) 6 89 (m 4H) 7 11 (m 2H) 7 22 (m 4H) 7 56 (m 2H)



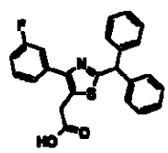
A21

[2-Benzhydryl-4-(4-phenoxy-phenyl)-thiazol-5-yl]-acetic acid LC/MS (an10p8). Rt 4 04 min *m/z* 478 [M + H] ^{1}H NMR ($CDCl_3$) δ 3.88 (s 2H) 5 87 (s 1H) 7 07 (m 4H) 7 14 (m 1H) 7 25-7.41 (m 12H) 7 58 (m 2H)



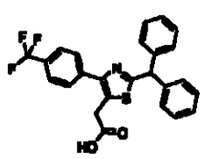
A22

{4-(4-Fluoro-phenyl)-2-[(4-hydroxy-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid. ^{1}H NMR ($CDCl_3$) δ 3 77 (s 2H) 5 82 (s 1H) 6 70 (m 2H) 7 02 7 15 (m 5H) 7 26 7 30 (m 4H) 7 53 (m 2H)



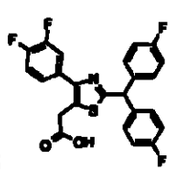
A23

[2-Benzhydryl-4-(3-fluoro-phenyl)-thiazol-5-yl]-acetic acid. LC/MS (an10p8): Rt 2 69 min *m/z* 404 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 88 (s 2H) 5 90 (s 1H) 7 07 (m 1H) 7.26-7 41 (m 13H).



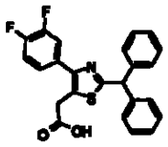
A24

[2-Benzhydryl-4-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-acetic acid LC/MS (an10p8) Rt 3 09 min *m/z* 455 [M + H] ^{1}H NMR ($CDCl_3$) δ 3.91 (s 2H) 5 91 (s 1H) 7 34 (m 10H) 7 72 (m 4H).



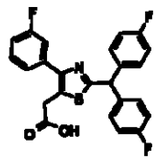
A25

[2-[Bis-(4-fluoro-phenyl)-methyl]-4-(3,4-difluoro-phenyl)-thiazol-5-yl]-acetic acid. LC/MS (an10p8): Rt 3 18 min *m/z* 458 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 86 (s 2H) 5 81 (s 1H) 7 04 (m 4H) 7 18-7 38 (m 8H) 7 48 (m 1H)



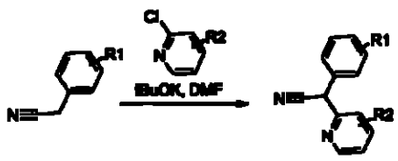
A26

[2-Benzhydryl-4-(3,4-difluoro-phenyl)-thiazol-5-yl]-acetic acid LC/MS (an10p8) Rt 2 88 min *m/z* 422 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 88 (s 2H) 5 81 (s 1H) 7 20 (m 1H) 7 26-7 37 (m 9H) 7 48 (m, 1H)

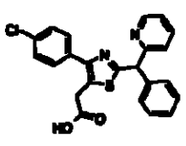


A27

[2-[Bis-(4-fluoro-phenyl)-methyl]-4-(3-fluoro-phenyl)-thiazol-5-yl]-acetic acid LC/MS (an10p8): Rt 3 08 min *m/z* 440 [M + H] ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 2H) 5 82 (s 1H), 7 04 (m 4H) 7 24-7 29 (m 6H) and 7 37 (m, 2H)



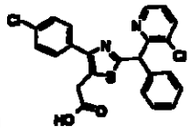
Synthesis of nitrile intermediates – Representative Procedure 7 (RP7) To a cooled (5 °C) solution of Potassium *tert*-butoxide (2 1 mmol) in dry DMF (0 6ml) was added a mixture of the benzonitrile (1 mmol) and the 2-Chloro-pyridine (1 1 mmol) in dry DMF (0 4ml) After O/N stirring at RT aq NH_4Cl and EtOAc were added The organic phase was separated dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified over silica gel chromatography to give the desired product, which precipitated upon treatment with Et_2O



A28

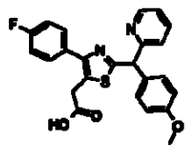
39

[4-(4-Chloro-phenyl)-2-(phenyl-pyridin-2-yl-methyl)-thiazol-5-yl]-acetic acid Title compound was prepared from 3-bromo-4-(4-chloro-phenyl)-4-oxo-butyric acid and 2-phenyl-2-pyridin-2 yl-thioacetamide according to RP6 and RP7 LC/MS (an10p8) Rt 3 00 min *m/z* 422 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 86 (s 2H) 6 2 (s 1H) 7 2-8.0 (m 12H) 8.7 (d 1H)



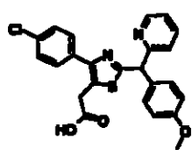
A29

{4-(4-Chloro-phenyl)-2-[(3-chloro-pyridin-2-yl)-phenyl-methyl]-thiazol-5-yl}-acetic acid Title compound was prepared from 3-bromo-4-(4-chloro-phenyl)-4-oxo-butyric acid and 2-(3-Chloro-pyridin-2-yl)-2-phenyl-thioacetamide according to RP6 and RP7 LC/MS (an10p8) Rt 3 54 min *m/z* 454 5 [M + H]$^+$ ^{1}H NMR ($CDCl_3$) δ 3 83 (s 2H), 6 66 (s 1H), 7 2 7 3 (m 1H) 7 3-7 4 (m 5H) 7 5 (d 4H), 7 7 (dd 1H) 8 6 (dd 1H)



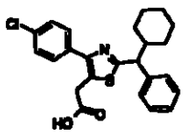
A30

{4-(4-Fluoro-phenyl)-2-[(4-methoxy-phenyl)-pyridin-2-yl-methyl]-thiazol-5-yl}-acetic acid Title compound was prepared from 3-bromo-4-(4-fluoro-phenyl)-4-oxo-butyric acid and 2-(4-methoxy-phenyl)-2-pyridin-2-yl-thioacetamide according to RP6 and RP7 LC/MS (an10p8) Rt 2 20 min *m/z* 434 [M + H]



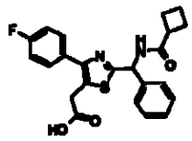
A31

{4-(4-Chloro-phenyl)-2-[(4-methoxy-phenyl)-pyridin-2-yl-methyl]-thiazol-5-yl}-acetic acid Title compound was prepared from 3-bromo-4-(4-chloro-phenyl)-4-oxo-butyric acid and 2-(4-methoxy-phenyl)-2-pyridin-2 yl-thioacetamide according to RP6 and RP7 LC/MS (an10p8) Rt 2 37 min *m/z* 450 5 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 75 (s, 3H) 3 78 (s 2H) 6 0 (s 1H) 6 9 (d 2H) 7 2 (t, 1H) 7 3 (m 4H), 7 4 (d 1H) 7 5 (d 2H) 7 6 (dt, 1H) 8 1 (d 1H).



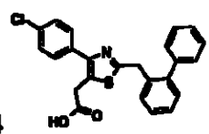
A32

[4-(4-Chloro-phenyl)-2-(cyclohexyl-phenyl-methyl)-thiazol-5-yl]-acetic acid Title compound was prepared from 3-bromo-4-(4-chloro-phenyl)-4-oxo-butyric acid and 2-cyclohexyl-2-phenyl-thioacetamide according to RP6 LC/MS (an10p8) Rt 3 20 min *m/z* 425.4 [M + H]



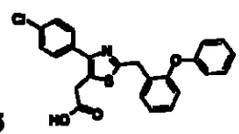
A33

[2-[(Cyclobutanecarbonyl-amino)-phenyl-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid Title compound was prepared from 3-bromo-4-(4-fluoro-phenyl)-4-oxo-butyric acid and 2-cyclobutyl 2-phenyl-thioacetamide according to RP6. LC/MS (an10p8): Rt 2 01 min m/z 425 [M + H] ^{1}H NMR ($CDCl_3$) δ 1 92 (m 2H) 2 19 (m 2H) 3.13 (p *J* = 8 4 Hz, 1H) 3 81(s 2H) 6 49 (d J = 7 5 1H (NH)) 7 13 (m 3H) 7 36 (m 4H) and 7 54 (m 2H).



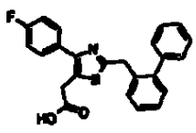
A34

[2-Biphenyl-2-ylmethyl-4-(4-chloro-phenyl)-thiazol-5-yl]-acetic acid. Title compound was prepared from 3-bromo-4-(4-chloro-phenyl)-4-oxo-butyric acid and 2-biphenyl-2-yl-thioacetamide according to RP6 LC/MS (an10p8) Rt 4 94 min *m/z* 419.4 [M + H]$^+$ ^{1}H NMR ($CDCl_3$) δ 3 83 (s 2H) 4 33 (s 2H) 7 3-7 5 (m 13H)



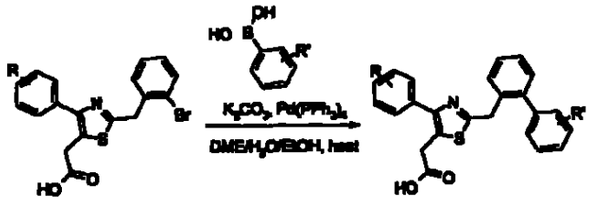
A35

[4-(4-Chloro-phenyl)-2-(2-phenoxy-benzyl)-thiazol-5-yl]-acetic acid. Title compound was prepared from 3-bromo-4-(4-chloro-phenyl)-4-oxo-butyric acid and 2-(2-phenoxy-phenyl)-thioacetamide according to RP6 LC/MS (an10p8) Rt 3 80 min *m/z* 435 4 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 82 (s 2H) 4 39 (s 2H) 6 9 (d 1H), 7 0 (d 2H) 7 1 (m 2H) 7.2-7 3 (m, 3H) 7 4 (t, 3H) 7 5 (d 2H)



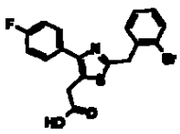
A36

[2-Biphenyl-2-ylmethyl-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid Title compound was prepared from 3-bromo-4-(4-fluoro-phenyl)-4-oxo-butyric acid and 2-biphenyl-2-yl thioacetamide according to RP6 LC/MS (an10p8) Rt 2.60 min *m/z* 403 $[M + H]^+$ ^1H NMR ($CDCl_3$) δ 3 78 (s 2H), 4 31 (s 2H) 7 1 (t 2H) 7 3-7 5 (m 11H)



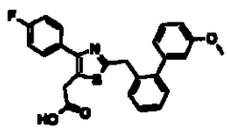
Representative procedure 8 (RP8)

A mixture of $Pd(PPh_3)_4$ (~50mg) K_2CO_3 (2 mmol), [2-(2-bromo-benzyl)- thiazol-5-yl] acetic acid (1 mmol) and the corresponding phenyl boronic acid (1 3 mmol) in DME/H2O/EtOH (7/3/2 20 mL) was heated at 150 °C for 10 minutes in a microwave After cooling water acetic acid and EtOAc were added The solid materials were filtered off and the filtrate was concentrated *in vacuo* The residue was taken up in hot acetonitrile and solid particles were filtered off The filtrate was allowed to cool to RT upon which the desired compound precipitated In some occasions the crude material was purified by chromatography



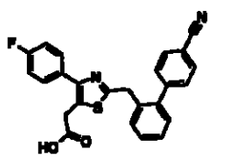
Intermediate-33

[2-(2-Bromo-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid Title compound was prepared from 3-bromo-4-(4-fluoro-phenyl)-4-oxo-butyric acid and 2-(2-bromo-phenyl)-thioacetamide according to RP6 LC/MS (an10p8) Rt 2.22 min *m/z* 405 4 $[M + H]^+$ ^1H NMR ($CDCl_3$) δ 3 85 (s 2H) 4 55 (s 2H), 7 1 (m 3H) 7.3 (t, 1H) 7 4 (d 1H) 7 5-7 6 (m 3H)



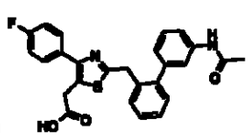
A37

[4-(4-Fluoro-phenyl)-2-(3 -methoxy-biphenyl-2-ylmethyl)-thiazol-5-yl]-acetic acid Title compound was prepared from [2-(2-bromo-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid and 3-methoxyphenyl boronic acid according to RP8 LC/MS (an10p8) Rt 2 65 min *m/z* 433 $[M + H]^+$ ^1H NMR ($CDCl_3$) δ 3 76 (s 3H) 3 81(s 2H), 4 43 (s 2H) 6 8-6 9 (m, 2H) 7 1 (t 1H) 7 3-7 5 (m 7H) 7 7 (m 2H)



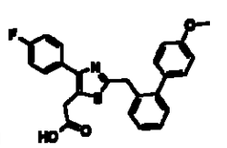
A38

[2-(4 -Cyano-biphenyl-2-ylmethyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid. Title compound was prepared from [2-(2-bromo-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid and 4-cyanophenyl boronic acid according to RP8. LC/MS (an10p8) Rt 2.47 min *m/z* 428 $[M + H]^+$ ^1H NMR ($CDCl_3$) δ 3 84 (s, 2H) 4 36 (s 2H) 7 1 (t, 2H) 7 3-7 5 (m 8H), 7 7 (d 2H)



A39

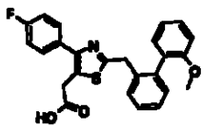
[2-(3'-Acetylamino-biphenyl-2-ylmethyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid Title compound was prepared from [2-(2-bromo-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid and 3-acetamidobenzene boronic acid according to RP8 LC/MS (an10p8) Rt 2 18 min *m/z* 460 $[M + H]^+$ ^1H NMR ($CDCl_3$) δ 1 98 (s, 3H) 3 78 (s, 2H) 4 3 (s 2H) 7 0-7 1 (m, 4H) 7 2 7 4 (m 2H) 7.4 (m 4H), 7 6 (m 2H)



A40

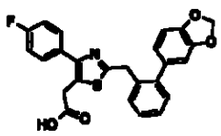
[4-(4-Fluoro-phenyl)-2-(4 -methoxy-biphenyl-2-ylmethyl)-thiazol-5-yl]-acetic acid Title compound was prepared from [2 (2-bromo-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid and 4-methoxyphenyl boronic acid according to RP8 LC/MS

(an10p8) Rt 2.60 min *m/z* 433 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 82 (s, 2H) 3.84(s 3H) 4 37 (s 2H) 6.9 (d 2H) 7 1 (t 2H) 7 2-7 3 (m 5H) 7.4 (m 1H) 7 5 (m 2H)



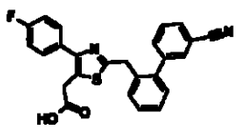
A41

[4-(4-Fluoro-phenyl)-2-(2 -methoxy-biphenyl-2-ylmethyl)-thiazol-5-yl]-acetic acid. Title compound was prepared from [2-(2-bromo-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid and 2-methoxyphenyl boronic acid according to RP8 LC/MS (an10p8) Rt 2 55 min *m/z* 433 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 71 (s 3H) 3.81 (s 2H) 4.3 (s 2H), 6 9-7 0 (m 2H) 7 1 (m 3H) 7 2-7 4 (m 4H) 7 4-7 5 (m 3H)



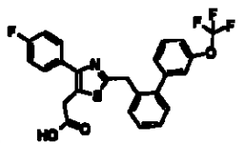
A42

[2-(2-Benzo[1,3]dioxol-5-yl-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid Title compound was prepared from [2-(2-Bromo-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid and 3,4-methylenedioxobenzene boronic acid according to RP8 LC/MS (an10p8) Rt 3 35 min *m/z* 447 [M + H] ^{1}H NMR ($CDCl_3$) δ 3 78 (s, 2H) 4 34 (s 2H) 5 96 (s, 2H) 6 7 (m 3H) 7 1 (t, 2H) 7 2-7 3 (m 3H) 7 3 (d 1H) 7 5 (t, 2H)



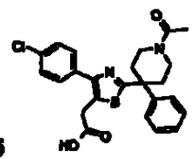
A43

[2-(3 -Cyano-biphenyl-2-ylmethyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid. Title compound was prepared from [2-(2-bromo-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid and 3-cyanophenyl boronic acid according to RP8. LC/MS (an10p8) Rt 3 157 min *m/z* 428 $[M + H]^+$ ^{1}H NMR ($CDCl_3$) δ 3 55 (s 2H) 3.9 (s 2H), 6 8 (m 2H) 7 0 (m 4H) 7 2-7 4 (m 6H).



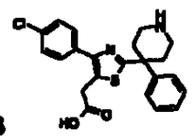
A44

[4-(4-Fluoro-phenyl)-2-(3 -trifluoromethoxy-biphenyl-2-ylmethyl)-thiazol-5-yl] acetic acid. Title compound was prepared from [2-(2-bromo-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid and 3-trifluoromethoxyphenyl boronic acid according to RP8 LC/MS (an10p8) Rt 3 91 min *m/z* 487 [M + H] ^{1}H NMR ($CDCl_3$): δ 3 78 (s 2H) 4.3 (s 2H) 7 1 (t, 2H) 7 3 (m 1H) 7 3 (t, 2H) 7 4-7 5 (m 7H)



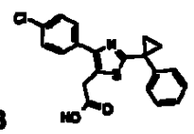
A45

[2-[(1-Acetyl-piperidin-4-yl)-phenyl-methyl]-4-(4-chloro-phenyl)-thiazol-5-yl] acetic acid Title compound was prepared from 3-bromo-4-(4-chloro-phenyl)-4-oxo-butyric acid and 1-acetyl-4-phenyl-piperidine-4-carbothioic acid amide 2-(1-acetyl-pipendin-4-yl)-2-phenyl thioacetamide according to RP6 LC/MS (an10p8) Rt 2 32 min *m/z* 454 5 [M + H]$^+$



A48

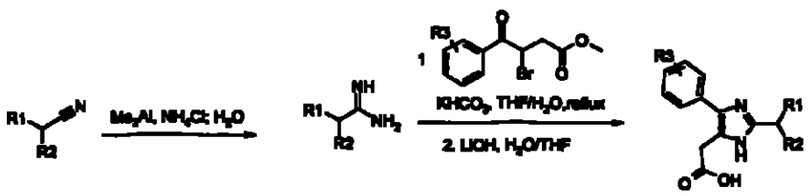
[4-(4-Chloro-phenyl)-2-(4-phenyl-piperidin-4-yl)-thiazol-5-yl]-acetic acid Title compound isolated as its HCl salt was prepared by reacting [2-[(1-acetyl-piperidin-4-yl)-phenyl-methyl]-4-(4-chloro-phenyl)-thiazol-5-yl]-acetic acid with 4N aq HCl at 95°C for 18 hours followed by evaporation of solvent: LC/MS (an10p8) Rt 2 07 min *m/z* 412 4 [M + H]

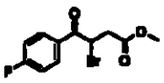


A46

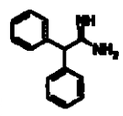
[4-(4-Chloro-phenyl)-2-(1-phenyl-cyclopropyl)-thiazol-5-yl]-acetic acid Title compound was prepared from 3-bromo-4-(4-chloro-phenyl)-4-oxo-butyric acid and 1 phenyl-cyclopropanecarbothioic acid amide according to RP6 LC/MS (an10p8) Rt 3 57 min *m/z* 369 8 [M + H]$^+$

General synthetic route to imidazole analogs



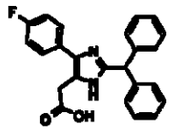
Intermediate-34 

3-Bromo-4-(4-fluorophenyl)-4-oxo-butyric acid methyl ester 3-Bromo-4-(4-fluorophenyl)-4-oxobutyric acid (15 mmol) was dissolved in methanol (60 ml) and thionyl chloride (17 mmol) was added at 0 C After stirring at 60 °C for 2 h the solvent was evaporated The residue was stripped with diethylether The product was used directly in the next step ^{1}H NMR ($CDCl_3$) δ 3 00 (m 1H) 3 33 (m, 1H) 3.67 (s 3H) 5.44 (t, 1H) 7 15 (t, 2H) 8.06 (t, 2H)



Intermediate-35

2,2-Diphenylacetamidine Prepared from diphenylacetonitrile according to R. A. Moss W Ma D C Merrer and S Xue (*Tetrahedron Lett.* 1995 *36*, 8761-8764) LC/MS (an10p8) Rt 1 57 min *m/z* 211 $[M+H]^+$



A48

[2-Benzhydryl-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-acetic acid A suspension of 2 2-diphenylacetamidine (10 mmol) and potassium carbonate (38 mmol) in THF/H2O (150 mL/50 mL) was heated to reflux 3-Bromo-4-(4-fluorophenyl)-4-oxo-butyric acid methyl ester (10 mmol) in THF (50 mL) was added slowly The reaction mixture was refluxed for 16 h and then concentrated The residue was dissolved in water (10 mL) and extracted with CH2Cl2 (10 mL). The organic phase was dried ($MgSO_4$) and concentrated to produce [2 benzhydryl-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-acetic acid methyl ester LC/MS (an10p8) Rt 3 64 min *m/z* 401 $[M+H]^+$ The methyl ester in THF was added excess LiOH H_2O in water The reaction was stirred at room temperature over night, 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 productwas subject to hydrolysis with LiOH in water/THF LC/MS (an10n8) Rt 1 43 min *m/z* 387 [M H]

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)

Sequence ID CRTH2 (protein sequence)

MSANATLKPLCPILEQMSRLQSHSNTSIRYIDHAAVLLEGLASLLGLVEN
GVILFVVGCRMRQTVVTTWVLHLALSDLLASASLPFFTYFLAVGHSWELG
TTFCKLHSSIFFLNMFASGFLLSAISLDRCLQVVRPVWAQNHRTVAAAHK
VCLVLWALAVLNTVPYFVFRDTISRLDGRIMCYYNVLLLNPGPDRDATCN
SRQAALAVSKFLLAFLVPLAIIASSHAAVSLRLQHRGRRRPGRFVRLVAA
VVAAFALCWGPYHVFSLLEARAHANPGLRPLVWRGLPFVTSLAFFNSVAN
PVLYVLTCPDMLRKLRRSLRTVLESVLVDDSELGGAGSSRRRRTSSTARS
ASPLALCSRPEEPRGPARLLGWLLGSCAASPQTGPLNRALSSTSS

Sequence ID CRTH2 (nucleotide sequence)

atgtcggc
caacgccaca ctgaagccac tctgccccat cctggagcag atgagccgtc
tccagagcca
cagcaacacc agcatccgct acatcgacca cgcggccgtg ctgctgcacg
ggctggcctc
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gccgccgccg
cacctcctcc accgcccgct cggcctcccc tttagctctc tgcagccgcc
cggaggaacc
gcggggcccc gcgcgtctcc tcggctggct gctgggcagc tgcgcagcgt
ccccgcagac
gggcccccctg aaccgggcgc tgagcagcac ctcgagttag

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

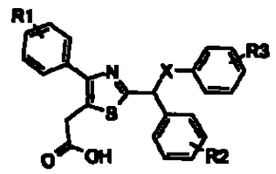
B IC_{50} value between 0 5 µM and 5 µM

C IC_{50} value higher than 5 µM

Tables 1 to 4 give the biological test results for the compounds synthesised above and for some additional compounds acquired from commercial sources.

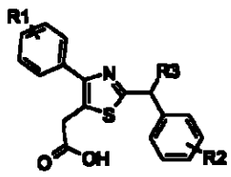
The ability of the compounds above to inhibit prostaglandin D2 induced eosinophil shape change is demonstrated by the examples in Figure 1

Table 1



	X	R1	R2	R3	Binding IC_{50}	Antag IC_{50}
A1	Bond	4-Cl	H	H	A	A
A4	Bond	4-F	H	H	A	A
A5	CH_2	4-Cl	H	H	A	B
A7	CH_2	4-F	4-Cl	H	A	A
A8	Bond	4-Cl	4-Cl	H	A	A
A9	CH_2	4-Cl	4-Cl	H	A	B
A10	Bond	4-F	4-Cl	H	A	A
A11	Bond	H	H	H	B	A
A12	Bond	4-MeO	H	H	A	B
A13	Bond	4-Cl	4-F	H	A	A
A14	Bond	4-F	4-F	4-F	A	A
A15	Bond	4-F	4-MeO	H	A	A
A16	Bond	4-Cl	4-MeO	H	A	A
A17	Bond	4-Cl	3 4-DiF	H	A	C
A18	Bond	4-F	3 4-DiF	H	A	A
A19	NHCO	4-F	H	4-CF_3	A	C
A20	Bond	4-F	4-MeO	4-MeO	A	A
A21	Bond	4-PhO	H	H	A	B
A22	Bond	4-F	4-OH	H	A	A
A23	Bond	3-F	H	H	A	A
A24	Bond	4-CF_3	H	H	B	C
A25	Bond	3 4-DiF	4-F	4-F	A	A
A26	Bond	3,4-DiF	H	Ph	A	A
A27	Bond	3-F	4-F	4-F	A	A

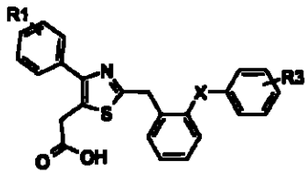
Table 2



	R1	R2	R3	Binding IC_{50}	Antag IC_{50}
A28	4-Cl	H		A	B
A29	4-Cl	H		A	
A30	4-F	4-MeO		A	
A31	4-Cl	4-MeO		A	A
A32	4-Cl	H		B	
A8	4-Cl	H	Et	A	

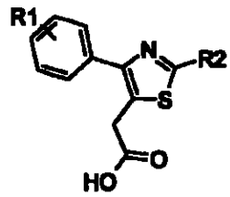
52

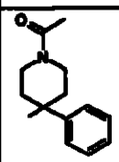
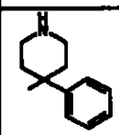
Table 3



	X	R1	R2	Binding IC_{50}	Antag IC_{50}
A34	Bond	4-Cl	H	A	A
A35	O	4-Cl	H	B	
A36	Bond	4-F	H	A	A
A37	Bond	4-F	3-MeO	A	A
A38	Bond	4-F	4-CN	A	A
A39	Bond	4-F	3-NHAc	B	
A40	Bond	4-F	4-MeO	A	A
A41	Bond	4-F	2-MeO	A	
A42	Bond	4-F	3,4-OCH_2O	A	A
A43	Bond	4-F	3-CN	A	
A44	Bond	4-F	3-OCF_3	A	

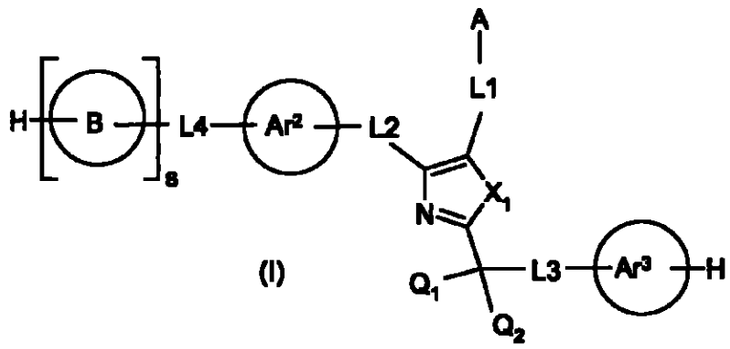
Table 4



	R1	R2	Binding IC_{50}	Antag IC_{50}
A45	4-Cl		A	B
A46	4-Cl		B	C

Claims

1 A compound of formula (I) or a salt, hydrate or solvate thereof



(I)

wherein

X_1 is -S- -O- -N=N –NR_7- -CR_7=CR_8- -CR_7=N- wherein R_7 and R_8 are independently hydrogen or C_1-C_3 alkyl

A is a carboxyl group –COOH or a carboxyl bioisostere

rings Ar^2 and 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

ring B is as defined for Ar^2 and Ar^3 or an optionally substituted N-pyrrolidinyl N-piperidinyl or N-azepinyl ring

s is 0 or 1

L1 represents a divalent radical of formula –$(Alk^1)_m$- and L2 and L4 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 -$NRSO_2$- -C(=O)NR- -NRCONH- NRC(=NR)NH or =N-NR wherein R is hydrogen or C_1 C_3 alkyl or a divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical

L3 represents a divalent radical of formula $-(Alk^3)_m-(Z)_n-(Alk^2)_p-$ wherein m n p Alk^2 and Z are as defined in relation to L2 and L4 and Alk3 is an optionally substituted straight or branched chain C_1-C_2 alkylene or C_1 C_2 alkenylene radical which may contain a compatible –O- -S- or –NR link wherein R is hydrogen or C_1-C_3 alkyl

Q_1 represents hydrogen or (C_1-C_6)alkyl

Q_2 represents

(I) (C_1-C_6)alkyl (C_1-C_6)alkoxy hydroxy hydroxy(C_1 C_6)alkyl nitrile (-CN) phenyl phenoxy monocyclic heteroaryl or heteroaryloxy with 5 or 6 ring atoms, $-CONR^AR^B$ NR^BCOR^A $-NR^BSO_2R^A$ or $-NR^ACONR^AR^B$ wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring and when Q is phenyl phenoxy or monocyclic heteroaryl or heteroaryloxy with 5 or 6 ring atoms the phenyl or heteroaryl ring is optionally substituted by any of (C_1-C_6)alkyl (C_1-C_6)alkoxy hydroxy hydroxy(C_1-C_6)alkyl (C_1 C_3)alkylthio halo, fully or partially fluorinated (C_1-C_3)alkyl (C_1-C_3)alkoxy or (C_1 C_3)alkylthio trifluoromethylthio nitro nitrile (-CN) $-COOR^A$ $-COR^A$ $-OCOR^A$ SO_2R^A $-CONR^AR^B$ $-SO_2NR^AR^B$ NR^AR^B $-NR^BCOR^A$ $-NR^BCOOR^A$ $NR^BSO_2R^A$ or $NR^ACONR^AR^B$ wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring or

(II) hydrogen but only when in L3 Z represents an optionally substituted divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical

or Q_1 and Q_2 taken together with the carbon atom to which they are attached form a C_3-C_8 cycloalkyl ring or a monocyclic non-aromatic heterocyclic ring with 4-8 ring atoms

and wherein the total length of L2 and L3 does not exceed that of an unbranched saturated chain of 10 carbon atoms

2. A compound as claimed in claim 1 wherein (i) the length of each of L2 L3 and L4 does not exceed that of an unbranched saturated chain of 5 atoms and (ii) the total length of L2 L3 and L4 does not exceed that of an unbranched saturated chain of 7 atoms and (iii) none of L1 L2 L3 and L4 includes more than two R substituents different from hydrogen

3 A compound as claimed in claim 1 or claim 2 wherein L3 is a bond Q_1 is hydrogen and Q_2 is phenyl or monocyclic heteroaryl with 5 or 6 ring atoms optionally substituted by any of (C_1-C_6)alkyl (C_1-C_6)alkoxy hydroxy hydroxy(C_1-C_6)alkyl (C_1-C_3)alkylthio halo, fully or partially fluorinated (C_1-C_3)alkyl (C_1-C_3)alkoxy or (C_1-C_3)alkylthio trifluoromethylthio nitro nitrile (-CN) -$COOR^A$ -COR^A -$OCOR^A$ SO_2R^A -$CONR^AR^B$ -$SO_2NR^AR^B$ -NR^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-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

4 A compound as claimed in claim 1 or claim 2 wherein L3 is a bond Q_1 is hydrogen and Q_2 is phenyl optionally substituted by any of 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)$NHSO_2$- (C_1-C_3alkyl)$_2NSO_2$- -$CONR^AR^B$ and -NR^BCOR^A wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

5 A compound as claimed in claim 1 or claim 2 wherein L3 is -CH_2- -O- -S- -SO_2- –NHC(=O)- -CH=CH NR_{11} or -$NR_{11}CH_2$- wherein R_{11} is hydrogen or C_1-C_3 alkyl

6 A compound as claimed in claim 1 or claim 2 wherein Q_2 is hydrogen and L3 represents a divalent radical of formula –$(Alk^3)_m$-$(Z)_n$-$(Alk^2)_p$- wherein m is 0 n is 1 and Z is a phenylene radical optionally substituted by one or more of 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)$NHSO_2$- (C_1-C_3alkyl)$_2NSO_2$- $CONR^AR^B$ and -NR^BCOR^A wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

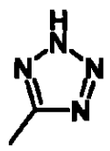
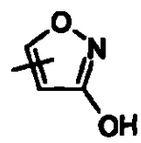
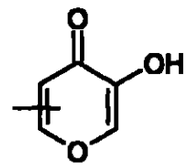
7 A compound as claimed in claim 6 wherein Z is a 1 2-phenylene radical optionally substituted by one or more of fluoro, chloro bromo $(C_1$-$C_3)$alkyl trifluoromethyl $(C_1$-$C_3)$alkoxy trifluoromethoxy trifluoromethylthio dimethylamino cyano $(C_1$-C_3alkyl$)SO_2$- NH_2SO_2- $(C_1$-C_3alkyl$)NHSO_2$- $(C_1$-C_3alkyl$)_2NSO_2$- $CONR^AR^B$ and NR^BCOR^A wherein R^A and R^B are independently hydrogen or a $(C_1$ $C_3)$alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

8 A compound as claimed in claim 6 or claim 7 wherein Q_1 is hydrogen.

9 A compound as claimed in any of the preceding claims wherein X_1 is –S-

10 A compound as claimed in any of the preceding claims wherein A is a carboxyl group –COOH

11 A compound as claimed in any of claims 1 to 9 wherein A is a carboxyl bioisostere selected from $-SO_2NHR$ and -P(=O)(OH)(OR) wherein R is hydrogen methyl or ethyl $-SO_2OH$ -P(=O)(OH)(NH_2) –C(=O)NHCN and groups of formulae

12. A compound as claimed in any of the preceding claims wherein L1 represents a bond $–CR_{11}R_{12}$- $–CH_2CR_{11}R_{12}$- $–OCR_{11}R_{12}$- $–SCR_{11}R_{12}$- $–NR_{11}CH_2$- or $–NR_{11}$ wherein R_{11} and R_{12} are independently hydrogen or C_1-C_3 alkyl the bond marked with an asterisk being the one connected to the ring containing X^1

13 A compound as claimed in any of claims 1 to 11 wherein L1 represents $–CH_2$- or $–CH(CH_3)$-

14 A compound as claimed in any of the preceding claims wherein Ar^3 is phenyl thienyl naphthyl or 2 3- or 4-pyridyl any of which is optionally substituted

15. A compound as claimed in claim 14 wherein optional substituents in Ar^3 are selected from fluoro, chloro, bromo $(C_1$-$C_3)$alkyl trifluoromethyl $(C_1$-$C_3)$alkoxy

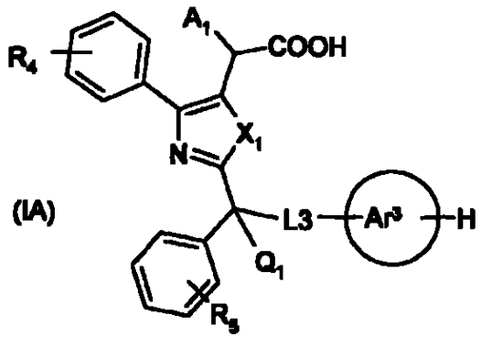
trifluoromethoxy trifluoromethylthio dimethylamino cyano $(C_1\text{-}C_3alkyl)SO_2$- NH_2SO_2- $(C_1\text{-}C_3alkyl)NHSO_2$- $(C_1\text{-}C_3alkyl)_2NSO_2$- $-CONR^AR^B$ and NR^BCOR^A wherein R^A and R^B are independently hydrogen or a $(C_1\text{-}C_6)$alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

16 A compound as claimed in any of the preceding claims wherein L2 is a bond and Ar^2 is an optionally substituted phenyl thienyl furanyl pyrrolyl or pyridyl ring

17 A compound as claimed in claim 16 wherein optional substituents in Ar^2 are selected from fluoro chloro bromo $(C_1\text{-}C_3)$alkyl trifluoromethyl $(C_1\text{-}C_3)$alkoxy trifluoromethoxy trifluoromethylthio, dimethylamino cyano $(C_1\text{-}C_3alkyl)SO_2$- NH_2SO_2- $(C_1\text{-}C_3alkyl)NHSO_2$- $(C_1\text{-}C_3alkyl)_2NSO_2$- $-CONR^AR^B$ and $-NR^BCOR^A$ wherein R^A and R^B are independently hydrogen or a $(C_1\text{-}C_6)$alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

18 A compound as claimed in any of the preceding claims wherein a is 0

19 A compound of formula (IA) or a salt, hydrate or solvate thereof



(IA)

wherein A_1 is hydrogen or methyl X_1 Q_1 Ar^3 and L3 are as defined in claim 1 and R_4 and R_5 independently represent hydrogen or one or more optional substituents

20 A compound as claimed in claim 19 wherein A_1 is hydrogen

21 A compound as claimed in claim 19 or claim 20 wherein Q_1 is hydrogen

22 A compound as claimed in any of claims 19 to 21 wherein X_1 is –S-

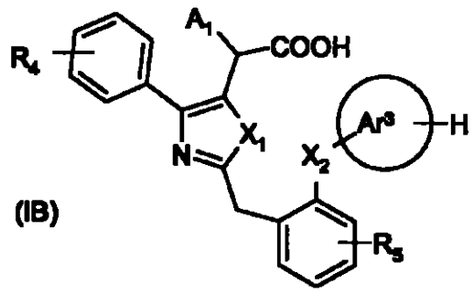
23 A compound as claimed in any of claims 19 to 22 wherein Ar^3 is optionally substituted phenyl

24 A compound as claimed in any of claims 19 to 23 wherein L3 is a bond -O- –S- or –NR wherein R is hydrogen or C_1-C_3 alkyl

25 A compound as claimed in claim 19 wherein A_1 is hydrogen Q_1 is hydrogen X_1 is –S- Ar^3 is optionally substituted phenyl and L3 is a bond

26 A compound as claimed in any of claims 19 to 25 wherein optional substituents R_4 and R_5 and optional substituents in Ar^3 are independently 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)$NHSO_2$- (C_1-C_3alkyl)$_2NSO_2$- -$CONR^AR^B$ and -NR^BCOR^A wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

27 A compound of formula (IB) or a salt, hydrate or solvate thereof



(IB)

wherein A_1 is hydrogen or methyl X_2 is a bond –CH_2- -O- –S- or –NR wherein R is hydrogen or C_1-C_3 alkyl and X_1 and Ar^3 are as defined in claim 1 and R_4 and R_5 independently represent hydrogen or one or more optional substituents.

28 A compound as claimed in claim 27 wherein A_1 is hydrogen

29 A compound as claimed in claim 27 or claim 28 wherein X_1 is –S-

30 A compound as claimed in any of claims 27 to 29 wherein Ar^3 is optionally substituted phenyl

31 A compound as claimed in any of claims 27 to 30 wherein X_2 is $-CH_2-$ or a bond

32 A compound as claimed in any of claims 27 to 31 wherein optional substituents R_4 and R_5 and optional substituents in Ar^3 are independently selected from fluoro chloro bromo (C_1-C_3)alkyl trifluoromethyl (C_1-C_3)alkoxy trifluoromethoxy trifluoromethylthio dimethylamino cyano $(C_1-C_3$alkyl$)SO_2-$ NH_2SO_2- $(C_1-C_3$alkyl$)NHSO_2-$ $(C_1-C_3$alkyl$)_2NSO_2-$ $-CONR^AR^B$ and NR^BCOR^A wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or R^A and R^B are linked to the same N atom to form a cyclic amino ring

33 A compound selected from the group consisting of

[2-benzhydryl-4-(4-chlorophenyl)-thiazol-5-yl]-acetic acid
[2-benzhydryl-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-[1-(4-chloro-phenyl)-2-phenyl-ethyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid
{4-(4-chloro-phenyl)-2-[(4-chloro-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid
[2-[(4-chloro-phenyl)-phenyl-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-[bis-(4-fluoro-phenyl)-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid
{4-(4-fluoro-phenyl)-2 [(4-methoxy-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid
{4-(4-chloro-phenyl)-2-[(4-methoxy-phenyl)-phenyl-methyl]-thiazol-5-yl}-acetic acid
[2-[(3 4-difluoro-phenyl)-phenyl-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-[bis-(4-methoxy-phenyl)-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-benzhydryl-4-(3-fluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-[bis-(4-fluoro-phenyl)-methyl]-4-(3,4-difluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-benzhydryl-4-(3,4-difluoro-phenyl)-thiazol-5-yl]-acetic acid
[2-[bis-(4-fluoro-phenyl)-methyl]-4-(3-fluoro-phenyl)-thiazol-5-yl]-acetic acid

and salts hydrates and solvates thereof

34 A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 33 together with a pharmaceutically acceptable carrier

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35 Use of a compound as claimed in any of claims 1 to 33 in the manufacture of a composition for the treatment of disease responsive to modulation of CRTH2 receptor activity

36 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 claims 1 to 33

37 Use as claimed in claim 35 or a method as claimed in claim 36 wherein the disease is one associated with elevated levels of prostaglandin D2 (PGD2) or one or more active metabolites thereof

38 Use or a method as claimed in claim 37 wherein the disease is an inflammatory autoimmune respiratory or allergy disease

39 Use or method as claimed in claim 37 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 fasciitis hyper IgE syndrome sepsis septic shock, ischemic reperfusion injury in the heart, allograft rejection after transplantations and graft versus host disease

40 Use or method as claimed in claim 37 wherein the disease selected from asthma rhinitis allergic airway syndrome and allergic rhinobronchitis

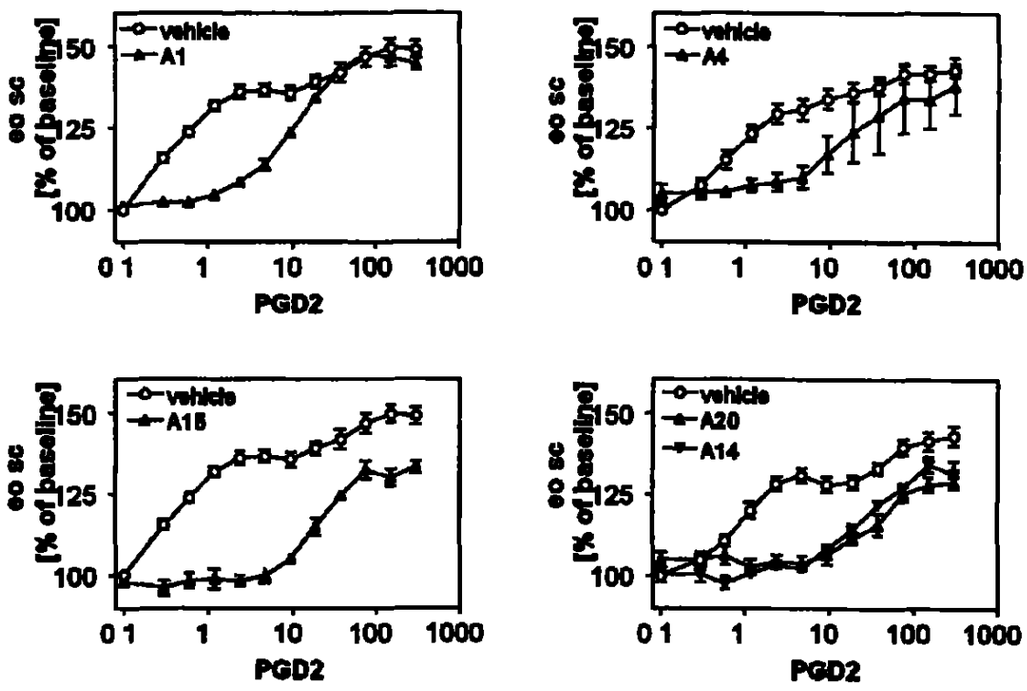
vehicle
A1
A4
A15
A20
A14
eo sc
[% of baseline]
150
125
100
0 1
1
10
100
1000
PGD2

Figure 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/005882

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/30 C07D417/06 C07D417/04 A61K31/426 A61K31/427
A61P11/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/02505 A (JANSSEN PHARMACEUTICA N V LACRAMPE JEAN FERNAND ARMAND FREYNE ED) 21 January 1999 (1999-01-21) table 3 compounds 29 256 274 277 285 293 298-300 page 20 lines 6-11	1-26 34-40
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document 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 September 2005	29/09/2005

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	Kollmannsberger M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/005882

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 987 265 A (JANSSEN PHARMACEUTICA N V) 22 March 2000 (2000-03-22) table 2 compounds 6 9 19 paragraphs 0059' 0060'	1-18 34-40
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A	NAGATOMI H ET AL STUDIES ON THE ANTI-INFLAMMATORY ACTIVITY AND ULCEROGENIC ADVERSE EFFECT OF THIAZOLE DERIVATIVES ESPECIALLY 2-AMINO-THIAZOLEACETIC ACID DERIVATIVES ARZNEIMITTEL FORSCHUNG DRUG RESEARCH EDITIO CANTOR VERLAG AULENDORF DE vol 5 no 34 1984 pages 599-603 XP001074027 ISSN 0004-4172 cited in the application table 1 compounds 19-27	1-40
A	BONINA F ET AL SYNTHESIS AND ANALGESIC ANTIINFLAMMATORY ACTIVITIES OF 2-ARYLETHENYL-4-ARYLTHIAZOLE-5-ACETIC ACIDS IL FARMACO ROME IT vol 42 no 12 December 1987 (1987-12) pages 905-913 XP001069993 ISSN 0014-827X cited in the application page 909 - page 911 table 1	1-40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/005882

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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 37-40 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

International Application No
PCT/EP2005/005882

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International Application No
PCT/EP2005/005882

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Uso de Ligandos de Receptor en Terapia

Está invención se relaciona con una clase de compuestos que son ligandos del receptor CRTH2 (molécula homóloga del Receptor Quimioatrayente expresada sobre células Ayudante T tipo 2) y su uso en el tratamiento de enfermedades que responden a la modulación de la actividad del receptor CRTH2 principalmente enfermedades que tienen un componente inflamatorio significativo La invención también se relacionan con los miembros novedosos de esa clase de ligandos y con las composiciones farmacéuticas que las contienen

Antecedentes de la invención

El ligando natural del receptor acoplado a la proteína G CRTH2 es la prostaglandina D2 Como su nombre lo dice el CRTH2 se expresa en las células ayudante T tipo 2 (Celulas TH2) pero también es conocido por ser expresado sobre las células eosinófilas y basófilas La activación de la célula como resultado de la unión del PGD2 al receptor CRTH2 da como resultado una respuesta biológica compleja que incluye la liberación de los mediadores inflamatorios Los niveles elevados PGD2 están por lo tanto asociados con muchas enfermedades que tienen un fuerte componente inflamatorio tal como el asma la rinitis y las alergias Bloquear la unión del PGD2 al receptor CRTH2 es por lo tanto una estrategia terapéutica util para el tratamiento de tales enfermedades

En algunos ligandos de molécula pequeña ed CRTH2 que actúan aparentemente como antagonistas de PGD2 son conocidos por ejemplo como se propone en las siguiente solicitudes 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 NSAID (drogas no esteroides antiinflamatorias) constituyen otra clase de agentes antiinflamatorios Un NSAID es el ácido 4-(4-clorofenil)-2 fenil tiazol 5 acético (fentiazac) Algunos otros compuestos han sido investigados como agentes antiinflamatorios (ver por ejemplo Nagatomi et al Arzneimittel-Forschung (1984) 34(5) 599 603 Bonina et al Farmaco Edizione Scientifica (1987) 42(12 905-13 Gieldanowski et al Archivum Immunologiae et Therapiae Experimentalis 1978 26

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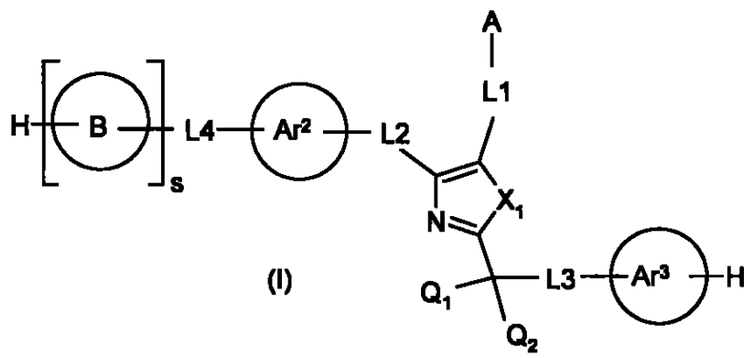
Breve Descripción de la Invención

Las estructuras de los compuestos antagonistas PGD2 a las que se refieren las publicaciones anteriores tienen un sistema de anillo con nucleo biciclico o tricíclico relacionado con el nucleo indol de la indometacina un agente antiinflamatorio conocido ahora conocido por unirse al CRTH2 La presente invención surge de la identificación de una clase de compuestos que tienen el nucleo monocíclico que contiene nitrógeno de 5 a 6 miembros tal cómo un anillo de tiazol cuyas porciones sustituyentes están orientadas por el núcleo monocíclico para interactuar con y unirse al CRTH2 La clase de compuestos con las cuales la invención está relacionada son así capaces de modular la activad CRTH2 y son utiles en el tratamiento de las enfermedades que se beneficien de tal modulación por ejemplo el asma la alergia y la rinitis

Descripción Detallada de la Invención

De acuerdo con la presente invención se suministra un compuesto de fórmula (I) o una sal hidrato o solvato de éste



(I)

en donde

X_1 es S O- N=N $-NR_7-$ $-CR_7=CR_8-$ $CR_7=N$ en donde R_7 y R_8 son independientemente hidrógeno o alquilo C_1 C_3

A es un grupo carboxilo –COOH o un carboxil bioisostere

Los anillos Ar^2 y Ar^3 independientemente cada uno representa un fenilo o un anillo heterocíclico de 5 o 6 miembros o un sistema de anillo bicíclico que consiste de un anillo carbocíclico de 5 o 6 miembros que está benzofusionado a un anillo heteroanlo monocíclico de 5 o 6 miembros dicho anillo o sistema de anillo es opcionalmente sustituido

El anillo B es como se definió Ar^2 y Ar^3 o un anillo N pirrolidinilo N piperidinilo o N azepinilo opcionalmente sustituido

s es 0 o 1

L1 representa un radical divalente de la fórmula $-(Alq^1)_m-$ y L2 y L4 cada uno independientemente representan un radical divalente de la fórmula $-(Alq^1)_m(Z)(Alq^2)_p-$
en donde

m n y p son independientemente 0 o 1

Alq^1 y Alq^2 son independientemente radicales alquileno C_1-C_3 o alquenileno C_2-C_3 de cadena recta o ramificada opcionalmente sustituidos que pueden contener un enlace –O– S o –NR compatible en donde R es hidrógeno o alquilo C_1 C_3 y

Z es –O– S C(=O) SO_2– SO– NR $NRSO_2$– C(=O)NR NRCONH NRC(=NR)NH o =N NR en donde R es hidrógeno o alquilo C_1 C_3 o un radical carbocíclico o heterocíclico monocíclico de 5 o 6 miembros divalente

L3 representa un radical divalente de la fórmula $-(Alq^3)_m-(Z)_n-(Alq^2)_p-$ en donde m n p Alq^2 y Z son como se definió en relación con L2 y L4 y Alq3 es un radical alquileno C_1 C_2 o alquenileno C_1 C_2 de cadena recta o ramificada opcionalmente sustituidos que pueden contener un enlace –O S o –NR compatible en donde R es hidrógeno o alquilo C_1-C_3

Q_1 representa hidrógeno o alquilo (C_1 C_8)

Q_2 representa

(i) alquilo (C_1-C_8) alcoxi (C_1 C_8) hidroxi hidroxi-alquilo (C_1 C_8) nitrilo (CN) fenilo fenoxi heteroarilo o heteroariloxi monocíclico con 5 o 6 átomos por anillo -$CONR^AR^B$ NR^BCOR^A $NR^BSO_2R^A$ o $NR^ACONR^AR^B$ en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1-C_8) o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico y cuando Q es fenilo fenoxi o heteroarilo monocíclio heteroariloxi con 5 o 6 átomos por anillo el anillo de fenilo o heteroarilo es opcionalmente sustituido por cualquiera de alquilo (C_1-C_8) alcoxi (C_1 C_8) hidroxi hidroxi-alquilo (C_1 C_8) alquiltio (C_1 C_3) halo alquilo (C_1 C_3) completa o parcialmente fluorinado o alquiltio(C_1-C_3) trifluorometiltio nitro nitrilO (CN) -$COOR^A$ -COR^A $OCOR^A$ SO_2R^A -$CONR^AR^B$ $SO_2NR^AR^B$ NR^AR^B NR^BCOR^A NR^BCOOR^A $NR^BSO_2R^A$ o $NR^ACONR^AR^B$ en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1 C_8) o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico o

(ii) hidrógeno pero sólo cuando en L3 Z representa un radical carbocíclico o heterocíclico de 5 o 6 miembros divalente opcionalmente sustituido

o Q_1 y Q_2 tomados juntos con el átomo de carbono al cual ellos están unidos forman un anillo de cicloalquilo C_3-C_8 o una anillo heterocíclico no aromático monocíclico con 4-6 átomos por anillo

y en donde la longitud total de L2 y L3 no excede aquella de una cadena saturada no ramificada de 10 átomos de carbono

En una definición más estrecha de los compuestos (I) (i) la longitud de cada uno de L2 L3 y L4 no excede aquella de la cadena saturada no ramificada de 5 átomos y (ii) la longitud total de L2 L3 y L4 no excede aquella de la cadena saturada no ramificada de 7 átomos y (iii) ninguno de L1 L2 L3 y L4 incluye más de dos sustituyentes R diferentes de hidrogeno

Los compuestos con los cuales la invención está relacionada se definen por referencia a la fórmula (I) como resultado de estudios hacia la elucidación del sitio de unión de ligando del CRTH2 Tales estudios conducen a la conclusión total de que un farmacóforo general que comprende una porción negativamente cargada representada por AL1 y dos porciones aromática y/o hidrófoba representadas por H(B) L4Ar^{2}L2 y el anillo que contiene X_1 o el anillo que contiene X_1 junto con el fragmento H(Ar^3)L3C(Q_1)(Q_2)- orientado en un triángulo aproximado formarían una disposición para la interacción con el sitio de unión del receptor Se concluyó que los agrupamientos AL1 H(B) L4Ar^{2}L2 sustituyentes deben estar sobre los átomos del anillo adyacente del anillo que contiene X_1 Los ligadores L1 L2 L3 y L4 suministran alguna flexibilidad a la molécula para facilitar la unión óptima Las restricciones sobre las longitudes de y las sustituciones en los ligadores L2 L3 y L4 están en orden para restringir el tamaño y la complejidad molecular total de las estructuras para uso de acuerdo con la invención Para evitar la duda la longitud total de L2 y L3 es para los propósitos de esta descripción y reivindicaciones la suma n2+n3 donde n2 es el numero de átomos conectados en la cadena más corta de átomos desde el átomo terminal al átomo terminal del ligador L2 y n3 es el numero de átomos conectados en la cadena más corta de átomos desde el átomo terminal al átomo terminal de ligador L2 Preferiblemente los compuestos con los cuales la invención está relacionada deben tener un peso molecular de no más de 600 Los sustituyentes opcionales en cualquier elemento de los compuestos (I) se permiten como en la definición de los compuestos (I) Tales sustituyentes pueden modular propiedades farmacocinéticas y de solubilidad así como también recoger interacciones de unión adicionales con el receptor

En otro aspecto la invención suministra el uso de un compuesto como se define y se discute aquí en la elaboración y el tratamiento de una enfermedad que responde a la modulación de la actividad del receptor CRTH2

En otro aspecto la invención suministra un método de tratamiento de un sujeto que sufre de una enfermedad que responde a la modulación de la actividad del CRTH2 la cual comprende administrar al sujeto una cantidad de un compuesto (I) como se definió y se discutió aquí efectivo para mejorar la enfermedad

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En particular los compuestos con los cuales la invención está relacionada son utiles para el tratamiento de la enfermedad asociada con niveles elevados de prostaglandina D2 (PGD2) o uno o más metabolitos activos de estos

Ejemplos de tales enfermedades incluyen asma rinitis síndrome alérgico de vías aéreas rinobronquitis alérgica bronquitis enfermedad pulmonar obstructiva crónica (COPD) poliposis nasal sarcoidosis pulmón de campesino pulmón fibroide fibrosis cistica tos crónica conjuntivitis dermatitis atópica enfermedad de Alzheimer esclerosis lateral amiotrófica complejo de demencia de SIDA enfermedad de Huntington demencia frontotemporal demencia del cuerpo Lewy demencia vascular síndrome de Guillain Barre poliradiculoneuropatía desmielinizante cronica neuropatia motora multifocal plexopatía esclerosis multiple encefalomielitis panencefalitis degeneración cerebelar y en encefalomielitis trauma del CNS migraña ataques artritis reumatoide espondilitis anquilosante enfermedad de Behçet s bursitis síndrome del tunel carpiano enfermedad del intestino inflamatorio enfermedad de Crohn colitis ulcerativa dermatomiositis Síndrome de Ehlers-Danlos (EDS) fibromialgia dolor miofacial osteoartritis (OA) osteonecrosis artritis sonática síndrome de Reiter's (artritis reactiva) sarcoidosis esclerodema Síndrome de Sjogren enfermedad de tejido blando Enfermedad de Still tendinitis poliarteritis Nodossa Granulomatosis de Wegener miositis (polimiositis dermatomiositis) gota arteroscleros is lupus eritematoso lupus sistémico eritematoso (SLE) diabetes tipo I síndrome nefrítico glomerulonefritis falla renal aguda y crónica fascitis eosinofilia síndrome hiper IgE sepsis choque séptico daño por reperfusión isquémica en el corazón rechazo de aloinjerto después de transplantes y enfermedad de injerto versus huésped

Sin embargo los compuestos con los cuales la invención está relacionada son principalmente de valor para el tratamiento de asma rinitis síndrome alérgico de vias aéreas y rinobronquitis alérgica

Como se utiliza aquí el término alquilo (C C_b) en donde a y b son enteros se refiere a un radical alquilo de cadena recta o ramificada que tiene de a a b átomos de carbono Así 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 and n-hexilo

Como se utiliza aquí el término radical alquileno (C_a-C_b) divalente en donde a y b son enteros se refiere a una cadena de hidrocarburos saturada que tiene de a a b átomos de carbono y dos valencias no satisfechas

Como se utiliza aquí el término alquenilo (C_a-C_b) en donde a y b son enteros se refiere a una porción alquenilo de cadena recta o ramificada que tiene de a a b átomos de carbono que tienen al menos un doble enlace en cualquiera estereoquímica E o Z donde sea aplicable El término incluye por ejemplo vinilo alilo 1 y 2 butenilo y 2 metil 2 propenilo

Como se utiliza aquí el termino radical alquenileno (C_a-C_b) divalente significa una cadena de hidrocarburo que tiene de a a a átomos de carbono al menos un doble enlace al menos dos valencias no satisfechas

Como se utiliza aquí el término alquinilo C_a-C_b en donde a y b son enteros se refiere a grupos de hidrocarburo de cadena recta o cadena ramificada que tienen de dos a seis átomos de carbono y que tienen además un triple enlace Ese termino incluiría etinilo 1 y 2 propinilo 1 2 y 3-butinilo 1 2 3- y 4-pentinilo 1 2 3- 4- and 5 hexinilo 3-metil-1 butinilo 1 metil-2 pentinilo

Como se utiliza aquí el término radical alquinileno (C_a-C_b) divalente en donde a y b son enteros se refiere a una cadena de hidrocarburo divalente que tiene de 2 a 6 átomos de carbono al menos un triple enlace y dos valencias no satisfechas

Como se utiliza aquí el término carbocíclico se refiere a un radical mono- bi- o tricíclico que tiene hasta 16 átomos por anillo todos los cuales son carbono e incluye anlo y cicloalquilo

Como se utiliza aquí el término cicloalquilo se refiere a un radical carbocíclico saturado monocíclico que tiene de 3-8 átomos de carbono e incluye por ejemplo ciclopropilo ciclobutilo ciclopentilo ciclohexilo cicloheptilo y ciclooctilo

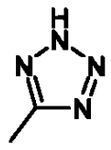
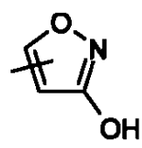
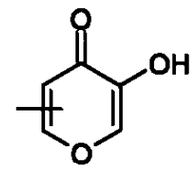
Como se utiliza aquí el término no calificado anlo se refiere a un radical aromático carbocíclico mono- bi- o tri-cíclico e incluye radicales que tienen dos anillos

aromáticos carbocíclicos monocíclicos los cuales están directamente ligados a un enlace covalente Ilustrativos de tales radicales son fenilo bifenilo y naftilo

Como se utiliza aquí el termino no calificado heteroarilo se refiere a un radical aromático mono- bi o tri cíclico que contiene uno o más heteroátomos seleccionados de S N u O e incluye radicales que tienes dos de tales anillos monocíclicos o uno de tales anillos monocíclicos y un anillo arilo monocíclico los cuales están directamente ligados por un enlace covalente Ilustrativos de tales radicales son tienilo benztienilo furilo benzfurilo pirrolilo imidazolilo benzimidazolilo tiazolilo benztiazolilo isotiazolilo benzisotiazolilo pirazolilo oxazolilo benzoxazolilo isoxazolilo benzisoxazolilo isotiazolilo triazolilo benztriazolilo tiadiazolilo oxadiazolilo piridinilo piridazinilo pirimidinilo piridazinilo triazinil indolilo e indazolilo

Como se utiliza aquí el término heterociclilo o heterocíclico incluye heteroarilo como se definió anteriormente y además significa un radical no aromático mono- di- o tri cíclico que contiene uno o más heteroátomos seleccionados de S N y O y a grupos que consisten de un radical no aromático monocíclico que contiene uno o más de tales heteroátomos que está covalentemente ligado a otro de tales radicales o a un radical carboxílico monocíclico Ilustrativos de tales radicales son pirrolilo furanilo tienilo piperidinilo imidazolilo oxazolilo isoxazolilo tiazolilo tiadiazolilo pirazolilo piridinilo pirrolidinilo pirimidinilo morfolinilo piperazinilo indolilo morfolinilo benzfuranilo piranilo isoxazolilo bencimidazolilo metilenodioxifenilo etilenodioxifenilo y los grupos maleimido y succinimido

El término carboxilo bioisostere es un término familiar a los químicos de medicina (ver por ejemplo "The Organic Chemistry of Drug Design and Drug Action de Richard B Silverman pub Academic Press 1992) y se refiere a un grupo el cual tiene características ácido-base similares a aquellas del grupo carboxilo Los carboxil bioisosteres bien conocidos incluyen SO_2NHR o P(=O)(OH)(OR) en donde R es por ejemplo hidrógeno metilo o etilo SO_2OH $P(=O)(OH)(NH_2)$ –C(=O)NHCN y grupos de las fórmulas

A menos que se especifique otra cosa en el contexto en el cual este ocurre el término sustituido como se aplica a cualquier porción aquí significa sustituido con hasta cuatro sustituyentes compatibles cada uno de los cuales independientemente puede ser por ejemplo alquilo (C_1 C_8) alcoxi (C_1-C_8) hidroxi hidroxi –alquilo (C_1 C_8) mercapto mercapto – alquilo (C_1 C_8) alquiltio (C_1 C_8) halo (que incluye fluor bromo y cloro) alquilo (C_1 C_3) completa o parcialmente fluorinado alcoxi (C_1-C_3) o alquiltio (C_1 C_3) tal como trifluorometilo trifluorometoxi y trifluorometiltio nitro nitrilo (CN) oxo fenilo fenoxi heteroarilo o heteroariloxi monocíclico con 5 o 6 átomos con anillo $COOR^A$ $-COR^A$ $OCOR^A$ 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 donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1 C_8) o en el caso donde R^A y R^B estén ligados al mismo atomo N R^A y R^B tomados juntos con aquel nitrógeno pueden formar un anillo amino cíclico Donde el sustituyente es fenilo fenoxi o heteroarilo monocíclico o heteroariloxi con 5 o 6 átomos por anillo el anillo de fenilo o heteroarilo de éstos puede en si mismo ser sustituido por cualquiera de los sustituyentes anteriores excepto feil fenoxi heteroarilo o heteroariloxi Un sustituyente opcional puede ser uno de los grupos sustituyentes anteriores

Como se utiliza aquí el término sal incluye adición de base adición de ácido y sales cuaternarias Los compuestos de la invención que son ácidos pueden formar sales incluyendo sales farmacéuticamente aceptables con bases tales como hidróxidos de metal alcalino por ejemplo hidróxidos de sodio y potasio hidróxidos de metal alcalino terreo 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 etil pipendina dibenzilamina y similares Aquellos compuestos (I) que son básicos pueden formar sales que incluyen sales farmacéuticamente aceptables con ácidos inorgánicos por ejemplo con ácidos hidrohálico tal como ácidos clorhídrico o bromhídrico ácido sulfurico ácido nítrico o ácido fosfórico y similares y con acidos

orgánicos por ejemplo con ácidos acético tartárico succínico fumárico maleico málico salicílico cítrico metanosulfónico p-toluenosulfónico benzoico benzenosunfónico glutámico láctico y mandélico y similares

Los compuestos con los cuales la invención está relacionada que pueden existir en una o más formas hesteroisoméricas en razón de la presencia de átomos asimétricos o restricciones rotacionales pueden existir como un numero de esteroisómeros con hestereoquímica R o S en cada uno de los centros quirales o como atropisomeros con estereoquímica R o S en cada eje quiral La invención incluye todos los tales enantiómeros y diastereoisómeros y mezclas de éstos

El uso de prodrogas tales como ésteres y de compuestos (I) con los cuales la invención está relacionada también es parte de la invención

Para uso de acuerdo con la invención las siguientes características estructurales son habitualmente prefendas en combinación compatible en los compuestos (I)

Q_1 es hidrógeno y Q_2 es fenilo o heteroarilo monocíclico con 5 o 6 átomos por anillo opcionalmente sustituido con cualquiera de alquilo (C_1 C_6) alcoxi (C_1 C_6) hidroxi hidroxi –alquilo (C_1 C_6) alquiltio (C_1 C_3) halo alquilo (C_1-C_3) completa o parcialmente fluorinado alcoxi (C_1 C_3)o alquiltio (C_1 C_3) trifluorometiltio nitro nitrilo (CN) $COOR^A$ $-COR^A$ $OCOR^A$ SO_2R^A $CONR^AR^B$ $SO_2NR^AR^B$ NR^AR^B NR^BCOR^A NR^BCOOR^A $NR^BSO_2OR^A$ o $NR^ACONR^AR^B$ en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1-C_6) o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino ciclico o

Q_1 es hidrógeno y Q_2 es fenilo opcionalmente sustituido por cualquiera de fluor cloro bromo alquilo (C_1 C_3) trifluorometilo alcoxi (C_1 C_3) trifluorometoxi trifluorometiltio dimetilamino ciano (alquilo C_1 C_3) SO_2- NH_2SO_2- (alquilo C_1 C_3)$NHSO_2$- (alquilo C_1 C_3)$_2NSO_2$- $-CONR^AR^B$ y NR^BCOR^A En donde R^A y R^B son independientmente hidrógeno o un grupo alquilo (C_1 C_6) o R^A y R^B están ligados al mismo átomo de N para formar un anillo de amino cíclico

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L3 es CH_2- O- -S -SO_2- –NHC(=O)- -CH=CH NR_{11} o $NR_{11}CH_2$- en donde R_{11} es hidrógeno o alquilo C_1 C_3 o

L3 representa un radical divalente de fórmula $–(Alq^3)_m-(Z)_n-(Alq^2)_p$- en donde m es 0 n es 1 y Z es un radical fenileno radicalmente sustituido por uno o más de flúor cloro bromo alquilo (C_1 C_3) trifluorometilo alcoxi (C_1 C_3) trifluoromethoxi trifluorometiltio dimetilamino ciano (alquilo C_1-C_3)SO_2- NH_2SO_2- (alquilo C_1-C_3l)$NHSO_2$- (alquilo C_1-C_3)$_2NSO_2$- $CONR^AR^B$ y NR^BCOR^A En donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1-C_6) o R^A y R^B están ligados al mismo átomo N para formar un anillo amino cíclico En estos casos Z puede ser por ejemplo un radical 1 2 fenileno opcionalmente sustituido por uno o más de flúor cloro bromo alquilo (C_1 C_3) trifluorometilo alcoxi(C_1-C_3) trifluorometoxi trifluorometiltio dimetilamino ciano (alquilo C_1 C_3)SO_2- NH_2SO_2- (alquilo C_1 C_3)$NHSO_2$- (alquilo C_1 C_3)$_2NSO_2$- -$CONR^AR^B$ y NR^BCOR^A en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1 C_6) o R^A y R^B estan ligados al mismo átomo de N para formar un anillo amino cíclico

En particular Q_1 puede ser hidrógeno X_1 puede ser –S y A puede ser un grupo carboxilo –COOH

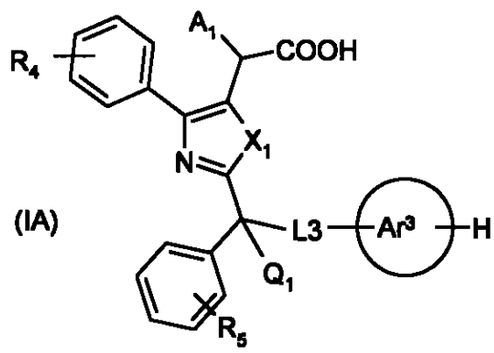
L1 es un enlace $–CR_{11}R_{12}$- $–CH_2CR_{11}R_{12}$- $–OCR_{11}R_{12}$- $–SCR_{11}R_{12}$- $NR_{11}CH_2$- o $–NR_{11}$ en donde R_{11} y R_{12} son independientemente hidrógeno o alquilo C_1 C_3 en enlace marcado con el asterisco es aquel conectado al anillo que contiene X^1 Por ejemplo L1 puede ser $–CH_2$- o $–CH(CH_3)$

Ar^3 es fenilo tienilo naftilo o 2 3- o 4-pindilo cualquiera de los cuales es opcionalmente sustituido por ejemplo por uno o más sustituyentes seleccionados de fluor cloro bromo alquilo (C_1 C_3) trifluorometilo alcoxi (C_1 C_3) trifluorometoxi trifluorometiltio dimetilamino ciano (alquilo C_1 C_3)SO_2- NH_2SO_2- (alquiloC$_1$ C_3)$NHSO_2$- (alquilo C_1 C_3)$_2NSO_2$- $CONR^AR^B$ y NR^BCOR^A en donde R^A y R^B son independientemente hidrogeno a un grupo alquilo (C_1-C_6) o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico

L2 es un enlace y Ar^2 es un anillo fenilo tienilo furanilo pirolilo o pindilo opcionalmente sustituido los sustituyentes opcionales son seleccionados de fluor cloro bromo alquilo (C_1-C_3) trifluorometilo alcoxi(C_1-C_3) trifluorometoxi trifluorometiltio dimetilamino ciano (alquiloC_1 C_3)SO_2- NH_2SO_2- (alquiloC_1 C_3)$NHSO_2$- (alquiloC_1-C_3)$_2NSO_2$- -$CONR^AR^B$ y NR^BCOR^A en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1-C_8) o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico

s es 0

Una subclase preferida de los compuestos con los cuales la invención está relacionada consiste de los compuestos de fórmula (IA) y sales hidratos y solvatos de éstos



En donde A_1 es hidrógeno o metilo X_1 Q_1 Ar^3 y L3 son como se definió y se discutió anteriormente y R_4 y R_5 independientemente representan hidrógeno o uno o más sustituyentes opcionales En esta subclase se prefiere habitualmente que

A_1 es hidrógeno

Q_1 es hidrógeno

X_1 es –S-

Ar^3 es opcionalmente fenilo sustituido

L3 es un enlace -O- –S- o –NR en donde R es hidrógeno o alquilo C_1 C_3

Particularmente preferido en esta subclase son los compuestos (IA) en donde A_1 es hidrógeno Q_1 es hidrógeno X_1 es –S Ar^3 es fenilo opcionalmente sustituido y L3 es un enlace

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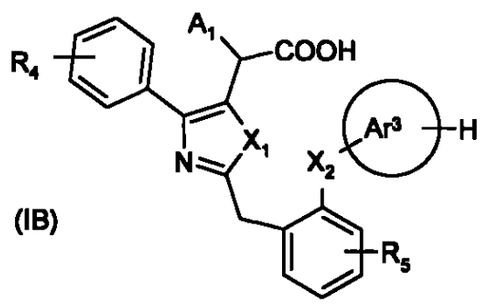
En esta subclase los sustituyentes opcionales R_4 y R_5 son sustituyentes opcionales en Ar^3 son preferiblemente independientemente seleccionados de fluor cloro bromo alquilo C_1 C_3) trifluorometilo alcoxi(C_1-C_3) trifluorometoxi trifluorometiltio dimetilamino ciano (alquilo C_1-C_3)SO_2- NH_2SO_2- (alquiloC_1 C_3)$NHSO_2$- (alquiloC_1 C_3)$_2NSO_2$- $CONR^AR^B$ y NR^BCOR^A en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1 C_6) o R^A y R^B están ligados al mismo átomo de N para formar un anillo aminocíclico

Una subclase preferida de compuestos con los cuales la invención está relacionado consiste de los compuestos de fórmula (IA) y sales hidratos y solvatos de estos



(IB)

En donde A_1 es hidrógeno o metilo X_2 es un enlace $-CH_2-$ O- –S o –NR en donde R es hidrógeno o alquilo C_1 C_3 y X_1 y Ar^3 son como se definió en la reivindicación 1 y R_4 y R_5 independientemente representan hidrógeno o uno o más sustituyentes opcionales En esta subclase se prefiere habitualmente que

A_1 es hidrógeno

X_1 es –S

Ar^3 es fenilo opcionalmente sustituido

X_2 es $-CH_2-$ o un enlace

En esta subclase los sustituyentes opcionales R_4 y R_5 y los sustituyentes opcionales en Ar^3 son independientemente seleccionados de fluor cloro bromo alquilo (C_1-C_3) trifluorometilo alcoxi(C_1 C_3) trifluorometoxi trifluorometiltio dimetilamino ciano (alquilo C_1-C_3)SO_2- NH_2SO_2- (alquiloC_1-C_3)$NHSO_2$- (alquilo C_1-C_3)$_2$ NSO_2- $CONR^AR^B$ y NR^BCOR^A en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1-C_6) o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico

Ejemplos específicos de compuestos con los cuales la invención está relacionada incluyen

Ácido [2 benzidril-4-(4-clorofenil) tiazol-5-il]-acético
Ácido [2 benzidril-4-(4-fluoro-fenil)-tiazol-5-il]-acético
Ácido [2-[1 (4-cloro-fenil)-2 fenil-etil]-4-(4-fluoro-fenil)-tiazol 5-il]-acético
Ácido {4-(4-cloro-fenil)-2-[(4-cloro-fenil)-fenil-metil]-tiazol-5-il}-acético
Ácido [2 [(4-cloro-fenil) fenil metil]-4-(4-fluoro-fenil)-tiazol-5-il]-acético
Ácido [2 [bis-(4-fluoro-fenil) metil]-4 (4-fluoro-fenil)-tiazol-5-il]-acético
Ácido {4 (4-fluoro-fenil)-2 [(4-metoxi-fenil) fenil-metil] tiazol-5-il}-acético
Ácido {4-(4-cloro-fenil)-2-[(4-metoxi fenil)-fenil-metil]-tiazol-5-il}-acético
Acido [2 [(3 4-difluoro-fenil)-fenil-metil]-4-(4-fluoro-fenil) tiazol 5 il]-acético
Acido [2-[bis-(4-metoxi fenil)-metil]-4-(4-fluoro-fenil)-tiazol 5 il]-acético
Acido [2 benzidril-4-(3-fluoro-fenil) tiazol-5-il]-acético
Acido [2 [bis-(4-fluoro-fenil) metil]-4-(3 4-difluoro-fenil)-tiazol-5-il]-acético
Ácido [2 benzidril-4 (3 4-difluoro-fenil) tiazol 5-il]-acético
Ácido [2 [bis-(4-fluoro-fenil)-metil]-4 (3-fluoro-fenil)-tiazol-5-il]-acético

y sales y solvatos de éstos

La invención también incluye composiciones farmacéuticas que comprenden un compuesto de fórmula (II) o (IIA) junto con un vehículo farmaceuticamente aceptable

Composiciones

Como se mencionó anteriormente los compuestos con los cuales la invencion esta relacionada son capaces de modular actividad CRTH2 y son útiles para el tratamiento de enfermedades que se benefician de tal modulación Ejemplos de tales enfermedades son referidas anteriormente e incluyen asma rinitis síndrome alérgico de vías aéreas y rinobronquitis alérgica

Se entenderá que el nivel de dosis especifica para cualquier paciente particular dependerá de una variedad de factores que incluyen la actividad de el compuesto específico empleado la edad el peso del cuerpo la salud general el sexo la dieta el tiempo de administración la ruta de administración la tasa de excreción la

combinación de droga y la severidad del tratamiento que experimenta la enfermedad particular Los niveles de dosis óptima y la frecuencia de dosificación se determinarán mediante ensayo clínico como se requiere en la técnica farmacéutica

Los compuestos con los cuales la invención está relacionada se pueden preparar para administración mediante cualquier ruta consistente con sus propiedades farmacocinéticas Las composiciones oralmente administrables pueden estar en la forma de tabletas cápsulas polvos gránulos pastillas preparaciones líquidas o de gel tales como soluciones o suspensiones orales típicas o parenterales estériles Las tabletas y las cápsulas para administración oral pueden ser en forma de presentacion de dosis unitaria y pueden contener excipientes convencionales tales como agentes ligantes por ejemplo melaza acacia gelatina sorbitol tragacanto o polivinil pirrolidona llenadores por ejemplo lactosa azucar almidón de maiz fosfato de calcio sorbitol o lisina lubricante para tableteo por ejemplo estearato de magnesio talco polietilenglicol o sílice desintegrantes por ejemplo almidón de papa o agentes humectantes aceptables tales como lauril sulfato de sodio Las tabletas pueden ser recubiertas de acuerdo con métodos bien conocidos en la práctica farmacéutica normal Las preparaciones líquidas orales pueden estar en la forma de por ejemplo suspensiones acuosas o aceitosas soluciones emulsiones melazas o elixires o pueden estar presentes como un producto seco para la reconstitución con agua u otro vehículo adecuado antes de uso Tales preparaciones líquidas pueden contener adictivos convencionales tales como agentes de suspensión por ejemplo sorbitol melaza metil celulosa melaza de glucosa grasas comestibles hidrogenadas en gelatina agentes emulsificantes por ejemplo lecitina monooleato sorbitán o acacia vehículos no acuosos (que pueden incluir aceites comestibles) por ejemplo aceite de almendra aceite de coco fraccionado ésteres aceitosos tales como glicina propilenglicol o etil alcohol preservativos por ejemplo metil o propil p-hidroxibenzoato o ácido sórbico y si se desea agentes saborizantes o colorantes convencionales

Para la aplicación tópica a la piel la droga puede ser hecha en una crema locion o ungüento Las formulaciones en crema o ungüento que se pueden utilizar para la droga son formulaciones convencionales bien conocidas en la técnica por ejemplo como se describió en los textos estándar de farmacia tales como la Pharmacopoeia Británica

Para la aplicación tópica al ojo la droga puede ser hecha en una solución o suspensión en un vehículo acuoso o no acuoso estéril adecuado Los aditivos por ejemplo amortiguadores tales como metabisulfito de sodio o edeato de de disodio los preservativos que incluyen agentes bactericidas y funguicidas tales como acetato fenil mercurico o nitrato cloruro de benzalconio o clorhezidina y agentes espesantes tales como hipromelosa también pueden estar incluidos

La droga también se puede formular para inhalación por ejemplo como pulverizado nasal o como polvo seco o inhaladores de aerosol

El ingrediente activo también se puede administrar parenteralmente en un medio estéril Dependiendo del vehículo y la concentración utilizados como la droga puede ser suspendida o disuelta en el vehículo Ventajosamente los adyuvantes tales como los anestésicos locales preservativos y agentes amortiguantes se pueden disolver en el vehículo

Los compuestos con los cuales la invención está relacionada se pueden administrar solos o como parte de una terapia de combinación con otras drogas utilizadas para el tratamiento de enfermedades con componentes inflamatorios mayores En el caso de asma rinitis síndrome alérgico de vías aéreas tales drogas incluyen corticosteroides agonistas beta inhalados de larga actuación beta agonistas cromolina nedocromil teofillina antagonistas de receptor leucotrieno antihistaminas y anticolinérgicos (por ejemplo ipratropio) y son a menudo administrados como pulverizados nasales polvos secos o inhaladores de aerosol

En el caso de la artritis y las enfermedades inflamatorias relacionadas otras drogas conocidas incluyen un glucocorticoides los NSAID (Drogas Antiinflamatorias No Esteroides – inhibidores de síntesis de prostataglandina convencionales inhibidores COX 2 salicilatos) y los DMARD (drogas antirreumáticas que modifican la enfermedad tales como metorexato sulfasalazina oro ciclosporina)

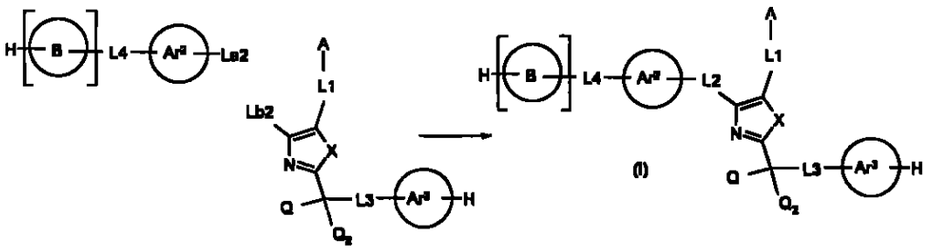
Rutas Sintéticas

Existen multiples estrategias sintéticas para las síntesis de los compuestos (I) con los cuales la presente invención está relacionada pero todos confían en la química conocida conocida por los químicos orgánicos sintéticos Así los compuestos de

acuerdo con la fórmula (I) se pueden sintetizar de acuerdo con los procedimientos descritos en la literatura estándar y son bien conocidos por el experto en la técnica Las fuentes de literatura típica son *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) artículos de revisión tales como los encontrados en *Synthesis*" *Acc Chem Res* *Chem Rev*" o las fuentes de literatura primaria identificadas por las busquedas de la literatura estándar en línea o de fuentes secundarias tales como *Chemical Abstracts* o *Beilstein*"

En la siguiente discusión de rutas sintéticas el anillo Ar^1 es el anillo mostrado en la fórmula (I) que contiene X_1

El ligador L2 se puede formar al unir dos fragmentos apropiadamente funcionalizados y si es necesario adecuadamente protegidos que contienen La2 y Lb2 como porciones reactivas como se subrayó adelante La2 Y Lb2 se definieron como cualesquiera porciones que puedan reaccionar mediante por ejemplo una sustitución nucleofílica adición a enlaces múltiples o reacción de ciclisación para formar un ligador L2 dado como en



Por ejemplo el ligador L2-es $-Alq^1\ Z\ (Alq^2)_p-$ se puede formar al reaccionar $HBL4Ar^2-Alq^1$ grupo saliente con un derivado nucleofílico $H\ Z-(Alq^2)_p-Ar^1(L1A)L3Ar^3H$ en donde Z puede ser O S o NR y Alq^1 puede ser un grupo alquilo Las reacciones también se pueden hacer al revisar la funcionalización de La2 y Lb2 para hacer la conexión entre Z y Alq^2 Los ligadores que tienen Z son SO o SO_2 se pueden obtener mediante oxidaciones de los derivados $1-(Alq^1)_m-S-(Alq^2)_p-$ correspondientes durante las condiciones apropiadas

Los ejemplos representativos adicionales –L2 siendo $-Alq^1\ Z\ (Alq^2)_p-$ en dnde Z es NH(CO) o $NHSO_2$ se pueden formar al reaccionar $HBL4Ar^2-(Alq^1)\ NH_2$ con un

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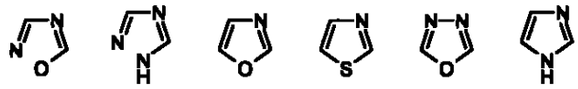
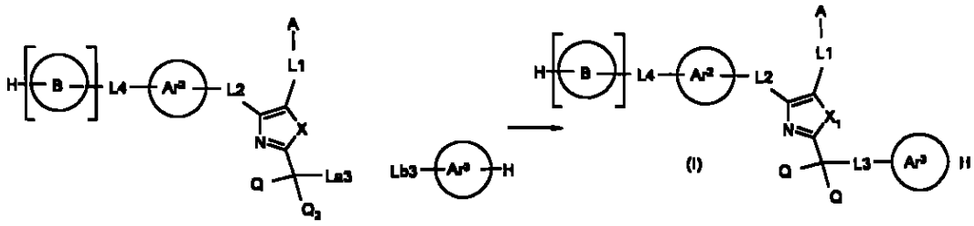
derivado acilante grupo saliente $CO-(Alq^2)_p-Ar^1(L1A)L3Ar^3H$ o grupo saliente $-SO_2-(Alq^2)_p-Ar^1(L1A)L3Ar^3H$ respectivamente Alternativamente la conversión se puede hacer directamente con los ácidos $HO-CO-(Alq^2)_p-Ar^1(L1A)L3Ar^3H$ y $HO-SO_2-(Alq^2)_p-Ar^1(L1A)L3Ar^3H$ respectivamente utilizando reactivos y acoplamiento adecuado tales como diciohexilcarbodiimida (DCC) y promotores tales como 1 hidroxibenzotriazol Análogamente –L2 siendo $-Alq^1\ Z\ (Alq^2)_p-$ en donde Z es NH(CO)NH se puede formar al reaccionar $HBL4Ar^2-(Alq^1)\ NH_2$ con un derivado de isocianato $OCN\ (Alq^2)_p-Ar^1(L1A)L3Ar^3H$ utilizando catálisis de ácido o base adecuada Las reacciones se pueden hacer al reverar la funcionalización de La2 and Lb2 para suministrar los retro-enlaces en el caso de NH(CO) o $NHSO_2$ Análogamente las conexiones se pueden hacer entre Z y Alq^2

De manera similar L2 es $-(Alq^1)_m-Z\ (Alq^2)_p-$ en donde Z es un sistema heterocíclico de 5-miembros ejemplificado por



Pueden ser hechas de acuerdo con procedimientos de ciclización estándar utilizando solventes apropiados catalizadores y temperaturas Por ejemplo la formación de 1 2 4-triazol se puede hacer con La2 siendo acilhidrazida y Lb2 siendo amida o tioamida o la orientación inversa de La2 y Lb2 1 2 4-Oxadiazol se puede formar de La2 siendo amidoxima y Lb2 siendo éster carboxílico o la orientación inversa de La2 y Lb2 1 3 4-Oxadiazol se puede formar de La2 siendo acilhidrazida y Lb2 siendo éster carboxílico o la orientación inversa de La2 y Lb2 El tiazol se puede hacer de La2 siendo tioamida y Lb2 siendo una □ halocetona o la orientación inversa de La2 y Lb2

De manera análoga los compuestos de fórmula (I) se pueden hacer al formar los ligadores L3 o L4 de acuerdo con procedimientos subrayados para L2 como se describe adelante Así La y Lb se definen como cualquiera porciones que pueden reaccionar mediante por ejemplo una sustitución nucleofílica adicion a enlaces múltiples o reacción de ciclización para formar un ligador dado L como se ejemplificó adelante



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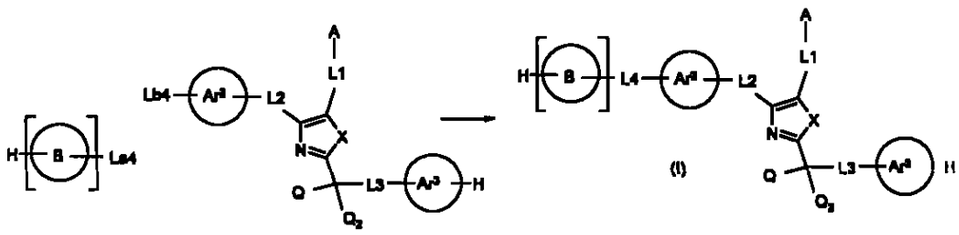
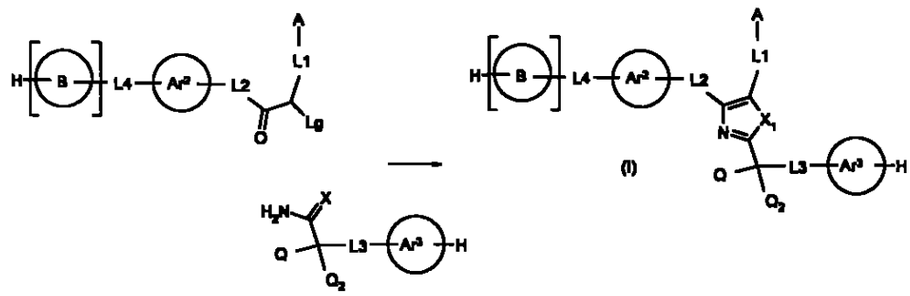
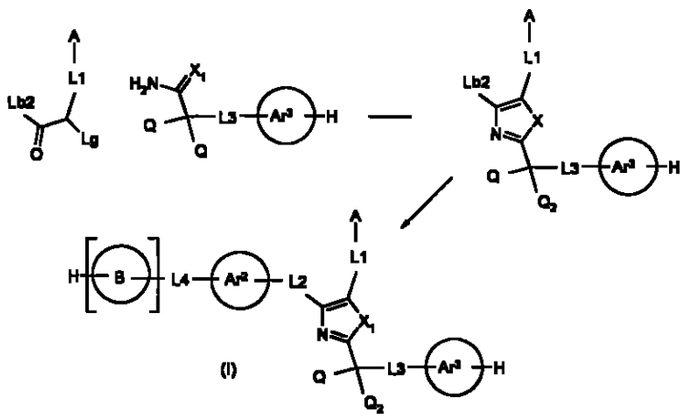


La porción Ar^1 puede también ser el andamio central que se utiliza para conectar las partes L1 L2 y L3 de una manera escalonada Esto se puede hacer por vía de sustituciones aromáticas del núcleo Ar^1 patra unir L1 L2 y/o L3 que pueden ser adicionalmente funcionalizadas para dar los compuestos de fórmula I finales

Adicionalmente la porción X_1 azol de 5 miembros se puede también ensamblar por vía de las reacciones de ciclización de anillo convencional con los reactivos que contienen las unidades L1 L2 y L3 que contienen los apéndices completos como se ejemplificó adelante donde Lg es un grupo saliente tal como halógeno



O en formas que pueden ser adicionalmente funcionalizadas en las estructuras de fórmula final (I) como se describió previamente Una de tales ilustraciones es dada adelante



(I)

Por ejemplo los 1 2 4-triazoles se pueden hacer de acilhidrazidas y amidas o tioamidas 1 2 4-oxadiazoles de amidoximas y ésteres carboxílicos 1 3 4-oxadiazoles de acilhidrazidas y ésteres carboxílicos tiazoles de tioamidas y □ halocetonas pirazinas pirimidinas y piridinas por vía de varias reacciones de condensación y cicloadición

Los bloques de construcción utilizados en las reacciones están comercialmente disponibles o se hacen de acuerdo con procedimientos estándar bien conocidos por aquellos expertos en la técnica como se describe en *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 u otra fuente de literatura adecuada

Estos ejemplos describen estrategias específicas para la síntesis de compuestos (I) X1 es S

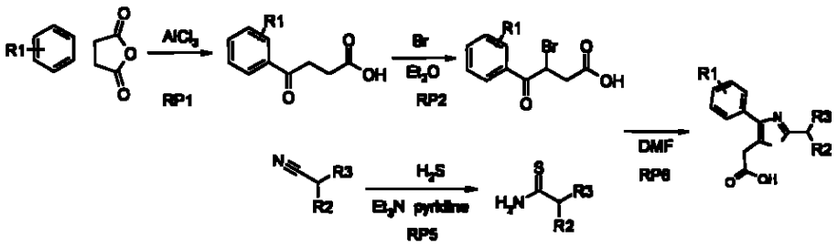
Los siguientes ejemplos ilustran la preparación de compuestos a los que esta invención concierne Algunos compuestos se sintetizan y algunos se adquieren de fuentes comerciales En los Ejemplos

Comentarios generales

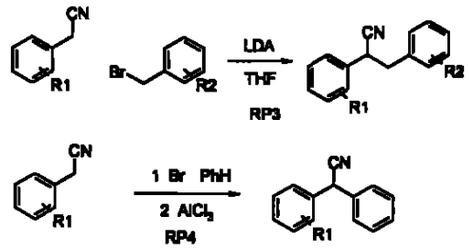
Se obtiene el espectro RMN en un instrumento Bruker Avance AMX 300 MHz Para algunos compuestos solo se reportan señales ^{1}H RMN características seleccionadas Se realiza LC/MS en un instrumento Agilent 1100-series Los métodos LC/MS son como sigue An10p8 Columna XTerra MS C18 Flujo 1 0 mL/min Gradiente 0-5 min 15 100% MeCN en agua 5-7½ min 100% MeCN Modificador 5 mM de formato de

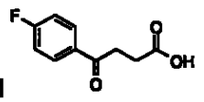
amonio modo MS ionisación API ES (pos) An10n8 Columna XTerra MS C18 Flujo 1 0 mL/min Gradiente 0-5 min 15 100% MeCN en agua 5-7½ min 100% MeCN Modificador 5 mM de formato de amonio modo MS ionisación API ES (neg)

Ruta sintética general I



Rutas sintéticas para intermedios de nitrilo

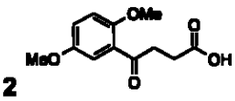




Intermedio-1

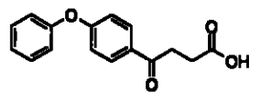
Acido 4-(4-Fluoro-fenil)-4-oxo-butírico – Procedimiento Representativo 1a (RP1a) Se disuelve anhídndo succínico (1 0 g 10 mmol) en 4-fluorobenceno (3 75 ml 40 mmol) y se enfría a -9° C bajo nitrógeno Se agrega $AlCl_3$ (2 67 g 20 mmol) y la temperatura se mantiene entre 9 y 0° C durante 4½ horas Se le permite a la reacción calentar a temperatura ambiente y se agita durante la noche La mezcla de reacción se vierte en HCl acuoso 4 M (10 ml) a 0° C y el precipitado se filtra y se lava con agua El sólido se recristaliza de tolueno para dar 1 40 g (71 %) de un sólido incoloro LC/MS (an10n8) Ta 0 26 min *m/z* 195 [M – H] 413 [2M 2H+Na] ^{1}H RMN ($CDCl_3$) δ 2 84 (t *J* = 6 5 Hz 2H) 3 31 (t *J* = 6 5 Hz 2H) 7 16 (m 3H) 8 03 (m 2H)

En una vía análoga se fabrican los siguientes compuestos



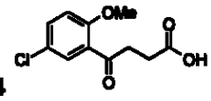
Intermedio 2

Ácido 4-(2 5-Dimetoxi-fenil)-4-oxo-butírico LC/MS (an10n8) Ta 0 50 min *m/z* 237 [M-H] 497 [2M-2H+Na] ^{1}H RMN (DMSO-d_6) δ 2 53 (t *J* = 6 0 Hz 2H) 3 16 (t *J* = 6 3 Hz 2H) 3 73 (s 3H) 3 85 (s 3H) 7 12 7 14 (m 3H) ^{13}C RMN/APT (DMSO-d_6) δ 29 1 (CH2) 39 2 (CH2) 56 4 (CH3) 57 2 (CH3) 114 5 (CH) 115 0 (CH) 120 4 (CH) 128 5 (C) 153 8 (C) 174 7 (CO) 200 2 (CO)



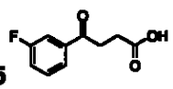
Intermedio-3

Ácido 4-Oxo-4-(4 fenoxi fenil) butírico ^{1}H RMN (DMSO-d6) δ 2 57 (t *J* = 6 22 2H) 3 21 (t *J* = 6 22 2H) 7 05 (m 2H) 7 13 (m 2H) 7 25 (m 1H) 7 47 (m 2H) 8 01 (m 2H) 12 13 (br s 1H (COOH))



Intermedio-4

Acido 4-(5-cloro-2-metoxi fenil)-4-oxo butírico ^{1}H RMN (DMSO-d_6) δ 2 53 (t *J* = 6 6 Hz 2H) 3 15 (t *J* = 6 0 Hz 2H) 3 90 (s 3H) 7 23 (d *J* = 8 9 Hz 1H) 7 53 (d *J* = 2 6 Hz 1H) 7 60 (dd *J* = 2 9 8 9 Hz 1H) y 12 11 (br s 1H)



Intermedio-5

Acido 4-(3 Fluoro fenil)-4-oxo-butirico – Procedimiento Representativo 1b (RP1b) En un frasco secado con llama bajo nitrógeno se disuelve anhídrido succínico (471 mg 4 7 mmol) en THF seco (5 mL) La mezcla se enfría a 78° C Se agrega bromuro de 3-Fluoro-fenil-magnesio en THF (1N 5 mL 5 mmol) lentamente La mezcla se agita a 78° C durante 3 h entonces se le permite elevarse a temperatura ambiente La mezcla se transfiere en HCl 1N (ac) entonces se extrae con CH_2Cl_2 La capa orgánica se seca y se evapora El residuo se purifica por cromatografía flash sobre SiO_2 para dar 350 mg (38%) del compuesto del título ^{1}H RMN ($CDCl_3$) δ 2 84 (t *J* = 6 5 Hz 2H) 3 31 (t *J* = 6 5 Hz 2H) 7 30 (m 1H) 7 47 (td *J* = 8 1 5 7 1H) 7 68 (m 1H) 7 79 (m 1H)

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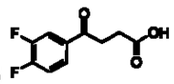
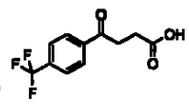
Los siguientes compuestos se preparan mediante un procedimiento análogo



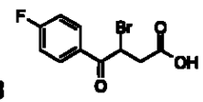
Intermedio-6

Ácido 4-(3 4-Difluoro fenil)-4-oxo-butírico ^{1}H RMN ($CDCl_3$) δ 2 57 (t J = 6 2 Hz 2H) 3 25 (t J = 6 2 Hz 2H) 7 60 (m 1H) 7 87 (m 1H) 8 02 (m 1H) 12 17 (br s 1H)



Intermedio-7

Ácido 4-Oxo-4-(4-trifluorometil fenil) butírico 4 Yodobenzotrifluoruro (500 µL 3 4 mmol) se disuelve en dietiléter seco (5 mL) En un frasco secado con llama bajo nitrógeno Se agrega magnesio (83 mg 3 4 mmol) y la mezcla se agita a temperatura ambiente durante 45 min Anhídrido succínico se disuelve en THF (5 mL) En un frasco secado con llama bajo nitrógeno entonces se enfría a 78 C Se agrega lentamente el reactivo de Grignard hecho fresco La mezcla se le permite calentar a temperatura ambiente durante 3 h La mezcla se transfiere en NH_4Cl (ac) entonces se extrae con CH_2Cl_2 La capa orgánica se seca ($MgSO_4$) entonces se evapora El producto se purifica por cromatografía flash sobre SiO_2 para dar 250 mg (30%) ^{1}H RMN ($CDCl_3$) δ 2 86 (t J = 6 4 Hz 2H) 3 35 (t J = 6 4 Hz 2H) 7 76 (d J = 8 3 Hz 2H) 8 10 (d J = 8 3 Hz 2H)



Intermedio-8

Ácido 3 Bromo-4-(4-Fluoro-fenil)-4-oxo-butírico – Procedimiento Representativo 2 (PR2) ácido 4-(4-Fluoro-fenil)-4-oxo-butírico (1 20 g 6 12 mmol) se suspende en éter (10 mL) a temperatura ambiente Se agrega bromo (0 34 ml 6 73 mmol) en forma de gota Después de 4 horas la reacción se concentra y el residuo se recristaliza de éter/heptano para dar 1 26 g (75 %) cristales naranja pálido ^{1}H RMN ($CDCl_3$) δ 3 16 (dd J = 2 2 6 9 Hz 1H) 3 56 (dd J = 3 5 6 9 Hz 1H) 5 41 (dd J = 2 2 3 5 Hz 1H) 7 19 (m 2H) 8 08 (m 2H) ^{13}C RMN/APT ($CDCl_3$) δ 190 9 175 6 168 3 164 9 132 3 132 1 116 6 116 3 38 8 38 3

En una vía análoga los siguientes compuestos se hacen

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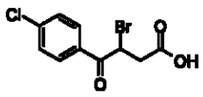
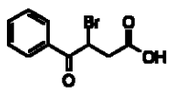


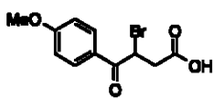
Intermedio-9

Ácido 3 Bromo-4-(4-cloro fenil)-4-oxo-butírico ^{1}H RMN ($CDCl_3$ 300 MHz) δ 3 18 (dd *J* = 5 7 17 5 Hz 1H) 3 52 (dd *J* = 8 5 17 5 Hz 1H) 5 43 (dd *J* = 5 8 8 5 Hz 1H) 6 99 (d *J* = 8 9 Hz 2H) 8 10 (d *J* = 8 9 Hz 2H)



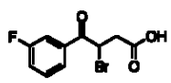
Intermedio-10

Ácido 3-Bromo-4-oxo-4 fenil butírico LC/MS (an10p8) Ta 2 69 min *m/z* 257/259 [M+H] 279/281 [M+Na] ^{1}H RMN ($CDCl_3$) δ 3 17 (dd *J* = 5 7 17 6 Hz 1H) 3 56 (dd *J* = 8 7 17 6 Hz 1H) 5 46 (dd *J* = 5 7 8 7 Hz 1H) 7 52 (m 2H) 7 64 (m 1 H) 8 05 (m 2 H)



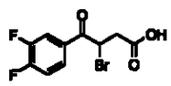
Intermedio-11

Acido 3 Bromo-4-(4-metoxi fenil)-4-oxo butirico ^{1}H RMN ($CDCl_3$) δ 3 17 (dd *J* = 5 7 17 7 Hz 1H) 3 55 (dd *J* = 9 0 17 7 Hz 1H) 3 91 (s 3H) 5 40 (dd *J* = 5 5 8 9 Hz 1H) 7 51 (d *J* = 8 7 Hz 2H) 7 98 (d *J* = 8 7 Hz 2H)



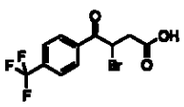
Intermedio 12

Acido 3 Bromo-4-(3-fluoro-fenil)-4-oxo butirico ^{1}H RMN ($CDCl_3$) δ 3 18 (m 1H) 3 54 (m 1H) 5 39 (m 1H) 7 34 (m 1H) 7 50 (m 1H) 7 83 (m 2H) y 10 11 (br s 1H)



Intermedio-13

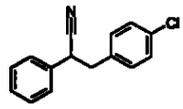
Acido 3-Bromo-4-(3 4-difluoro-fenil)-4-oxo-butirico ^{1}H RMN ($CDCl_3$) δ 3 16 (dd *J* = 17 7 5 3 Hz 1H) 3 55 (dd *J* = 17 7 9 0 Hz 1H) 5 32 (dd J = 9 0 5 5 Hz 1H) 7 31 (m 1H) 7 85 (m 2H)



Intermedio 14

93

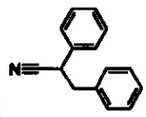
Acido 3-Bromo-4-oxo-4-(4-trifluorometil fenil)-butírico ^{1}H RMN ($CDCl_3$) δ 3 19 (dd J = 17 7 5 5 Hz 1H) 3 59 (dd J = 17 5 9 0 Hz 1H) 5 44 (dd J = 9 0 5 5 Hz 1H) 7 79 (d J = 2 8 Hz) y 8 16 (d J = 3 0 Hz)



Intermedio-15

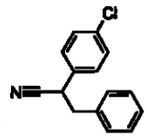
3 (4-Cloro-fenil) 2 fenil-propionitrilo – Procedimiento Representativo 3 (RP3) La reacción se preforma bajo N_2 en un frasco de vidrio secado con llama Se agrega bencilcianuro (1 2 mL 10 mmol) lentamente (durante un periodo de 40 min) a una solución de LDA (10 mmol) en THF (10 mL) a 78 C La mezcla se agita durante 1 h a 78 C y entonces se agrega lentamente (durante un periodo de 16 min) a una solución de bromuro de 4-clorobencilo en THF (10 mL) a 78 C La mezcla se agita durante 1 h a 78 C y se deja durante la noche que alcance temperatura ambiente Se agrega NH_4Cl saturado ac ala mezcla de reacción y la mezcla acuosa se extrae con EtOAc La fase orgánica se lava con solución salina se seca ($MgSO_4$) y se concentra y el residuo se recristaliza de heptano para dar 1 26 g (53%) de un polvo cafe claro ^{1}H RMN ($CDCl_3$) δ 3 16 (m 2H) y 4 01 (t J = 7 2 Hz 1H) 7 05 (d J = 8 3 Hz 2H) 7 32 (m 7H)

En una vía análoga los siguientes compuestos se hacen



Intermedio-16

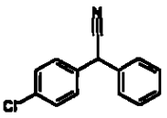
2 3 Difenil-propionitrilo ^{1}H RMN ($CDCl_3$) δ 3 19 (m 2H) y 4 02 (t J = 7 9 Hz 1H)



Intermedio-17

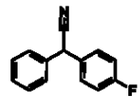
2-(4-Cloro-fenil)-3 fenil propionitrilo ^{1}H RMN ($CDCl_3$) δ 3 16 (m 2H) y 4 14 (t J = 7 2 Hz 1H)

94

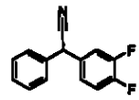
Intermedio-18 

(4-Cloro-fenil) fenil-acetonitrilo – Procedimiento Representativo 4 (RP4) La reacción se preforma bajo N_2 y un frasco de vidrio secado con llama 4-Clorobencil cianuro (1 mL 7 8 mmol) se disuelve en benceno (10 mL) y se calienta a reflujo Se agrega bromo (442 µL 8 6 mmol) durante 30 min La mezcla se agita 20 min a reflujo entonces se enfría a aproximadamente 40 C y se agrega durante 30 min una mezcla de reflujo de cloruro de aluminio (1 g 7 8 mmol) en benceno (10 mL) La mezcla se agita 1 h a reflujo entonces se enfría a t a La mezcla se transfiere en hielo y HCl conc (50 mL) entonces se extrae con dietil éter La capa orgánica se seca ($MgSO_4$) y se concentra en vacío para dar aceite café El producto se purifica por cromatografía flash sobre SiO_2 para dar 523 mg (28%) aceite amarillo ^{1}H RMN ($CDCl_3$) δ 5 14 (s 1H) y 7 36 (m 9H) APT ($CDCl_3$) δ 42 42 (CH)

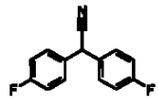
En una vía análoga los siguientes compuestos se hacen

Intermedio 19 

(4 Fluoro-fenil) fenil-acetonitrilo ^{1}H RMN ($CDCl_3$) δ 5 15 (s 1H) 7 08 (m 2H) 7 36 (m 7H)

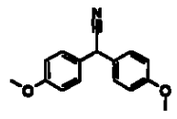
Intermedio-20 

(3 4-Difluoro fenil) fenil-acetonitrilo ^{1}H RMN ($CDCl_3$ 300 MHz) δ 5 12 (s 1H) 7 15 (m 3H) 7 41 (m 5H)

Intermedio-21 

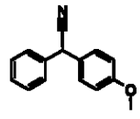
Bis-(4-fluoro-fenil)-acetonitrilo 4 4 Difluorobenzhidrol (1 g 4 54 mmol) se disuelve en TFA (10 mL) Se agrega cianuro de potasio (620 mg 9 53 mmol) y la mezcla se enfría a 0 C Se agrega ácido sulfúrico (conc 3 mL) lentamente La mezcla se agita a temperatura ambiente durante 5h entonces se apaga con H_2O y acetato de etilo La

fase orgánica se lava con agua y solución salina se seca ($MgSO_4$) y se concentra El residuo se purifica por cromatografía flash sobre SiO_2 para dar 450 mg (43%) del compuesto del título ^1H RMN ($CDCl_3$) δ 5 14 (s 1H) 7 09 (m 4H) y 7 32 (m 4H) ^{13}C RMN (APT $CDCl_3$) δ 41 53 (CH)



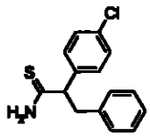
Intermedio-22

Bis-(4-metoxi-fenil)-acetonitrilo 4 4 Dimetoxibenzhidrol (5 g 20 mmol) se disuelve en y CH_2Cl_2 seco (50 mL) entonces se enfría a 0° C Se agrega tionilcloruro (1 5 mLl 20 mmol) lentamente La mezcla se agita a temperatura ambiente durante 4h La mezcla se concentra bajo vacío El producto se disuelve en CH_2Cl_2 seco (10 mL) y se agrega a una mezcla de cianuro de potasio (2 6 g 40 mmol) y 18-corona-6 (500 mg) se disuelve en CH_2Cl_2 seco (20 mL) La mezcla se agita durante la noche a temperatura ambiente La mezcla se transfiere en agua entonces se extrae con CH_2Cl_2 La capa orgánica se lava con agua y solución salina se seca ($MgSO_4$) y se concentra El residuo se recristaliza de acetato de etilo para dar 2 54 g (50%) del compuesto del título ^1H RMN ($CDCl_3$) δ 3 82 (s 6H) 5 07 (s 1H) 6 90 (m 4H) 7 25 (m 4H)



Intermedio 23

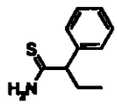
(4-Metoxi fenil)-fenil-acetonitrilo (4-Metoxifenil)acetonitrilo (5 mL 37 mmol) se disuelve en benceno seco (10 mL) en un frasco secado con llama bajo nitrógeno La mezcla se calienta a reflujo y se agrega bromo (1 9 mL 37 mmol) en porciones pequeñas durante 2 h La mezcla se agita a reflujo durante 30 min entonces se agrega a una mezcla de reflujo de $AlCl_3$ (4 9 g 37 mmol) en benceno (30 mL) over 80 min La mezcla se agita a reflujo durante 1 h entonces se enfría a temperatura ambiente La mezcla se transfiere en HCl 1N y hielo entonces se extrae con dietiléter La capa orgánica se seca ($MgSO_4$) y se concentra El producto se purifica por cromatografía flash sobre SiO_2 para dar 1 3 g (16%) del compuesto del título ^1H RMN ($CDCl_3$) δ 3 82 (s 3H) 5 12 (s 1H) 6 90 (m 2H) 7 27 (m 2H) 7 37 (m 5H)



Intermedio-24

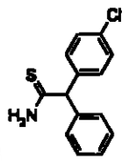
2 (4-Cloro-fenil)-3-fenil tiopropionamida – Procedimiento Representativo 5 (RP5) 2 (4-Cloro-fenil)-3-fenil propionitrilo (200 mg 0 8 mmol) se disuelve en pirdina (5 mL) y trietilamina (1 mL) La mezcla se satura con sulfuro de hidrógeno y se agita bajo una atmósfera de sulfuro de hidrógeno temperatura ambiente durante 3 días La mezcla se extrae con EtOAc El extracto se lava con solución salina se seca ($MgSO_4$) y se concentra para dar 250 mg del producto crudo que se usa directamente en la siguiente etapa ^{1}H RMN (DMSO d6) δ 3 17 (dd *J* = 8 1 13 8 Hz 1H) 3 75 (dd *J* = 7 0 13 8 Hz 1H) 4 03 (t *J* = 7 5 Hz 1H) y 7 20 (m 9H)

En una vía análoga los siguientes compuestos se hacen



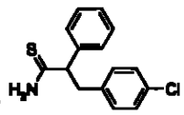
Intermedio-25

2 Fenil tiobutiramida LC/MS (an10p8) Ta 2 9 min *m/z* 180 [M + 1] ^{1}H RMN ($CDCl_3$) δ 0 93 (t 3H) 2 01 (m 1H) 2 41 (m 1H) 3 75 (dd 1H) 6 75 (br s 1H) 7 36 (m 5H) 7 58 (br s 1H)



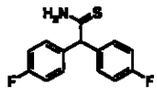
Intermedio-26

2-(4-Cloro fenil) 2 fenil tioacetamida ^{1}H RMN ($CDCl_3$) δ 5 59 (s 1H)



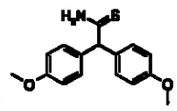
Intermedio 27

3-(4-Cloro-fenil) 2-fenil tiopropionamida ^{1}H RMN (DMSO-d_6) δ 3 14 (m 1H) 3 77 (dd *J* = 6 6 13 9 Hz 1H) 4 00 (t *J* = 7 73 Hz 1H)



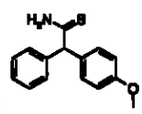
Intermedio-28

2 2-Bis-(4-fluoro-fenil) tioacetamida ^{1}H RMN ($CDCl_3$) δ 5 57 (s 1H) 6 76 (br s 1H (NH)) 7 08 (m 4H) y 7 23 (m 4H) y 7 68 (br s 1H (NH))



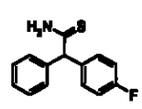
Intermedio 29

2 2-Bis-(4-metoxi fenil)-tioacetamida LC/MS (an10p8) Ta 2 96 min *m/z* 288 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 81 (s 6H) 5 54 (s 1H) 6 83 (bs 1H (NH)) 6 90 (m 4H) 7 18 (m 4H) 7 73 (br s 1H (NH))



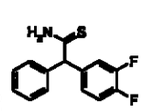
Intermedio-30

2-(4-Metoxi fenil) 2-fenil tioacetamida ^{1}H RMN ($CDCl_3$) δ 3 82 (s 3H) 5 59 (s 1H) 6 83 (bs 1H (NH)) 6 90 (m 2H) 7 18 (m 2H) 7 35 (m 5H) 7 76 (bs 1H (NH))



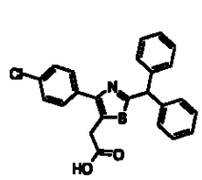
Intermedio-31

2-(4-Fluoro fenil)-2-fenil tioacetamida ^{1}H RMN ($CDCl_3$) δ 5 61 (s 1H) 6 84 (br s 1H (NH)) 7 06 (m 2H) 7 26 (m 2H) 7 37 (m 5H) 7 86 (br s 1H (NH))



Intermedio-32

2-(3 4-Difluoro-fenil)-2-fenil tioacetamida ^{1}H RMN ($CDCl_3$) δ 5 56 (s 1H) 6 81 (br s 1H (NH)) 7 04 (m 1H) 7 14 (m 2H) 7 25 (m 2H) 7 38 (m 3H) 7 92 (br s 1H (NH))

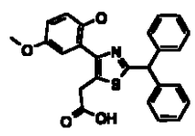


A1

48

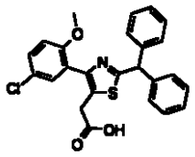
Acido [2 Benzhidril-4-(4-cloro fenil) tiazol-5 il]-acético – Procedimiento Representativo 6 (RP6) ácido 3-Bromo-4-(4-clorofenil)-4-oxo-butinco (119 mg 0 4 mmol) y 2 2-difenil-tioacetamida (91 mg 0 4 mmol) se disuelven en DMF (1 mL) y se calientan a 100 C durante 10 minutos en un horno microondas La mezcla de reacción se vierte en agua a 0° C La precipitación se filtra y se recristaliza de CH_2Cl_2 para dar 77 mg (54%) polvo amarillo ^{1}H RMN (DMSO-d_6) δ 3 91 (s 2H) 5 96 (s 1H) 7 37 (m 10H) 7 52 (d *J* = 8 48 Hz 2H) 7 60 (d *J* = 8 67 Hz 2H) 12 82 (br s 1H (COOH))

En una vía análoga los siguientes compuestos se hacen



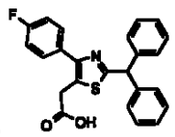
A2

Ácido [2 Benzhidril-4-(2 5-dimetoxi fenil)-tiazol-5-il]-acético LC/MS (an10p8) Ta 3 18 min *m/z* 446 [M + 1] ^{1}H RMN (DMSO-d6) δ 3 59 (s 2H) 5 92 (s 1H) 6 85 (d *J* = 3 0 Hz 1H) 6 96 (dd *J* = 8 9 y 3 0 Hz) 7 04 (d *J* = 8 5 Hz) 7 22 7 45 (m 10H)



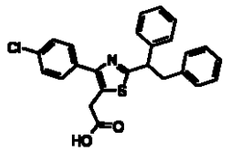
A3

Ácido [2-Benzhidril-4-(5-cloro-2-metoxi-fenil) tiazol-5 il]-acético LC/MS (an10p8) Ta 3 70 min *m/z* 450 [M + 1] ^{1}H RMN (DMSO-d_6) δ 3 60 (s 2H) 3 73 (s 3H) 5 93 (s 1H) 7 14 (d *J* = Hz 1H) 7 28 (m 3H) 7 36 (m 8H) 7 44 (m 1H)



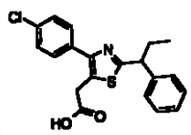
A4

Ácido [2 Benzhidril-4-(4-fluoro-fenil)-tiazol-5-il]-acético LC/MS (an10p8) Ta 2 93 min *m/z* 404 [M + 1] ^{1}H RMN ($CDCl_3$) δ 3 85 (s 2H) 5 88 (s 1H) 7 12 (m 2H) 7 25 7 38 (m 10H) 7 58 (m 2H)



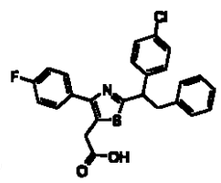
A5

Acido [4-(4-Cloro-fenil)-2-(1 2-difenil-etil)-tiazol-5-il]-acético LC/MS (an10p8) Ta 4 74 min *m/z* 434 [M + 1] ^{1}H RMN (DMSO d_6) δ 3 32 (m 1H) 3 61 (m 1H) 3 85 (s 2H (CH_2)) 4 75 (m 1H (CH))



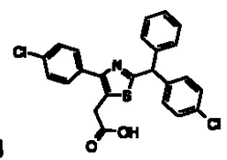
A6

Acido [4-(4-Cloro-fenil) 2-(1 fenil-propil)-tiazol-5 il]-acetico LC/MS (an10p8) Ta 3 1 min *m/z* 372 [M+1]



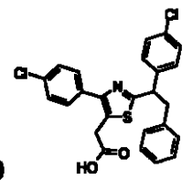
A7

Ácido [2-[1-(4-Cloro fenil) 2-fenil-etil]-4-(4-fluoro-fenil) tiazol-5 il]-acético ^{1}H RMN (DMSO-d_6) δ 3 32 (m 1H) 3 61 (m 1H) 3 84 (s 2H (CH_2)) 4 80 (m 1H (CH))



A8

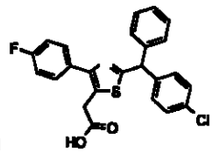
Ácido {4-(4-Cloro fenil)-2-[(4-cloro-fenil) fenil-metil] tiazol-5 il}-acético ^{1}H RMN (DMSO d6) δ 3 91 (s 2H) 6 01 (s 1H) 7 37 (m 9H) 7 50 (d *J* = 8 10 Hz 2H) 7 60 (d *J* = 8 29 Hz 2H)



A9

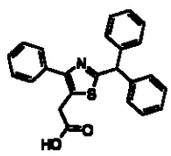
100

Ácido {4-(4-Cloro fenil)-2 [1-(4-cloro-fenil) 2 fenil-etil]-tiazol-5-il}-acético LC/MS (an10p8) Ta 5 17 min *m/z* 469 [M+1] ^{1}H RMN (DMSO-d_6) δ 3 32 (m 1H) 3 61 (dd *J* = 6 90 y 13 94 1H) 3 86 (s 2H (CH_2)) y 4 81 (t *J* = 7 90 1H (CH))



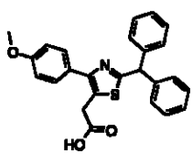
A10

Ácido [2-[(4-Cloro-fenil) fenil-metil]-4-(4 fluoro fenil) tiazol-5-il]-acético LC/MS (an10p8) Ta 5 04 min *m/z* 438 [M + 1] ^{1}H RMN (DMSO d_6) δ 3 83 (s 2H) 5 86 (s 1H) 7 11 (m 2H) 7 20-7 40 (m 9H) 7 55 (m 2H)



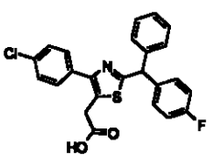
A11

Ácido (2 Benzhidril-4-fenil tiazol-5-il)-acético LC/MS (an10p8) Ta 3 95 min *m/z* 386 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 85 (s 2H) 6 01 (s 1H) 7 22 7 48 (m 12H) y 7 60 (m 2H)



A12

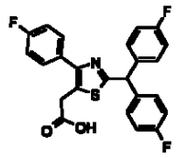
Acido [2-Benzhidril-4-(4-metoxi fenil) tiazol-5-il]-acético LC/MS (an10p8) Ta 3 52 min *m/z* 416 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 84 (s 3H) 3 85 (s 2H) 5 86 (s 1H) 6 97 (m 2H) 7 26-7 37 (m 10H) y 7 54 (m 2H)



A13

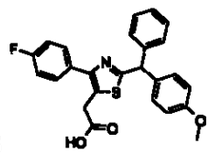
Ácido {4-(4-Cloro-fenil) 2 [(4 fluoro fenil)-fenil-metil] tiazol-5-il}-acético LC/MS (an10p8) Ta 0 98 min *m/z* 438 [M + H] ^{1}H RMN (DMSO-d_6) δ 3 91 (s 2H) 6 00 (s

1H) 7 19 (m 2H) 7 29 (m 1H) 7 36-7 43 (m 6H) 7 54 (m 2H) 7 59 (m 2H) 12 87 (br s 1H)



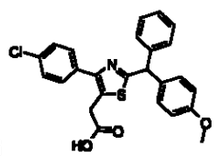
A14

Acido [2 [Bis-(4-fluoro fenil)-metil]-4-(4-fluoro fenil) tiazol-5-il]-acético LC/MS (an10p8) Ta 4 81 min *m/z* 440 [M + H] ^{1}H RMN (DMSO-d_6) δ 3 89 (s 2H) 6 03 (s 1H) 7 19 (m 4H) 7 30 (m 2H) 7 41 (m 4H) 7 62 (m 2H)



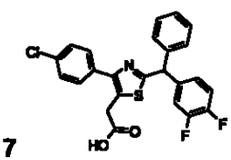
A15

Acido {4-(4-Fluoro fenil)-2-[(4-metoxi fenil) fenil metil] tiazol-5-il} acético LC/MS (an10p8) Ta 3 45 min *m/z* 434 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 81 (s 3H) 3 84 (s 2H) 5 81 (s 1H) 6 89 (m 2H) 7 12 (m 2H) 7 24 (m 2H) 7 28-7 38 (m 5H) 7 58 (m 2H) ^{13}C-APT ($CDCl_3$) δ 32 79 (CH_2) 54 62 55 65 (CH_3/CH)



A16

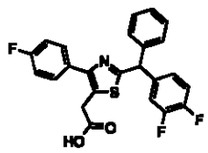
Acido {4-(4-Cloro-fenil)-2 [(4-metoxi fenil)-fenil-metil] tiazol-5-il}-acético LC/MS (an10p8) Ta 3 71 min *m/z* 450 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 81 (s 3H) 3 84 (s 2H) 5 84 (s 1H) 6 87 (m 2H) 7 21 (m 2H) 7 24-7 36 (m 5H) 7 41 (m 2H) 7 55 (m 2H) ^{13}C APT ($CDCl_3$) δ 32 83 (CH_2) 54 57 55 66 (CH_3 / CH)



A17

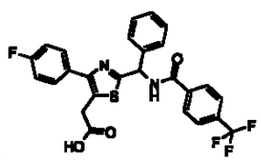
Ácido {4-(4-Cloro fenil)-2-[(3 4-difluoro-fenil) fenil metil] tiazol-5 il}-acético LC/MS (an10p8) Ta 3 98 min *m/z* 456 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 89 (s 2H) 5 79

(s 1H) 7 04 (m 1H) 7 15 (m 2H) 7 25-7 40 (m 5H) 7 44 (m 2H) 7 53 (m 2H) ^{13}C APT ($CDCl_3$) δ 32 60 (CH_2) 54 54 (CH)



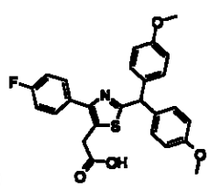
A18

Ácido [2-[(3 4-Difluoro-fenil)-fenil metil]-4-(4-fluoro-fenil) tiazol-5 il]-acético LC/MS (an10p8) Ta 3 76 min *m/z* 440 [M + H] ^1H RMN ($CDCl_3$) δ 3 88 (s 2H) 5 83 (s 1H) 7 03 (m 1H) 7 14 (m 4H) 7 28-7 44 (m 5H) 7 58 (m 2H) ^{13}C-APT ($CDCl_3$) δ 32 65 (CH_2) 54 46 (CH)



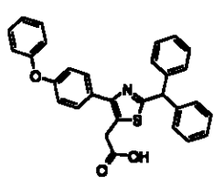
A19

Ácido {4-(4-Fluoro-fenil)-2 [fenil-(4-trifluorometil-benzoilamino)-metil] tiazol 5-il} acético LC/MS (an10p8) Ta 2 88 min *m/z* 515 [M + H] ^1H RMN (DMSO-d_6) δ 3 90 (s 2H) 6 64 (d *J* = 8 2 Hz 1H) 7 30 (m 2H) 7 36-7 45 (m 3H) 7 54 7 65 (m 4H) 7 87 (d *J* = 8 2 Hz 2H) 8 16 (d *J* = 8 2 Hz 2H) 9 87 (m 1H (NH)) y 12 82 (s 1H (OH))



A20

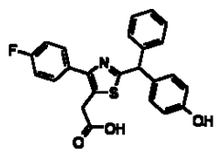
Ácido [2-[Bis-(4-metoxi fenil)-metil]-4-(4-fluoro-fenil) tiazol-5 il]-acético LC/MS (an10p8) Ta 2 17 min *m/z* 464 [M + H] ^1H RMN ($CDCl_3$) δ 3 81 (s 6H) 3 83 (s 2H) 5 77 (s 1H) 6 89 (m 4H) 7 11 (m 2H) 7 22 (m 4H) 7 56 (m 2H)



A21

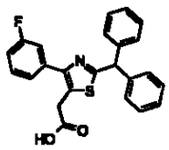
103

Ácido [2 Benzhidril-4-(4 fenoxi fenil)-tiazol-5-il]-acético LC/MS (an10p8) Ta 4 04 min *m/z* 478 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 88 (s 2H) 5 87 (s 1H) 7 07 (m 4H) 7 14 (m 1H) 7 25-7 41 (m 12H) 7 58 (m 2H)



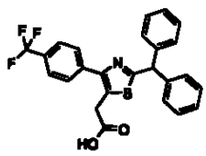
A22

Ácido (4-(4-Fluoro-fenil) 2-[(4-hidroxi fenil) fenil-metil] tiazol-5-il)-acético ^{1}H RMN ($CDCl_3$) δ 3 77 (s 2H) 5 82 (s 1H) 6 70 (m 2H) 7 02 7 15 (m 5H) 7 26-7 30 (m 4H) 7 53 (m 2H)



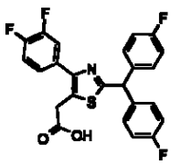
A23

Acido [2-Benzhidril-4-(3 fluoro fenil)-tiazol-5-il]-acético LC/MS (an10p8) Ta 2 69 min *m/z* 404 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 88 (s 2H) 5 90 (s 1H) 7 07 (m 1H) 7 26 7 41 (m 13H)



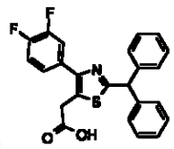
A24

Acido [2 Benzhidril-4-(4-trifluorometil-fenil)-tiazol-5-il]-acético LC/MS (an10p8) Ta 3 09 min *m/z* 455 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 91 (s 2H) 5 91 (s 1H) 7 34 (m 10H) 7 72 (m 4H)



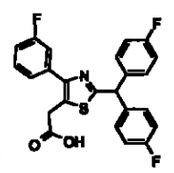
A25

Ácido [2 [Bis-(4-fluoro fenil)-metil]-4-(3,4-difluoro fenil)-tiazol-5-il]-acético LC/MS (an10p8) Ta 3 18 min *m/z* 458 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 88 (s 2H) 5 81 (s 1H) 7 04 (m 4H) 7 18-7 36 (m 6H) 7 46 (m 1H)



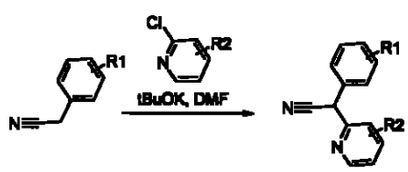
A26

Acido [2 Benzhidril-4-(3 4-difluoro fenil) tiazol-5-il]-acético LC/MS (an10p8) Ta 2 88 min *m/z* 422 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 88 (s 2H) 5 81 (s 1H) 7 20 (m 1H) 7 26-7 37 (m 9H) 7 48 (m 1H)

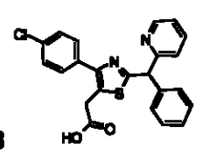


A27

Acido [2-[Bis-(4-fluoro fenil)-metil]-4-(3 fluoro fenil) tiazol-5-il]-acético LC/MS (an10p8) Ta 3 08 min *m/z* 440 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 92 (s 2H) 5 82 (s 1H) 7 04 (m 4H) 7 24-7 29 (m 6H) y 7 37 (m 2H)



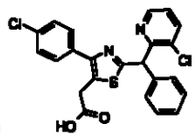
Síntesis de intermedios de nitrilo – Procedimiento Representativo 7 (RP7) A una solución fría (5 °C) de *Terc*-butóxido de potasio (2 1 mmol) en DMF seco (0 6ml) se agrega una mezcla del benzonitrilo (1 mmol) y la 2-Cloro-pirídina (1 1 mmol) en DMF seco (0 4ml) Luego O/N se agita a Ta se agregan NH_4Cl ac y EtOAc La fase orgánica se separa se seca sobre $MgSO_4$ y se concentra *en vacío* El residuo se purifica sobre cromatografía de gel de sílice para dar el producto deseado el cual se precipita hasta tratamiento con Et_2O



A28

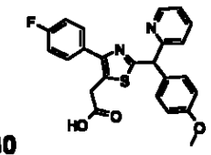
Ácido [4-(4-Cloro fenil)-2-(fenil piridin 2-il-metil) tiazol-5 il]-acético

Se prepara el compuesto del título de ácido 3 bromo-4-(4-cloro-fenil)-4-oxo-butírico y 2 fenil-2 pirídin 2 il tioacetamida de acuerdo con RP6 y RP7 LC/MS (an10p8) Ta 3 00 min *m/z* 422 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 86 (s 2H) 6 2 (s 1H) 7 2-8 0 (m 12H) 8 7 (d 1H)



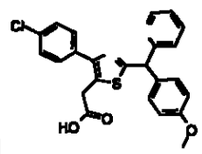
A29

Ácido {4-(4-Cloro fenil) 2-[(3-cloro-piridin 2-il) fenil-metil]-tiazol-5 il)-acético Se prepara el compuesto del título de ácido 3-bromo-4-(4-cloro-fenil)-4 oxo-butírico y 2 (3-Cloro-pirídin-2 il)-2 fenil tioacetamida de acuerdo con RP6 y RP7 LC/MS (an10p8) Ta 3 54 min *m/z* 454 5 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 83 (s 2H) 6 66 (s 1H) 7 2 7 3 (m 1H) 7 3-7 4 (m 5H) 7 5 (d 4H) 7 7 (dd 1H) 8 6 (dd 1H)



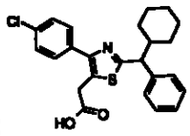
A30

Ácido {4-(4-Fluoro fenil) 2-[(4-metoxi fenil)-piridin 2 il metil] tiazol-5-il}-acetico Se prepara el compuesto del título de ácido 3-bromo-ácido 4 (4-Fluoro-fenil)-4-oxo-butírico y 2 (4-metoxi-fenil)-2 pirídin 2 il-tioacetamida de acuerdo con RP6 y RP7 LC/MS (an10p8) Ta 2 20 min *m/z* 434 [M + H]



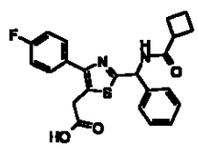
A31

Acido {4-(4-Cloro fenil)-2 [(4-metoxi-fenil)-piridin 2 il-metil] tiazol-5-il)-acético Se prepara el compuesto del título de ácido 3-bromo-4-(4-cloro-fenil)-4-oxo-butírico y 2 (4-metoxi-fenil)-2 pirídin-2 il-tioacetamida de acuerdo con RP6 y RP7 LC/MS (an10p8) Ta 2 37 min *m/z* 450 5 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 75 (s 3H) 3 78 (s 2H) 6 0 (s 1H) 6 9 (d 2H) 7 2 (t 1H) 7 3 (m 4H) 7 4 (d 1H) 7 5 (d 2H) 7 6 (dt 1H) 8 1 (d 1H)



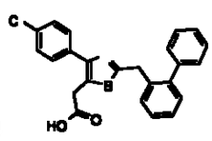
A32

Ácido [4-(4-Cloro fenil)-2-(ciclohexil-fenil metil)-tiazol-5 il]-acético Se prepara el compuesto del título de ácido 3-bromo-4-(4-cloro-fenil)-4-oxo-butírico y 2 ciclohexil-2 fenil-tioacetamida de acuerdo con RP6 LC/MS (an10p8) Ta 3 20 min *m/z* 425 4 [M + H]



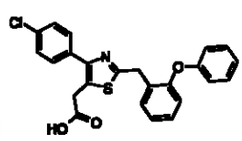
A33

Ácido [2 [(Ciclobutanecarbonil-amino)-fenil-metil]-4-(4-fluoro-fenil)-tiazol-5 il] acético Se prepara el compuesto del título de ácido 3-bromo-ácido 4-(4-Fluoro-fenil)-4-oxo-butírico y 2-ciclobutil-2 fenil-tioacetamida de acuerdo con RP6 LC/MS (an10p8) Ta 2 01 min m/z 425 [M + H] ^{1}H RMN ($CDCl_3$) δ 1 92 (m 2H) 2 19 (m 2H) 3 13 (p *J* = 8 4 Hz 1H) 3 81(s 2H) 6 49 (d J = 7 5 1H (NH)) 7 13 (m 3H) 7 36 (m 4H) y 7 54 (m 2H)



A34

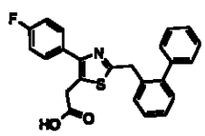
Ácido [2-Bifenil 2-ilmetil-4-(4-cloro fenil) tiazol-5-il]-acético Se prepara el compuesto del título de ácido 3 bromo-4-(4-cloro-fenil)-4-oxo-butírico y 2 bifenil-2 il tioacetamida de acuerdo con RP6 LC/MS (an10p8) Ta 4 94 min *m/z* 419 4 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 83 (s 2H) 4 33 (s 2H) 7 3-7 5 (m 13H)



A35

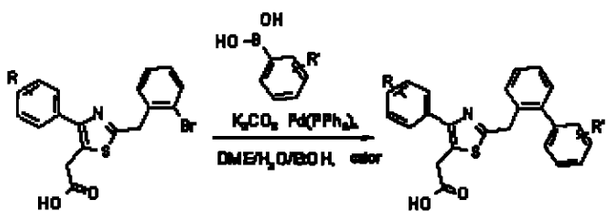
Ácido [4-(4-Cloro fenil)-2-(2 fenoxi bencil)-tiazol-5-il]-acético Se prepara el compuesto del título de ácido 3 bromo-4-(4-cloro-fenil)-4-oxo-butírico y 2 (2 fenoxi fenil) tioacetamida de acuerdo con RP6 LC/MS (an10p8) Ta 3 80 min *m/z* 435 4 [M

+ H] ^{1}H RMN ($CDCl_3$) δ 3 82 (s 2H) 4 39 (s 2H) 6 9 (d 1H) 7 0 (d 2H) 7 1 (m 2H) 7 2 7 3 (m 3H) 7 4 (t 3H) 7 5 (d 2H)



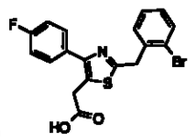
A36

Acido [2 Bifenil 2-ilmetil-4-(4-fluoro-fenil) tiazol-5-il]-acético Se prepara el compuesto del título de ácido 3-bromo-ácido 4-(4-Fluoro-fenil)-4-oxo-butírico y 2 bifenil-2 il-tioacetamida de acuerdo con RP6 LC/MS (an10p8) Ta 2 60 min *m/z* 403 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 78 (s 2H) 4 31 (s 2H) 7 1 (t 2H) 7 3 7 5 (m 11H)



Procedimiento Representativo 8 (RP8)

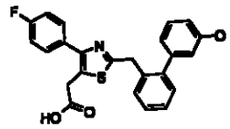
Una mezcla de $Pd(PPh_3)_4$ (~50mg) K_2CO_3 (2 mmol) ácido [2 (2 bromo-bencil) tiazol 5-il] acético (1 mmol) y el correspondiente acido fenil borónico (1 3 mmol) en DME/H2O/EtOH (7/3/2 20 mL) se calienta a 150°C durante 10 minutos en un microondas Después de enfriamiento se agregan agua ácido acético y EtOAc Los materiales sólidos se filtran y el filtrado se concentra en vacío El residuo se pone en acetonitrilo caliente y las partículas sólidas se filtran El filtrado se le permite enfriar a Ta hasta que el compuesto deseado se precipita En algunas ocasiones el material crudo se purifica por cromatografía



Intermedio-33

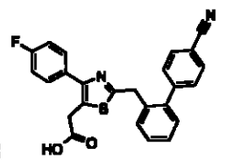
Acido [2-(2 Bromo bencil)-4-(4-fluoro-fenil)-tiazol-5-il]-acético Se prepara el compuesto del título de ácido 3-bromo-ácido 4-(4 Fluoro-fenil)-4-oxo-butírico y 2 (2 bromo-fenil)-tioacetamida de acuerdo con RP6 LC/MS (an10p8) Ta 2 22 min *m/z*

405 4 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 85 (s 2H) 4 55 (s 2H) 7 1 (m 3H) 7 3 (t 1H) 7 4 (d 1H) 7 5-7 6 (m 3H)



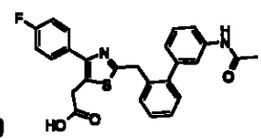
A37

Acido [4-(4-Fluoro fenil) 2-(3 -metoxi-bifenil 2 ilmetil) tiazol-5 il]-acético Se prepara el compuesto del título de ácido [2 (2 bromo-bencil)-4 (4 fluoro-fenil) tiazol 5 il]-acético y ácido 3-metoxifenil borónico de acuerdo con RP8 LC/MS (an10p8) Ta 2 65 min *m/z* 433 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 76 (s 3H) 3 81(s 2H) 4 43 (s 2H) 6 8-6 9 (m 2H) 7 1 (t 1H) 7 3-7 5 (m 7H) 7 7 (m 2H)



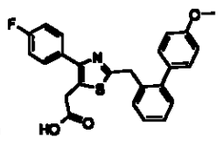
A38

Ácido [2-(4 -Ciano-bifenil 2-ilmetil)-4-(4-fluoro fenil) tiazol 5 il]-acético Se prepara el compuesto del título de ácido [2 (2 bromo-bencil)-4-(4-fluoro-fenil) tiazol 5-il]-acético y ácido 4-cianofenil borónico de acuerdo con RP8 LC/MS (an10p8) Ta 2 47 min *m/z* 428 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 84 (s 2H) 4 36 (s 2H) 7 1 (t 2H) 7 3-7 5 (m 8H) 7 7 (d 2H)



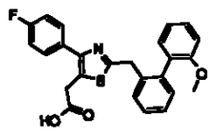
A39

Ácido [2-(3 -Acetilamino-bifenil 2 ilmetil)-4-(4-fluoro-fenil) tiazol-5-il]-acético Se prepara el compuesto del título de ácido [2 (2 bromo-bencil)-4-(4-fluoro-fenil) tiazol 5 il]-acético y ácido 3-acetamidobenceno borónico de acuerdo con RP8 LC/MS (an10p8) Ta 2 18 min *m/z* 460 [M + H] ^{1}H RMN ($CDCl_3$) δ 1 98 (s 3H) 3 78 (s 2H) 4 3 (s 2H) 7 0-7 1 (m 4H) 7 2 7 4 (m 2H) 7 4 (m 4H) 7 6 (m 2H)



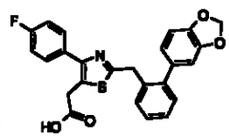
A40

Ácido [4-(4-Fluoro fenil) 2-(4 metoxi-bifenil-2-ilmetil) tiazol-5-il]-acético Se prepara el compuesto del título de ácido [2 (2 bromo-bencil)-4-(4-fluoro-fenil)-tiazol-5 il]-acético y ácido 4-metoxifenil borónico de acuerdo con RP8 LC/MS (an10p8) Ta 2 60 min *m/z* 433 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 82 (s 2H) 3 84(s 3H) 4 37 (s 2H) 6 9 (d 2H) 7 1 (t 2H) 7 2 7 3 (m 5H) 7 4 (m 1H) 7 5 (m 2H)



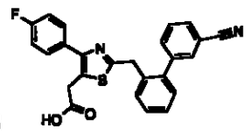
A41

Ácido [4-(4-Fluoro-fenil)-2-(2 -metoxi bifenil 2-ilmetil) tiazol-5-il]-acético Se prepara el compuesto del título de ácido [2 (2 bromo-bencil)-4-(4-fluoro-fenil) tiazol-5 il]-acético y 2 ácido metoxifenil borónico de acuerdo con RP8 LC/MS (an10p8) Ta 2 55 min *m/z* 433 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 71 (s 3H) 3 81 (s 2H) 4 3 (s 2H) 6 9-7 0 (m 2H) 7 1 (m 3H) 7 2 7 4 (m 4H) 7 4-7 5 (m 3H)



A42

Ácido [2-(2 Benzo[1 3]dioxol-5-il bencil)-4-(4-fluoro fenil) tiazol-5 il] acético Se prepara el compuesto del título de ácido [2-(2 Bromo-bencil)-4-(4 fluoro-fenil) tiazol 5 il] acético y ácido 3 4-metilenedioxobenceno borónico de acuerdo con RP8 LC/MS (an10p8) Ta 3 35 min *m/z* 447 $[M + H]^+$ ^{1}H RMN ($CDCl_3$) δ 3 78 (s 2H) 4 34 (s 2H) 5 96 (s 2H) 6 7 (m 3H) 7 1 (t 2H) 7 2 7 3 (m 3H) 7 3 (d 1H) 7 5 (t 2H)

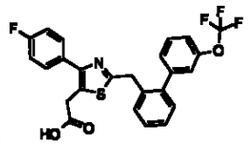


A43

Acido [2-(3 -Ciano-bifenil 2-ilmetil)-4-(4-fluoro-fenil) tiazol-5-il]-acetico Se prepara el compuesto del título de ácido [2 (2 bromo-bencil)-4-(4-fluoro-fenil)-tiazol-5-il]-acético y ácido 3 cianofenil borónico de acuerdo con RP8 LC/MS (an10p8) Ta 3 157 min *m/z*

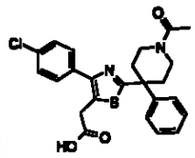
110

428 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 55 (s 2H) 3 9 (s 2H) 6 8 (m 2H) 7 0 (m 4H) 7 2 7 4 (m 6H)



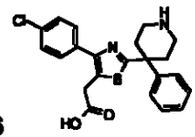
A44

Acido [4-(4-Fluoro-fenil) 2-(3 trifluorometoxi bifenil 2 ilmetil) tiazol 5 il]-acetico Se prepara el compuesto del título de [ácido 2 (2 bromo-bencil)-4-(4-fluoro-fenil) tiazol 5-il]-acético y ácido 3-trifluorometoxifenil borónico de acuerdo con RP8 LC/MS (an10p8) Ta 3 91 min *m/z* 487 [M + H] ^{1}H RMN ($CDCl_3$) δ 3 78 (s 2H) 4 3 (s 2H) 7 1 (t 2H) 7 3 (m 1H) 7 3 (t 2H) 7 4-7 5 (m 7H)



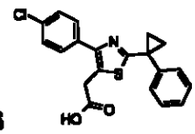
A45

Ácido [2-[(1-Acetil piperidin-4-il)-fenil-metil]-4-(4-cloro fenil) tiazol-5 il]-acetico Se prepara el compuesto del título de ácido 3-bromo-4-(4-cloro-fenil)-4-oxo-butírico y acido 1-acetil-4-fenil-piperidin-4-carbotioico amida 2 (1 acetil piperidin-4-il) 2 fenil-tioacetamida de acuerdo con RP6 LC/MS (an10p8) Ta 2 32 min *m/z* 454 5 [M + H]$^+$



A46

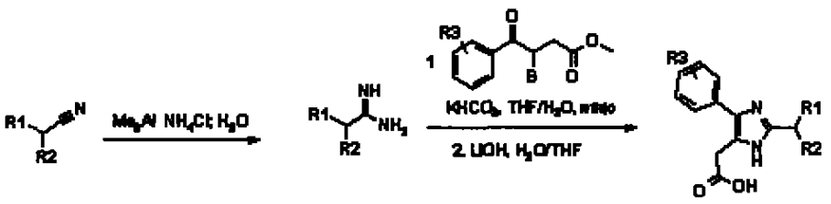
Ácido [4-(4-Cloro fenil) 2-(4-fenil piperidin-4-il)-tiazol-5-il]-acético El título del compuesto se aisla como sus sales de HCl se prepara al hacer reaccionar ácido [2 [(1-acetil-piperidin-4 il) fenil metil]-4-(4-cloro-fenil) tiazol 5 il]-acético con 4N ac HCl a 95°C durante 18 horas seguido por evaporación de solvente LC/MS (an10p8) Ta 2 07 min *m/z* 412 4 [M + H]

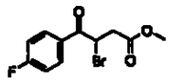


A46

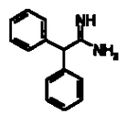
Ácido [4-(4-Cloro-fenil)-2-(1-fenil-ciclopropil)-tiazol-5-il]-acético Se prepara el compuesto del título de ácido 3 bromo-4-(4-cloro-fenil)-4-oxo-butírico y acido 1 fenil ciclopropanecarbotioico amida de acuerdo con RP6 LC/MS (an10p8) Ta 3 57 min *m/z* 369 8 [M + H]

Ruta sintetica general para análogos de imidazol

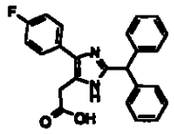


Intermedio-34 

Ácido 3-Bromo-4-(4-fluorofenil)-4-oxo-butírico metil ester Ácido 3 Bromo-4-(4 fluorofenil)-4-oxobutírico (15 mmol) se disuelve en metanol (60 ml) y tionil cloruro (17 mmol) se agrega at 0 °C Después de agitar a 80° C durante 2 h el solvente se evapora El residuo se pela con dietileter El producto se utiliza directamente en la siguiente etapa ^{1}H RMN ($CDCl_3$) δ 3 00 (m 1H) 3 33 (m 1H) 3 67 (s 3H) 5 44 (t 1H) 7 15 (t 2H) 8 06 (t 2H)

Intermedio-35 

2 2-Difenilacetamidina Preparado de difenilacetonitrilo de acuerdo con R A Moss W Ma D C Merrer y S Xue (*Tetrahedron Lett* **1995** *36* 8761-8764) LC/MS (an10p8) Ta 1 57 min *m/z* 211 [M+H]

A48 

Acido [2-Benzhidril-5-(4-fluoro-fenil)-3H-imidazol-4-il]-acético Una suspensión de 2 2-difenilacetamidine (10 mmol) y carbonato de potasio (38 mmol) en THF/H2O (150 mL/50 mL) luego se calienta a reflujo Ácido 3-Bromo-4-(4-fluorofenil)-4-oxo-butírico metil éster (10 mmol) en THF (50 mL) se agrega lentamente La mezcla de reacción

luego se refluye durante 16 h y entonces se concentra El residuo luego se disuelve en agua (10 mL) y se extrae con CH_2Cl_2 (10 mL) La fase orgánica se seca ($MgSO_4$) y se concentra produciendo ácido [2 benzhidril-5-(4-fluoro-fenil)-3H imidazol-4-il]-acético metil éster LC/MS (an10p8) Ta 3 64 min *m/z* 401 [M+H] Se agrega el metil ester en THF en exceso LiOH H_2O en agua La reacción se agita a temperatura ambiente durante la noche 3% HCl se agrega hasta que pH <1 y la mezcla se extrae con CH_2Cl_2 La fase orgánica se seca ($MgSO_4$) y se concentra para dar el producto fue susceptible a la hidrólisis con LiOH en agua/THF LC/MS (an10n8) Ta 1 43 min *m/z* 387 [M + H]

Ensayos Biológicos

Materiales y Métodos

Generación/origen de las construcciones de cADN La secuencia de codificación del receptor CRTH2 humano (no de acceso genbank NM_004778) se amplifica mediante PCR de una librería de cADN de hipocampo humano y se inserta en el casete de expresión pcADN3 1 (+) (invitrogen) por vía del 5 Hind/// y 3 EcoR/ Para generar una proteína de fusión (CRTH2 Rluc) luciferasa CRTH2 Renilla la secuencia de codificación CRTH2 SIN UN CODÓN DE PARADA y Rluc se amplifica se fusiona en cuadro por PCR y se subclona en el vector de expresión pcADN 3 1 (+) Zeo (invitrogen) La □-arrestín2 (□-arr2) N terminalmente etiquetada humana con GFP[2] (□arr2-GFP[2]) y Renilla luciferasa se compran de BioSignal Packard Inc (Montreal Canadá) La identidad de secuencia de la construcción se verifica por restricción de digestos de endonucleasa y secuenciamiento en ambas direcciones en Prisma ABI (Applied Biosystems Foster City CA)

ID de Secuencia CRTH2 (secuencia de proteína)

MSANATLKPLCPILEQMSRLQSHSNTSIRYIDHAAVLLHGLASLLGLVEN
GVILFVVGCRMRQTVVTTWVLHLALSDLLASASLPFFTYFLAVGHSWELG
TTFCKLHSSIFFLNMFASGFLLSAISLDRCLQVVRPVWAQNHRTVAAAHK
VCLVLWALAVLNTVPYFVFRDTISRLDGRIMCYYNVLLLNPGPDRDATCN
SRQAALAVSKFLLAFLVPLAIIASSHAAVSLRLQHRGRRRPGRFVRLVAA
VVAAFALCWGPYHVFSLLEARAHANPGLRPLVWRGLPFVTSLAFFNSVAN
PVLYVLTCPDMLRKLRRSLRTVLESVLVDDSELGGAGSSRRRRTSSTARS

ASPLALCSRPEEPRGPARLLGWLLGSCAASPQTGPLNRALSSTSS

ID de Secuencia CRTH2 (secuencia de nucleótido)

atgtcggc
caacgccaca ctgaagccac tctgccccat cctggagcag atgagccgtc tccagagcca
cagcaacacc agcatccgct acatcgacca cgcggccgtg ctgctgcacg ggctggcctc
gctgctgggc ctggtggaga atggagtcat cctcttcgtg gtgggctgcc gcatgcgcca
gaccgtggtc accacctggg tgctgcacct ggcgctgtcc gacctgttgg cctctgcttc
cctgcccttc ttcacctact tcttggccgt gggccactcg tgggagctgg gcaccacctt
ctgcaaactg cactcctcca tcttctttct caacatgttc gccagcggct tcctgctcag
cgccatcagc ctggaccgct gcctgcaggt ggtgcggccg gtgtgggcgc agaaccaccg
caccgtggcc gcggcgcaca aagtctgcct ggtgctttgg gcactagcgg tgctcaacac
ggtgccctat ttcgtgttcc gggacaccat ctcgcggctg gacgggcgca ttatgtgcta
ctacaatgtg ctgctcctga acccggggcc tgaccgcgat gccacgtgca actcgcgcca
ggcggccctg gccgtcagca agttcctgct ggccttcctg gtgccgctgg cgatcatcgc
ctcgagccac gcggccgtga gcctgcggtt gcagcaccgc ggccgccggc ggccaggccg
cttcgtgcgc ctggtggcag ccgtcgtggc cgccttcgcg ctctgctggg ggccctacca
cgtgttcagc ctgctggagg cgcgggcgca cgcaaacccg gggctgcggc cgctcgtgtg
gcgcgggctg cccttcgtca ccagcctggc cttcttcaac agcgtggcca acccggtgct
ctacgtgctc acctgccccg acatgctgcg caagctgcgg cgctcgctgc gcacggtgct
ggagagcgtg ctggtggacg acagcgagct gggtggcgcg ggaagcagcc gccgccgccg
cacctcctcc accgcccgct cggcctcccc tttagctctc tgcagccgcc cggaggaacc
gcggggcccc gcgcgtctcc tcggctggct gctgggcagc tgcgcagcgt ccccgcagac
gggccccctg aaccgggcgc tgagcagcac ctcgagttag

Transfección y Cultivo Celular Se hace crecer células COS-7 en medio Eagle modificado de Dulbecco (DMEM) 1885 complementado con 10% de suero bovino fetal 100 unidades/ml penicilina 1000µg/ml estreptomicina y se mantiene a 37 C en 10% atmósfera de CO_2 Se mantiene células HEK293 en Medio Esencial Mínimo (MEM) complementado con 10% (v/v) de suero de ternero fetal inactivo caliente (HIFCS) 2mM de Glutamax™ I 1% de aminoácidos no esenciales (NEAA) 1% de pirovato de sodio y 10 □g/ml de gentamicina Para experimentos de unión se transfectan transitoriamente células COS7 con el receptor CRTH2 utilizando un método de coprecipitación de ADN fosfato de calcio con la adición de cloroquina (como se

describe por Holst et al 2001•) Para desarrollar los ensayos de Transferencia de Energia por Resonancia de Bioluminicencia (BRET) funcional un clon de célula HEK293 estable que expresa □arr2 GFP^2 y CRTH2 Rluc se genera (células CRTH2 HEK293)

Ensayo de Unión 24h después de transfección de las células COS-7 se siembran en placas de 96 pozos en una densidad de 30 000 células/pozo Los experimentos de unión de competición en cuyas células se desarrollan alrededor de 18-24 h después de utilizar 0 1 nM [^{3}H]PGD2 (NEN 172 Ci/mmol) en un amortiguador de union que consiste de HBSS (GIBCO) y 10 mM HEPES Se diluyen ligandos de competición en DMSO que se mantienen constantes en 1% (v/v) del volumen de incubación final Se determina la unión no específica y total en la ausencia y presencia de 10 □M PGD2 Se conducen rutinariamente reacciones de unión durante 3h 4 C y se terminan mediante 2 lavadas (100 □l cada una) con hielo junto con amortiguador La radioactividad de determina mediante conteo de centelleo liquido en un TOPCOUNTER (Packard) seguido por incubación en la noche en Microscint 20 Se siembran células HEK293 estables en una densidad de 30000 células/poso 18 24h antes del ensayo de unión que se desarrolla esencialmente como se describe para las células CSO7 anteriores Se hace las determinaciones en duplicados

Ensayo BRET Se desarrollan ensayos BRET funcionales en las células HEK293 establemente que expresan el CRTH2 Rluc y GFP^2 □-arr2 humano Antes de su uso en células de ensayo BRET se separa y resuspenden en D-PBS con 1000 mg/L L Glucosa en una densidad de 2x10^6 células/mL Se diluye DeepBlueC™ a 50 µM en D-PBS con 1000 mg/L L Glucosa (sensible a la luz) 100 µL de suspensión celular se transfiere a pozos en una microplaca de 96 pozos (blanco OptiPlate) y colocado en el instrumento Mithras LB 940 (BERTHOLD TECHNOLOGIES Bad Wildbad Alemania) Agonista de 12 µL/pozo se inyecta luego mediante el inyector 1 y 10 µL/pozo DeepBlueC™ se inyecta simultáneamente mediante el inyector 2 Cinco segundos después de las inyecciones se mide la salida de la luz del pozo secuencialmente a 400 nm y 515 nm y la señal BRET (Indice mBRET) se calcula por el índice de fluorescencia emitida por el GFP^2 □-arr2 (515 nm) sobre la luz emitida por el receptor Rluc (400 nm) Se agregan antagonistas antes de colocar las microplacas en el Mithras LB 940 y se le permite incubar durante 15 minutos antes de la adición de

agonista y DeepBlueC™ Se disuelven los compuestos en DMSO y la concentración de DMSO final se mantiene constante en 1% en el ensayo

Ensayo de cambio de forma eosinófilo humana La sangre se muestrea de voluntarios saludables de acuerdo con un protocolo aprobado por el Ethics Committee de la Universidad de Graz y procesados segun se describió previamente (Bohm et al 2004) Preparaciones de Leucocitos polimorfonucleares (que contienen eosinófilos y neutrófilos) se preparan mediante sedimentación de dextrano de sangre completa citrada y gradientes de Histopaque Las células resultantes se lavan y resuspenden en amortiguador de ensayo (que comprenden PBS con Ca^{2+}/Mg^{2+} complementado con 0 1% BSA 10 mM HEPES y 10 mM glucosa pH 7 4) en 5 x 10^6 celulas/mL Las células se incuban con los antagonistas o vehículo (PBS o DMSO) durante 10 min a 37 C y luego estimulado con varias concentraciones de los agonistas (PGD2 o eotaxin) durante 4 min a 37 C Para retener la reacción se transfieren las muestras a hielo y se fijan con 250 µL de solución fija Las muestras se analizan inmediatamente en un citómetro de flujo FACSCalibur (Becton Dickinson) y se identifican los eosinófilos de acuerdo con su autofluorescencia en los canales FL 1 y FL 2 Las respuestas a los cambios de formas se cuantifican como porcentaje de la respuesta máxima para el PGD2 o eotaxin en la ausencia de un antagonista

Materiales

Los medios de cultivo de tejido y reactivos se compran de Gibco invitrogen corporation (Breda Holanda) PGD2 se obtiene de Cayman y [3H]PGD2 de NEN

Análisis de Datos

Se desarrolla análisis de curva con el software GraphPadPrism 3 0 (Graphpad Prism Inc San Diego USA) y se calculan los valores IC_{50} como una medición de las potencias antagonisticas

Referencias

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

Datos Biológicos

Se ensayan los compuestos en el ensayo de unión de receptor y el ensayo de antagonista funcional se descnbe adelante Y se evalúan sus valores IC_{50} Los compuestos se agrupan en tres clases

A valor IC_{50} menor de 0 5 µM

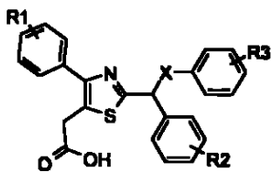
B valor IC_{50} entre 0 5 µM y 5 µM

C valor IC_{50} mayor de 5 µM

Las Tablas 1 a 4 den los resultados del ensayo biológico para los compuestos sintetizados anteriormente y para algunos compuestos adicionales adquindos de fuente comerciales

La capacidad de los compuestos anteriores para inhibir la prostaglandina D2 inducida por el cambio de forma de de eosinófilo se demuestra mediante los ejemplos en la Figura 1

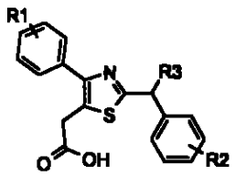
Tabla 1



	X	R1	R2	R3	Unión IC_{50}	Antag IC_{50}
A1	Enlace	4-Cl	H	H	A	A
A4	Enlace	4-F	H	H	A	A
A5	CH_2	4-Cl	H	H	A	B
A7	CH_2	4-F	4-Cl	H	A	A
A8	Enlace	4-Cl	4-Cl	H	A	A
A9	CH_2	4-Cl	4-Cl	H	A	B
A10	Enlace	4-F	4-Cl	H	A	A
A11	Enlace	H	H	H	B	A
A12	Enlace	4 MeO	H	H	A	B
A13	Enlace	4-Cl	4-F	H	A	A
A14	Enlace	4 F	4 F	4-F	A	A
A15	Enlace	4-F	4-MeO	H	A	A
A16	Enlace	4 Cl	4-MeO	H	A	A
A17	Enlace	4-Cl	3 4-DiF	H	A	C
A18	Enlace	4-F	3 4-DiF	H	A	A
A19	NHCO	4-F	H	4 CF_3	A	C
A20	Enlace	4 F	4 MeO	4-MeO	A	A
A21	Enlace	4 PhO	H	H	A	B
A22	Enlace	4 F	4 OH	H	A	A
A23	Enlace	3 F	H	H	A	A
A24	Enlace	4 CF_3	H	H	B	C
A25	Enlace	3 4 DiF	4 F	4-F	A	A
A26	Enlace	3 4	H	Ph	A	A

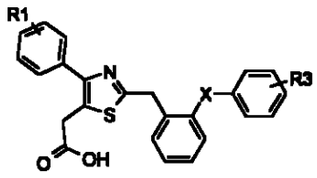
		DiF				
A27	Enlace	3-F	4 F	4-F	A	A

Tabla 2



	R1	R2	R3	Unión IC_{50}	Antag IC_{50}
A28	4-Cl	H		A	B
A29	4-Cl	H		A	
A30	4-F	4-MeO		A	
A31	4-Cl	4-MeO		A	A
A32	4-Cl	H		B	
A6	4-Cl	H	Et	A	

Tabla 3



	X	R1	R2	Unión IC_{50}	Antag IC_{50}
A34	Enlace	4-Cl	H	A	A
A35	O	4-Cl	H	B	
A36	Enlace	4-F	H	A	A
A37	Enlace	4-F	3-MeO	A	A
A38	Enlace	4-F	4-CN	A	A
A39	Enlace	4-F	3-NHAc	B	
A40	Enlace	4-F	4-MeO	A	A
A41	Enlace	4-F	2 MeO	A	
A42	Enlace	4-F	3 4-OCH_2O	A	A
A43	Enlace	4-F	3-CN	A	
A44	Enlace	4-F	3-OCF_3	A	

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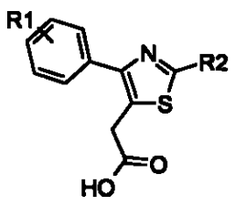
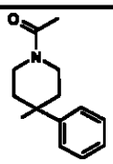
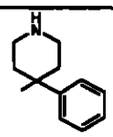
Tabla 4



	R1	R2	Unión IC_{50}	Antag IC_{50}
A45	4 Cl		A	B
A46	4-Cl		B	C

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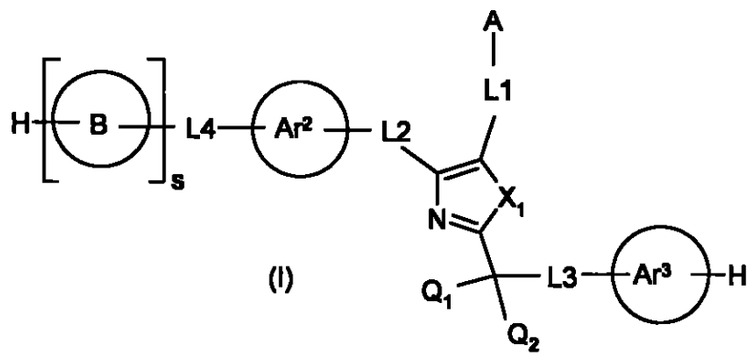
Reivindicaciones

1 Un compuesto de la fórmula (I) o una sal hidrato o solvato de éste



en donde

X_1 es -S- O- N=N –NR7 -CR7=CR8- -CR7=N en donde R7 y R8 son independientemente hidrógeno o alquilo C_1 C_3

A es un grupo carboxilo –COOH o un carboxil bioisostere

Los anillos Ar^2 y Ar^3 independientemente cada uno representa un fenilo o un anillo heterocíclico de 5 o 6 miembros o un sistema de anillo bicíclico que consiste de un anillo carbocíclico de 5 o 6 miembros que está benzofusionado a un anillo heteroanlo monocíclico de 5 o 6 miembros dicho anillo o sistema de anillo es opcionalmente sustituido

El anillo B es como se definió Ar^2 y Ar^3 o un anillo N pirrolidinilo N piperidinilo o N azepinilo opcionalmente sustituido

s es 0 o 1

L1 representa un radical divalente de la fórmula $–(Alq^1)_m$ y L2 y L4 cada uno independientemente representan un radical divalente de la fórmula $–(Alq^1)_m-(Z)_n-(Alq^2)_p-$

en donde

m n y p son independientemente 0 o 1

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Alq^1 y Alq^2 son independientemente radicales alquileno C_1 C_3 o alquenileno C_2-C_3 de cadena recta o ramificada opcionalmente sustituidos que pueden contener un enlace –O- S- o –NR compatible en donde R es hidrógeno o alquilo C_1-C_3 y

Z es –O- S C(=O)- -SO_2- SO NR NRSO_2- C(=O)NR NRCONH NRC(=NR)NH o =N NR en donde R es hidrógeno o alquilo C_1-C_3 o un radical carbocíclico o heterocíclico monocíclico de 5 o 6 miembros divalente

L3 representa un radical divalente de la fórmula –$(Alq^3)_m$-$(Z)_n$-$(Alq^2)_p$- en donde m n p Alq^2 y Z son como se definió en relación con L2 y L4 y Alq3 es un radical alquileno C_1 C_2 o alquenileno C_1 C_2 de cadena recta o ramificada opcionalmente sustituidos que pueden contener un enlace –O- S- o –NR compatible en donde R es hidrógeno o alquilo C_1 C_3

Q_1 representa hidrógeno o alquilo (C_1-C_6)

Q_2 representa

(i) alquilo (C_1 C_6) alcoxi (C_1 C_6) hidroxi hidroxi-alquilo (C_1 C_6) nitrilo (CN) fenilo fenoxi heteroarilo o heteroariloxi monocíclico con 5 o 6 átomos por anillo $CONR^AR^B$ NR^BCOR^A $NR^BSO_2R^A$ o $NR^ACONR^AR^B$ en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1-C_6) o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico y cuando Q es fenilo fenoxi o heteroarilo monocicilo heteroariloxi con con 5 o 6 átomos por anillo el anillo de fenilo o heteroarilo es opcionalmente sustituido por cualquiera de alquilo (C_1 C_6) alcoxi (C_1-C_6) hidroxi hidroxi-alquilo (C_1 C_6) alquiltio (C_1 C_3) halo alquilo (C_1-C_3) completa o parcialmente fluornado o alquiltio(C_1 C_3) trifluorometiltio nitro nitrilO (CN) -$COOR^A$ -COR^A $OCOR^A$ SO_2R^A $CONR^AR^B$ $SO_2NR^AR^B$ NR^AR^B NR^BCOR^A NR^BCOOR^A $NR^BSO_2R^A$ o $NR^ACONR^AR^B$ en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1 C_6) o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico o

(ii) hidrógeno pero sólo cuando en L3 Z representa un radical carbocíclico o heterocíclico de 5 o 6 miembros divalente opcionalmente sustituido

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o Q_1 y Q_2 tomados juntos con el átomo de carbono al cual ellos están unidos forman un anillo de cicloalquilo C_3-C_8 o una anillo heterocíclico no aromático monocíclico con 4-8 átomos por anillo

y en donde la longitud total de L2 y L3 no excede aquella de una cadena saturada no ramificada de 10 átomos de carbono

2 Un compuesto como se reivindica en la reivindicación 1 en donde (i) la longitud de cada uno de L2 L3 y L4 no excede aquella de la cadena saturada no ramificada de 5 átomos y (ii) la longitud total de L2 L3 y L4 no excede aquella de la cadena saturada no ramificada de 7 átomos y (iii) ninguno de L1 L2 L3 y L4 incluye más de dos sustituyentes R diferentes de hidrogeno

3 Un compuesto como se reivindica en la reivindicación 1 o reivindicación 2 en donde L3 es una unión Q_1 es hidrógeno y Q_2 es fenil o heteroarilo monicíclico con 5 a 6 átomos por anillo opcionalmente sustituido por cualquiera de alquilo (C_1 C_6) alcoxi (C_1-C_6) hidroxi hidroxi alquilo (C_1 C_6) alquiltio (C_1-C_3) halo alquilo (C_1-C_3) completa o parcialmente fluorinado o alquilo(C_1-C_3) alcoxi (C_1 C_3) o alquitio (C_1 C_3) trifluorometiltio nitro nitrilo (-CN) -$COOR^A$ COR^A $OCOR^A$ SO_2R^A $CONR^AR^B$ $SO_2NR^AR^B$ NR^AR^B NR^BCOR^A NR^BCOOR^A $NR^BSO_2R^A$ o $NR^ACONR^AR^B$ en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1-C_6) o R^A y R^B estan ligados al mismo átomo de N para formar un anillo amino cíclico

4 Un compuesto como se reivindica en la reivindicación 1 o reivindicación 2 en donde L3 es una unión Q_1 es hidrógeno y Q_2 es fenil opcionalmente sustituido por cualquiera de flúor cloro bromo alquilo (C_1 C_3) trifluorometil alcoxi (C_1 C_3) trifluorometoxi trifluorometiltio dimetilamino ciano (C_1 C_3alquilo)SO_2- NH_2SO_2- (C_1 C_3alquilo)$NHSO_2$- (C_1-C_3alquilo)$_2NSO_2$- $CONR^AR^B$ y NR^BCOR^A en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1-C_6) o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino ciclico

5 Un compuesto como se reivindica en la reivindicacion 1 o reivindicacion 2 en donde L3 es -CH_2- O- S SO_2- –NHC(=O) -CH=CH NR_{11} o $NR_{11}CH_2$ en donde R_{11} es hidrógeno o C_1-C_3 alquilo

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6 Un compuesto como se reivindica en la reivindicación 1 o reivindicación 2 en donde Q_2 es hidrógeno y L3 representan un radical divalente de la fórmula $-(Alq^3)_m-(Z)_n-(Alq^2)_p-$ en donde m es 0 n es 1 y Z es un radical fenilen opcionalmente sustituido por uno o más de flúor cloro bromo alquilo (C_1 C_3) trifluorometil alcoxi (C_1 C_3) trifluorometoxi trifluometiltio dimetilamino ciano (C_1-C_3alquilo)SO_2- NH_2SO_2- (C_1 C_3alquilo)$NHSO_2$- (C_1 C_3alquilo)$_2NSO_2$- $CONR^AR^B$ y NR^BCOR^A en donde R^A y R^B son independientemente hidrógeno o un grupo (C_1 C_6)alquilo o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico

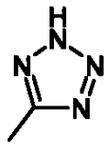
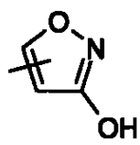
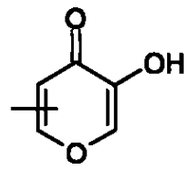
7 Un compuesto como se reivindica en la reivindicación 6 en donde Z es a 1 2 radical fenilen opcionalmente sustituido por uno o más de flúor cloro bromo (C_1 C_3)alquilo trifluorometil (C_1-C_3)alcoxi trifluorometoxi trifluometiltio dimetilamino ciano (C_1-C_3alquilo)SO_2- NH_2SO_2- (C_1-C_3alquilo)$NHSO_2$- (C_1-C_3alquilo)$_2NSO_2$- $CONR^AR^B$ y NR^BCOR^A en donde R^A y R^B son independientemente hidrógeno o un grupo (C_1 C_6)alquilo o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico

8 Un compuesto como se reivindica en la reivindicación 6 o reivindicación 7 en donde Q_1 es hidrógeno

9 Un compuesto como se reivindica en una cualquiera de las reivindicaciones precedentes en donde X_1 es –S-

10 Un compuesto como se reivindica en una cualquiera de las reivindicaciones precedentes en donde A es a grupo carboxilo –COOH

11 Un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 9 en donde A es un bioisóstero carboxilo seleccionado de -SO_2NHR y P(=O)(OH)(OR) en donde R es hidrógeno metil o etil -SO_2OH P(=O)(OH)(NH_2) –C(=O)NHCN y grupos de fórmula

12 Un compuesto como se reivindica en una cualquiera de las reivindicaciones precedentes en donde L1 representa una unión $-CR_{11}R_{12}-$ $-CH_2CR_{11}R_{12}-$ $-OCR_{11}R_{12}-$ $-SCR_{11}R_{12}-$ $NR_{11}CH_2-$ o $-NR_{11}$ en donde R_{11} y R_{12} son independientemente hidrógeno o alquilo C_1-C_3 el enlace marcado con un asterisco es uno conectado al anillo que contiene X^1

13 Un compuesto como se reivindica en una cualquiera de reivindicaciones 1 a 11 en donde L1 representa $-CH_2-$ o $-CH(CH_3)-$

14 Un compuesto como se reivindica en una cualquiera de las reivindicaciones precedentes en donde Ar^3 es fenil tienil naftilo o 2 3- o 4-pirdil cualquiera de los cuales es opcionalmente sustituido

15 Un compuesto como se reivindica en la reivindicación 14 en donde sustituyentes opcionales en Ar^3 son seleccionados de fluor cloro bromo alquilo (C_1 C_3) trifluorometil alcoxi (C_1 C_3) trifluorometoxi trifluometiltio dimetilamino ciano (C_1 C_3alquilo)SO_2- NH_2SO_2- (C_1 C_3alquilo)$NHSO_2-$ (C_1-C_3alquilo)$_2NSO_2-$ -$CONR^AR^B$ y NR^BCOR^A en donde R^A y R^B son independientemente hidrógeno o un (C_1 C_6)alquilo group o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico

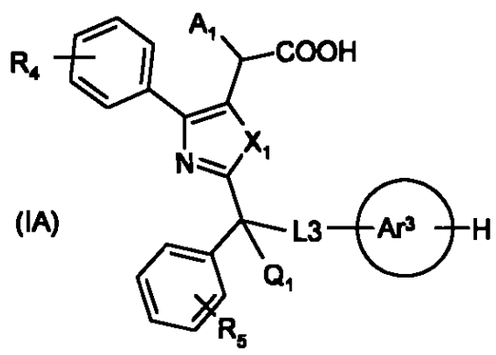
16 Un compuesto como se reivindica en una cualquiera de las reivindicaciones precedentes en donde L2 es una unión y Ar^2 es un anillo opcionalmente sustituido por fenilo tienilo furanilo pirrolilo o pirdilo

17 Un compuesto como se reivindica en la reivindicación 16 en donde sustituyentes opcionales en Ar^2 son seleccionados de fluor cloro bromo alquilo (C_1 C_3) trifluorometil alcoxi (C_1 C_3) trifluorometoxi trifluometiltio dimetilamino ciano (C_1 C_3alquilo)SO_2- NH_2SO_2- (C_1-C_3alquilo)$NHSO_2-$ (C_1-C_3alquilo)$_2NSO_2-$ -$CONR^AR^B$ y

NR^BCOR^A en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1-C_8) o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico

18 Un compuesto como se reivindica en una cualquiera de las reivindicaciones precedentes en donde s es 0

19 Un compuesto de la fórmula (IA) o una sal hidrato o solvato de éste



en donde A_1 es hidrógeno o metil X_1 Q_1 Ar^3 y L3 como se definió en la reivindicación 1 y R_4 y R_5 independientemente representa hidrógeno o uno o más sustituyentes opcionales

20 Un compuesto como se reivindica en la reivindicación 19 en donde A_1 es hidrógeno

21 Un compuesto como se reivindica en la reivindicación 19 o reivindicación 20 en donde Q_1 es hidrógeno

22 Un compuesto como se reivindica en una cualquiera de reivindicaciones 19 a 21 en donde X_1 es –S

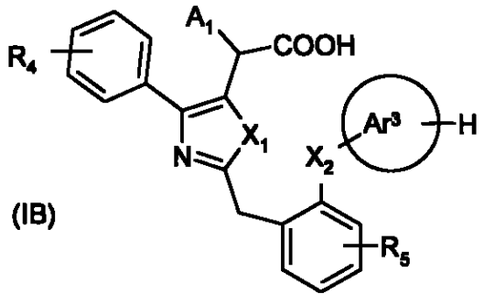
23 Un compuesto como se reivindica en una cualquiera de reivindicaciones 19 a 22 en donde Ar^3 fenilo es opcionalmente sustituido

24 Un compuesto como se reivindica en una cualquiera de reivindicaciones 19 a 23 en donde L3 es una unión O –S- o –NR en donde R es hidrógeno o C_1 C_3 alquilo

25 Un compuesto como se reivindica en la reivindicación 19 en donde A_1 es hidrógeno Q_1 es hidrógeno X_1 es –S Ar^3 es opcionalmente sustituido fenil y L3 es enlace

26 Un compuesto como se reivindica en una cualquiera de reivindicaciones 19 a 25 en donde sustituyentes opcionales R_4 y R_5 y sustituyentes opcionales en Ar^3 son independientemente seleccionados de fluor cloro bromo alquilo (C_1 C_3) trifluorometil alcoxi (C_1 C_3) trifluorometoxi trifluometiltio dimetilamino ciano (C_1-C_3alquilo)SO_2- NH_2SO_2- (C_1 C_3alquilo)$NHSO_2$- (C_1-C_3alquilo)$_2NSO_2$- $CONR^AR^B$ y NR^BCOR^A en donde R^A y R^B son independientemente hidrógeno o un grupo (C_1-C_8)alquilo o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico

27 Un compuesto de la fórmula (IB) o una sal hidrato o solvato de éste



(IB)

en donde A_1 es hidrógeno o metil X_2 es una unión –CH_2- O- –S o –NR en donde R es hidrógeno o C_1 C_3 alquilo y X_1 y Ar^3 como se definió en la reivindicación 1 y R_4 y R_5 independientemente representa hidrógeno o uno o más sustituyentes opcionales

28 Un compuesto como se reivindica en la reivindicación 27 en donde A_1 es hidrógeno

29 Un compuesto como se reivindica en la reivindicación 27 o reivindicación 28 en donde X_1 es –S-

30 Un compuesto como se reivindica en una cualquiera de reivindicaciones 27 a 29 en donde Ar^3 es opcionalmente fenilo sustituido

31 Un compuesto como se reivindica en una cualquiera de reivindicaciones 27 a 30 en donde X_2 es $-CH_2-$ o un enlace

32 Un compuesto como se reivindica en una cualquiera de reivindicaciones 27 a 31 en donde sustituyentes opcionales R_4 y R_5 sustituyentes opcionales en Ar^3 son independientemente seleccionados de fluor cloro bromo (C_1-C_3)alquilo trifluorometil $(C_1 C_3)$alcoxi trifluorometoxi trifluorometiltio dimetilamino ciano $(C_1-C_3$alquilo$)SO_2-$ NH_2SO_2- $(C_1 C_3$alquilo$)NHSO_2-$ $(C_1-C_3$alquilo$)_2NSO_2-$ $CONR^AR^B$ y NR^BCOR^A en donde R^A y R^B son independientemente hidrógeno o un grupo (C_1-C_6)alquilo o R^A y R^B están ligados al mismo átomo de N para formar un anillo amino cíclico

33 Un compuesto seleccionados del grupo que consiste de

ácido acético [2 benzidril-4-(4-clorofenil)-tiazol-5 il]-
ácido acético [2 benzidril-4 (4-fluoro-fenil)-tiazol-5-il]
ácido acético [2-[1-(4-cloro-fenil)-2 fenil-etil]-4-(4-fluoro-fenil) tiazol 5 il]-
ácido acético {4-(4-cloro-fenil)-2-[(4-cloro-fenil) fenil-metil]-tiazol-5-il}
ácido acético [2-[(4-cloro-fenil) fenil metil]-4-(4-fluoro-fenil)-tiazol-5-il]
ácido acético [2-[bis-(4-fluoro-fenil) metil]-4-(4-fluoro-fenil)-tiazol-5-il]
ácido acético {4-(4-fluoro-fenil) 2 [(4-metoxi fenil) fenil metil]-tiazol-5-il}-
ácido acético {4-(4-cloro-fenil)-2-[(4-metoxi fenil) fenil-metil] tiazol 5-il}-
ácido acético [2-[(3 4-difluoro-fenil)-fenil-metil]-4-(4 fluoro-fenil)-tiazol-5 il]-
ácido acético [2-[bis-(4-metoxi-fenil) metil]-4-(4-fluoro-fenil) tiazol 5-il]-
ácido acético [2 benzidril-4-(3-fluoro-fenil) tiazol 5-il]
ácido acético [2-[bis-(4-fluoro-fenil) metil]-4-(3 4 difluoro-fenil) tiazol-5-il]
ácido acético [2 benzidril-4-(3 4-difluoro-fenil) tiazol-5-il]
ácido acético [2-[bis-(4-fluoro-fenil)-metil]-4-(3-fluoro-fenil) tiazol 5-il]

y hidratos de sales y solvatos de estos

129

34 Una composición farmacéutica comprende un compuesto como se reivindica en una cualquiera de reivindicaciones 1 a 33 junto con un portador farmacéuticamente aceptable

35 El uso de un compuesto como se reivindica en una cualquiera de reivindicaciones 1 a 33 en la fabricación de una composición para el tratamiento de una enfermedad sensible a la modulación de la actividad de un receptor CRTH2

36 Un método para el tratamiento de una enfermedad sensible a la modulación de la actividad de un receptor CRTH2 que comprende administrar a un sujeto que sufre de dicha enfermedad y una cantidad efectiva de un compuesto como se reivindica en una cualquiera de reivindicaciones 1 a 33

37 Como se reivindica la reivindicación 35 o un método como se reivindica en la reivindicación 36 en donde la enfermedad está asociada con un elevado nivel de prostaglandina D2 (PGD2) o uno o más metabolitos activos de estos

38 El uso de un método como se reivindica en la reivindicación 37 en donde la enfermedad es una enfermedad inflamatoria auto inmune respiratoria o alérgica

39 El uso de un método como se reivindica en la reivindicación 37 en donde la enfermedad incluye asma rinitis síndrome alérgico de vías aéreas rinobronquitis alérgica bronquitis enfermedad pulmonar obstructiva crónica (COPD) poliposis nasal sarcoidosis pulmón de campesino pulmón fibroide fibrosis cística tos crónica conjuntivitis dermatitis atópica enfermedad de Alzheimer esclerosis lateral amiotrófica complejo de demencia de SIDA enfermedad de Huntington demencia frontotemporal demencia del cuerpo Lewy demencia vascular síndrome de Guillain Barre poliradiculoneuropatía desmielinizante crónica neuropatía motora multifocal plexopatia esclerosis multiple encefalomielitis panencefalitis degeneración cerebelar y en encefalomielitis trauma del CNS migraña ataques artritis reumatoide espondilitis anquilosante enfermedad de Behçet s bursitis síndrome del tunel carpiano enfermedad del intestino inflamatorio enfermedad de Crohn colitis ulcerativa dermatomiositis Síndrome de Ehlers-Danlos (EDS) fibromialgia dolor miofacial osteoartritis (OA) osteonecrosis artritis sonatica síndrome de Reiter's (artritis reactiva) sarcoidosis esclerodema Síndrome de Sjogren enfermedad de

130

tejido blando Enfermedad de Still tendinitis poliartentis Nodossa Granulomatisis de Wegener miositis (polimiositis dermatomiositis) gota arteroscleroSis lupus entematoso lupus sistémico entematoso (SLE) diabetes tipo I síndrome nefrítico glomerulonefritis falla renal aguda y crónica fascitis eosinofilia síndrome hiper IgE sepsis choque séptico daño por reperfusión isquémica en el corazón rechazo de aloinjerto después de transplantes y enfermedad de injerto versus huésped

40 El uso de un método como se reivindica en la reivindicación 37 en donde la enfermedad incluye asma rinitis síndrome alérgico de vías aéreas y ndobronquitis alérgica

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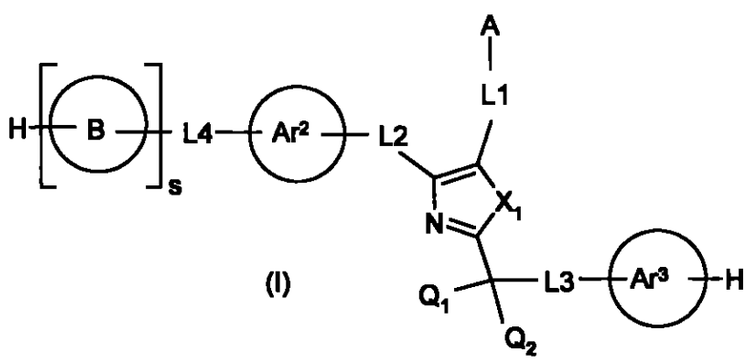
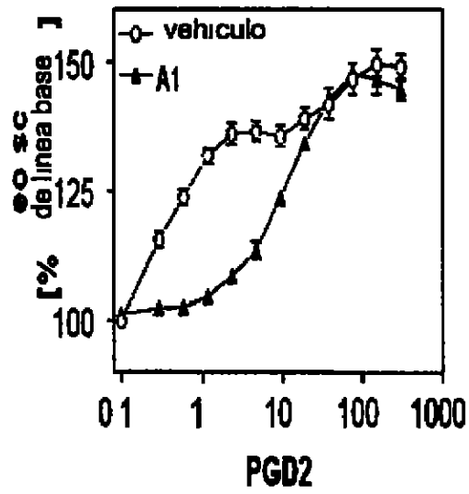
RESUMEN

Los compuestos de la fórmula (I) el tratamiento de una enfermedad que responde a la modulación de la actividad del receptor CRTH2 como es asma rinitis síndrome alérgico de vías aéreas y rdobronquitis alérgica



(I)

en donde **X1 es -S-, -O -N=N –NR7 -CR7=CR8-, -CR7=N en donde R7 y R8 son independientemente hidrógeno o alquilo C1-C3 A es un grupo carboxilo –COOH o un carboxili bioisostere** Los anillos Ar^2 y Ar^3 independientemente cada uno representa un fenilo o un anillo heterocíclico de 5 o 6 miembros o un sistema de anillo bicíclico que consiste de un anillo carbocíclico de 5 o 6 miembros que está benzofusionado a un anillo heteroarilo monocíclico de 5 o 6 miembros dicho anillo o sistema de anillo es opcionalmente sustituido El anillo B es como se definió Ar^2 y Ar^3 o un anillo N pirrolidinilo N piperidinilo o N azepinilo opcionalmente sustituido **s** es 0 o 1 **L1 L2 y L4** son radicales ligadores como se define en la descripción Q_1 y Q_2 representa sustituyentes como se define en la descripción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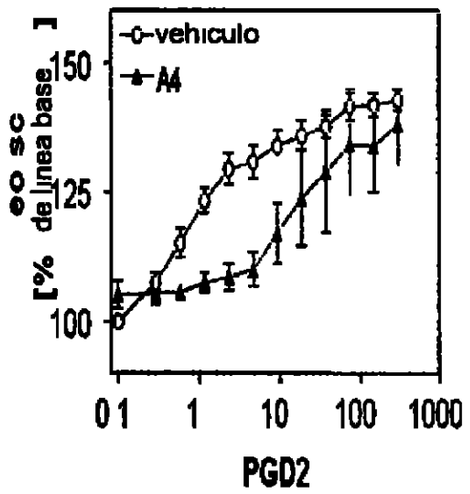
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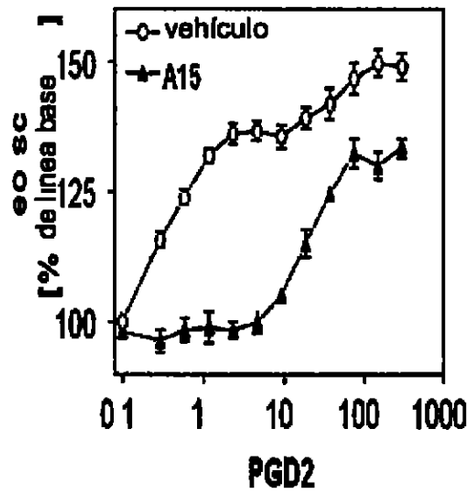
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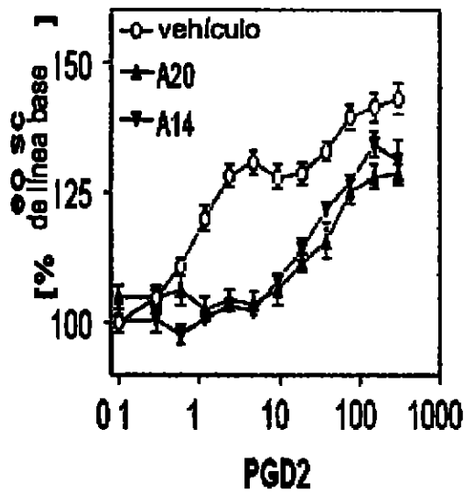
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To

see form PCT/ISA/220

PCT

RECD 27 SEP 2005
WIPO PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis* 1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/005882	30.05.2005	29 05.2004

International Patent Classification (IPC) or both national classification and IPC
C07D277/30 C07D417/06 C07D417/04, A61K31/426 A61K31/427 A61P11/06

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") However this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66 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 three 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	Authorized Officer
European Patent Office D-80298 Munich Tel +49 89 2399 0 Tx 523656 epmu d Fax +49 89 2399 4465	Kollmannsberger M Telephone No +49 89 2399-7364

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTH RITY

International application No
PCT/EP2005/005882

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 unless otherwise indicated under this item

☐ This opinion has been established on the basis of a translation from the original language into the following language which is the language of a translation furnished for the purposes of international search (under Rules 12 3 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

☒ in written format

☒ in computer readable form

c time of filing/furnishing

☐ contained in the international application as filed

☐ filed together with the international application in computer readable 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

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/EP2005/005882

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 37-40

because

☒ the said international application or the said claims Nos 37-40 relate to the following subject matter which does not require an international preliminary examination *(specify)*

see separate sheet

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

☒ the claims or said claims Nos 1-32 34-40 (in part) are so inadequately supported by the description that no meaningful opinion could be formed

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

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

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

☐ See separate sheet for further details

WRITTEN OPINION F THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/EP2005/005882

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	27-33 (in part)
	No	Claims	1-26,34-40
Inventive step (IS)	Yes	Claims	27-33 (in part)
	No	Claims	1-26,34-40
Industrial applicability (IA)	Yes	Claims	1-36
	No	Claims	

2 Citations and explanations

see separate sheet

13 X

Re Item III

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

III 1 The present claim 1 contains almost no fixed structural element and relates to an extremely large number of possible compounds Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds see examples 1-46 which all have a very similar structure Additionally the claims are so broadly drafted that they include a large number of known compounds The initial phase of the search revealed thus a very large number of documents relevant to the issue of novelty So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject matter for which protection might legitimately be sought (Article 6 PCT) The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claims (PCT Guidelines 9 19 and 9 23)

The search was restricted to those claimed compounds which appear to be supported and a generalisation of their structural formulae namely compounds of dependent claims 18 and 27 In which additionally the central moiety is a five-membered ring (i e thiazole oxazole or imidazole) Only illustrative documents have been cited for other parts of the claims The discussion under item V below is thus only complete for searched subject matter

III 2 Claims 37-40 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67 1(iv) PCT Consequently no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4)(a)(I) PCT)

Re Item V

Reasoned statement with regard to novelty inventive step or industrial applicability citations and explanations supporting such statement

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTH RITY (SEPARATE SHEET)

International application No PCT/EP2005/005882

V 1 Prior Art

The following documents have been cited

D1 WO 99/02505 A (JANSSEN PHARMACEUTICA N V LACRAMPE JEAN FERNAND ARMAND FREYNE ED) 21 January 1999 (1999-01 21)

D2 WO 01/10866 A (JANSSEN PHARMACEUTICA N V LACRAMPE JEAN FERNAND ARMAND FREYNE ED) 15 February 2001 (2001 02 15)

D3 EP A-0 987 265 (JANSSEN PHARMACEUTICA N V) 22 March 2000 (2000-03-22)

D4 US B1-6 268 363 (LEE HYUN IL ET AL) 31 July 2001 (2001 07-31)

D5 WO 03/006015 A (BRISTOL MYERS SQUIBB PHARMA COMPANY) 23 January 2003 (2003-01 23)

D6 WO 03/101981 A (ASTRAZENECA AB BIRKINSHAW TIMOTHY BONNERT ROGER COOK, ANTHONY RA) 11 December 2003 (2003 12 11)

D7 NAGATOMI H ET AL STUDIES ON THE ANTI-INFLAMMATORY ACTIVITY AND ULCEROGENIC ADVERSE EFFECT OF THIAZOLE DERIVATIVES ESPECIALLY 2-AMINO-THIAZOLEACETIC ACID DERIVATIVES ARZNEIMITTEL FORSCHUNG DRUG RESEARCH EDITIO CANTOR VERLAG AULENDORF DE vol 5 no 34 1984 pages 599-603 XP001074027 ISSN 0004-4172

D8 BONINA F ET AL SYNTHESIS AND ANALGESIC ANTIINFLAMMATORY ACTIVITIES OF 2 ARYLETHENYL-4-ARYLTHIAZOLE 5-ACETIC ACIDS IL FARMACO ROME IT vol 42 no 12 December 1987 (1987 12) pages 905-913 XP001069993 ISSN 0014-827X

In the following paragraphs references to the above documents relate to the parts indicated in the search report unless specified otherwise

V 2 Novelty (Art. 33(2) PCT)

Although the search was not complete (cf item III 1 above) it is clear that claims 1 26 34-40 are not novel over D1 D5 it is noted that D1 D3 disclose the compounds for the same use i e the treatment of asthma

Claims 27 33 are novel over the cited documents D1 D5 do not disclose benzyl-substituted thiazoles D6 discloses indoles as central moiety and the compounds of D7 and D8 lack the second aryl moiety

V 3 Inventive step (Art. 33(3) PCT)

Claims which are not novel also do not fulfil Art. 33(3) PCT For novel parts of the claims (i e claims 27-33 as far as they have been searched) D6 is seen as closest state of the art since D6 also discloses compounds which have anti inflammatory properties and act as CRTH2 receptor ligands The difference of the present claims with respect to D6 is essentially the replacement of the central indole by a thiazole/oxazole/imidazole From the cited documents it could not be foreseen that the resulting compounds would act as CRTH2 receptor ligands These claims fulfil thus Art 33(3) PCT

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant s or agent f1 reference TM1A	**FOR FURTHER ACTION** See item 4 below	
International application No. PCT/EP2005/005882	International filing date *(day/month/year)* 30 May 2005 (30.05 2005)	Priority date *(day/month/year)* 29 May 2004 (29 05.2004)
International Patent Classification (8th edition unless older edition ndicated) See relevant information in Form PCT/ISA/237		
Applicant 7TM PHARMA A/S		

1 This nternational preliminary report on patentability (Chapte I) is issued by the International Bureau on behalf of th International Searching Authority under Rul 44 *bis* 1( )

Th REPORT co nsists f total f 8 heets nc.lud ng th cover sheet

I the ttached sheets, any ref rence to the written opinion f the I ternational Searching Authority should be read as ref rence to the international preliminary report on patentab l ty (Chapter I) nstead.

3 This report co tains ndcation relating to the following items

- ☒ Box N I — Basis of the report
- ☐ Box N II — Priority
- ☒ Box N III — Non-establ shment f pi io w th regard to novelty ve tlvt. step and l l stri l applicabl ty
- ☐ Box N IV — Lack of unity of inventio
- ☒ Box N V — Reasoned stat ment nder Article 35(2) with regard to novelty l ventive step or ind stri l applicability itations and explanatio s pp rt g such t t. ent
- ☐ B N VI — Certain documents ted
- ☐ B N VII — Certain defects the internat nal applicat
- ☐ Box N VIII — Certain observations on the t rnational application

4 The International Bureau will commu icate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis* 1 but not except wh re the applicant makes an express request und.r Arti le 23(*), before the expiration of 30 mo ths from the priority date (R l 44*bis* 2)

	Date of issuance f this report 29 November 2006 (29 11 2006)
The I ternational Bureau of WIPO 34 chemin des Colombettes 1 11 Genev 0, Switzerland Facs l No +41 ?? 338 8? 70	Authorized off cer Yolaine Cussac e-m ll pt11@w po.i t

Form PCT/IB/373 (January ..004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To

see form PCT/ISA/220

PCT RECD 27 SEP 2005
WIPO PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis* 1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/005882	30 05 2005	29 05 2004

International Patent Classification (IPC) or both national classification and IPC
C07D277/30 C07D417/06, C07D417/04, A61K31/426 A61K31/427 A61P11/06

Applicant
7TM PHARMA A/S

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- ☒ Box No V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty inventive step or industrial applicability citations and explanations supporting such statement
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- ☐ Box No VII Certain defects in the international application
- ☐ Box No VIII Certain observations on the international application

2. **FURTHER ACTION**

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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	Authorized Officer
European Patent Office D-80298 Munich Tel +49 89 2399 0 Tx 523656 epmu d Fax +49 89 2399 4465	Kollmannsberger M Telephone No +49 89 2399-7364

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION F THE INTERNATI NAL SEARCHING AUTH RITY

International application No
PCT/EP2005/005882

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 unless otherwise indicated under this item

☐ This opinion has been established on the basis of a translation from the original language into the following language which is the language of a translation furnished for the purposes of international search (under Rules 12 3 and 23 1(b))

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a type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b format of material

☒ in written format

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c. time of filing/furnishing

☐ contained in the international application as filed

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☒ 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

WRITTEN OPINION OF THE INTERNATI NAL SEARCHING AUTHORITY

International application No
PCT/EP2005/005882

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 37-40

because

☒ the said international application or the said claims Nos 37-40 relate to the following subject matter which does not require an international preliminary examination *(specify)*

see separate sheet

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

☒ the claims or said claims Nos 1-32 34-40 (in part) are so inadequately supported by the description that no meaningful opinion could be formed

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

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

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

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/EP2005/005882

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	27-33 (in part)
	No	Claims	1-26 34-40
Inventive step (IS)	Yes	Claims	27-33 (in part)
	No	Claims	1-36 34-40
Industrial applicability (IA)	Yes	Claims	1-36
	No	Claims	

2 Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No
PCT/EP2005/005882

Re Item III

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

III 1 The present claim 1 contains almost no fixed structural element and relates to an extremely large number of possible compounds Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds see examples 1-46 which all have a very similar structure Additionally the claims are so broadly drafted that they include a large number of known compounds The initial phase of the search revealed thus a very large number of documents relevant to the issue of novelty So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject matter for which protection might legitimately be sought (Article 6 PCT) The non-compliance with the substantive provisions is to such an extent that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claims (PCT Guidelines 9 19 and 9 23)

The search was restricted to those claimed compounds which appear to be supported and a generalisation of their structural formulae namely compounds of dependent claims 18 and 27 in which additionally the central moiety is a five-membered ring (i e thiazole oxazole or imidazole) Only illustrative documents have been cited for other parts of the claims The discussion under item V below is thus only complete for searched subject matter

III 2 Claims 37-40 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67 1(iv) PCT Consequently no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4)(a)(I) PCT)

Re Item V

Reasoned statement with regard to novelty Inventive step or industrial applicability citations and explanations supporting such statement

V 1 Prior Art

The following documents have been cited

D1 WO 99/02505 A (JANSSEN PHARMACEUTICA N V LACRAMPE JEAN FERNAND ARMAND FREYNE ED) 21 January 1999 (1999-01 21)

D2 WO 01/10866 A (JANSSEN PHARMACEUTICA N V LACRAMPE JEAN FERNAND ARMAND FREYNE ED) 15 February 2001 (2001 02 15)

D3 EP A-0 987 265 (JANSSEN PHARMACEUTICA N V) 22 March 2000 (2000-03-22)

D4 US B1 6 268 363 (LEE HYUN IL ET AL) 31 July 2001 (2001 07-31)

D5 WO 03/006015 A (BRISTOL MYERS SQUIBB PHARMA COMPANY) 23 January 2003 (2003-01 23)

D6 WO 03/101981 A (ASTRAZENECA AB BIRKINSHAW TIMOTHY BONNERT ROGER COOK ANTHONY RA) 11 December 2003 (2003 12 11)

D7 NAGATOMI H ET AL STUDIES ON THE ANTI INFLAMMATORY ACTIVITY AND ULCEROGENIC ADVERSE EFFECT OF THIAZOLE DERIVATIVES ESPECIALLY 2-AMINO-THIAZOLEACETIC ACID DERIVATIVES ARZNEIMITTEL FORSCHUNG DRUG RESEARCH EDITIO CANTOR VERLAG AULENDORF DE vol 5 no 34 1984 pages 599-603 XP001074027 ISSN 0004-4172

D8 BONINA F ET AL SYNTHESIS AND ANALGESIC ANTIINFLAMMATORY ACTIVITIES OF 2 ARYLETHENYL-4-ARYLTHIAZOLE 5-ACETIC ACIDS IL FARMACO ROME IT vol 42 no 12, December 1987 (1987 12) pages 905-913 XP001069993 ISSN 0014-827X

In the following paragraphs references to the above documents relate to the parts indicated in the search report unless specified otherwise

V 2 Novelty (Art 33(2) PCT)

Although the search was not complete (cf item III 1 above) it is clear that claims 1 26 34-40 are not novel over D1 D5 It is noted that D1 D3 disclose the compounds for the same use i e the treatment of asthma

Claims 27-33 are novel over the cited documents D1 D5 do not disclose benzyl substituted thiazoles D6 discloses Indoles as central moiety and the compounds of D7 and D8 lack the second aryl moiety

V-3 Inventive step (Art 33(3) PCT)

Claims which are not novel also do not fulfil Art. 33(3) PCT For novel parts of the claims (i e claims 27-33 as far as they have been searched) D6 is seen as closest state of the art since D6 also discloses compounds which have anti inflammatory properties and act as CRTH2 receptor ligands The difference of the present claims with respect to D6 is essentially the replacement of the central indole by a thiazole/oxazole/imidazole From the cited documents it could not be foreseen that the resulting compounds would act as CRTH2 receptor ligands These claims fulfil thus Art 33(3) PCT

[redacted]

FORMATO DE DIGITALIZACIO
RELACION DE ANEXOS

Royal Technologies S.A

Item		Expediente No 06-129530	No de Folio
		No de unidades	√
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA X	1	✓
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS		

Observaciones

CONTIENE AUTO FINAL

149

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 06-129530 -00000-0000
Fec 2006-12-27 16 14 29 Dep 2020 NUECREACIONES
Tra. 11 PATENTEIYII
Eva. 378 FASENACIONALI
Act 411 PRESENTACION Folios 148

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 [ ]
- Dibujos de ser estos pertinentes [ ]
- 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 27 DIC. 2006

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

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá
2020

Doctor(a)
RODRIGUEZ DILIA MARIA

880

REFERENCIA	Radicación No	06 129530
	Solicitud internacional	PCT/EP2005/005882
	Fecha inicio fase nacional	29/12/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No	1932

Como resultado del examen de forma realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT) regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio se le comunica que

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

2 La solicitud no contiene el poder debidamente otorgado con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil Adicionalmente deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante cuando ésta fuere persona jurídica

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2 literal e) del capítulo quinto del título primero de la Circular Unica No 10 de 2001

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 09 FEB. 2007
adpa10