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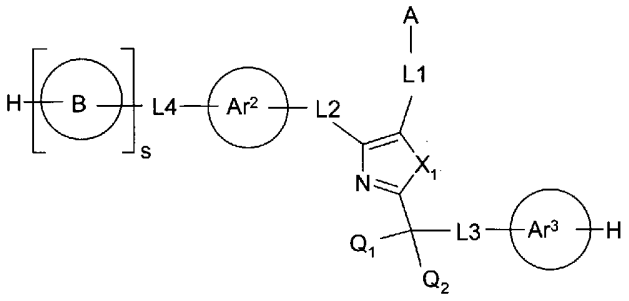
(54) Title: SUBSTITUTED THIAZOLEACETIC AS CRTH2 LIGANDS



(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_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, L2 and L4 are linker radicals as defined in the description; $Q_1$and Q_2 represent substituents as defined in the description.

WO 2005/116001 A1

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 03/101981, GB 2388540, WO 04/089885 and WO 05/018529.

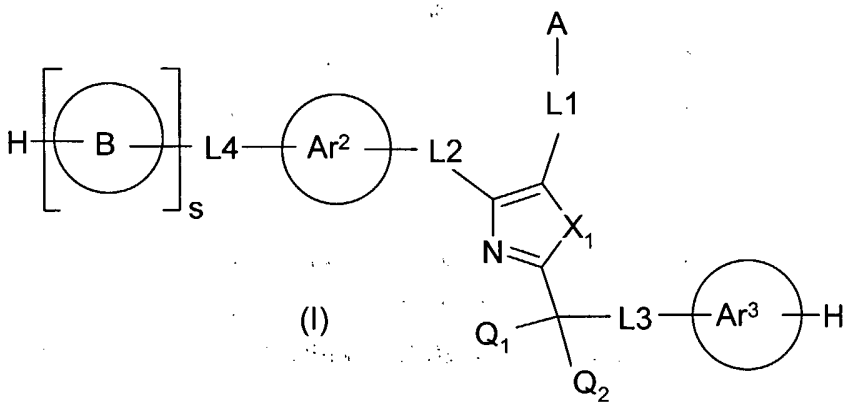
NSAIDs (non-steroidal anti-inflammatory drugs) constitute another class of anti-infalmmatory agents. One NSAID is 4-(4-chlorophenyl)-2-phenyl thiazole-5 acetic acid (fentiazac). Some other thiazole compounds have been investigate as anti-inflammatory agents (see for example Nagatomi et. al. Arzneimittel-Forschung (1984), 34(5), 599-603; Bonina et. al. Farmaco, Edizione Scientifica (1987), 42(12, 905-13; Gieldanowski 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 $H(B)_sL4Ar^2L2$ and either the ring containing X_1 or the ring containing X_1 together with the $H(Ar^3)L3C(Q_1)(Q_2)$- 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-, $H(B)_sL4Ar^2L2$- 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 polyradiculoneurophathy, multifocal motor neuropathy, plexopathy, multiple sclerosis, encephalomyelitis, panencephalitis, cerebellar degeneration and encephalomyelitis, CNS trauma, migraine, stroke, rheumatoid arthritis, ankylosing spondylitis, Behçet's Disease, bursitis, carpal tunnel syndrome, inflammatory bowel disease, Crohn´s disease, ulcerative colitis, dermatomyositis, Ehlers-Danlos Syndrome (EDS), fibromyalgia, myofascial pain, osteoarthritis (OA), osteonecrosis, psoriatic arthritis, Reiter's syndrome (reactive arthritis), sarcoidosis, scleroderma, Sjogren's Syndrome, soft tissue disease, Still's Disease, tendinitis, polyarteritis Nodossa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis, lupus erythematosus, systemic lupus erythematosus (SLE), type I diabetes, nephritic syndrome, glomerulonephritis, acute and chronic renal failure, eosinophilia fascitis, hyper IgE syndrome, sepsis, septic shock, ischemic reperfusion injury in the heart, allograft rejection after transplantations, and graft versus host disease.

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

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

As used herein the term "divalent (C_a-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-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-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-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-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.

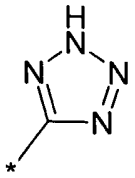
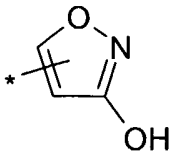
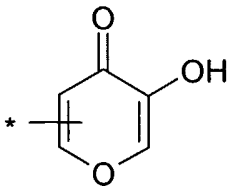
As used herein the term "cycloalkyl" refers to a monocyclic saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

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, pyridazinyl, triazinyl, indolyl and indazolyl.

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

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, benzenesunfonic, glutamic, lactic, and mandelic acids and the like.

Compounds with which the invention is concerned which may exist in one or more stereoisomeric form, because of the presence of asymmetric atoms or rotational restrictions, can exist as a number of stereoisomers with R or S stereochemistry at each chiral centre or as atropisomeres with R or S stereochemistry at each chiral axis. The invention includes all such enantiomers and diastereoisomers and mixtures thereof.

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

For use in accordance with the 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 $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkylthio, halo, fully or partially fluorinated $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy or $(C_1\text{-}C_3)$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 $(C_1\text{-}C_6)$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, $(C_1\text{-}C_3)$alkyl, trifluoromethyl, $(C_1\text{-}C_3)$alkoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, cyano, $(C_1\text{-}C_3$alkyl$)SO_2$-, NH_2SO_2-, $(C_1\text{-}C_3$alkyl$)NHSO_2$-, $(C_1\text{-}C_3$alkyl$)_2NSO_2$-, $-CONR^AR^B$, and $-NR^BCOR^A$. wherein R^A and R^B are independently hydrogen or a $(C_1\text{-}C_6)$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 $C_1\text{-}C_3$ alkyl; or

L3 represents a divalent radical of formula $-(Alk^3)_m\text{-}(Z)_n\text{-}(Alk^2)_p$- wherein m is 0, n is 1, and Z is a phenylene radical optionally substituted by one or more of fluoro, chloro, bromo, $(C_1\text{-}C_3)$alkyl, trifluoromethyl, $(C_1\text{-}C_3)$alkoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, cyano, $(C_1\text{-}C_3$alkyl$)SO_2$-, NH_2SO_2-, $(C_1\text{-}C_3$alkyl$)NHSO_2$-, $(C_1\text{-}C_3$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 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;

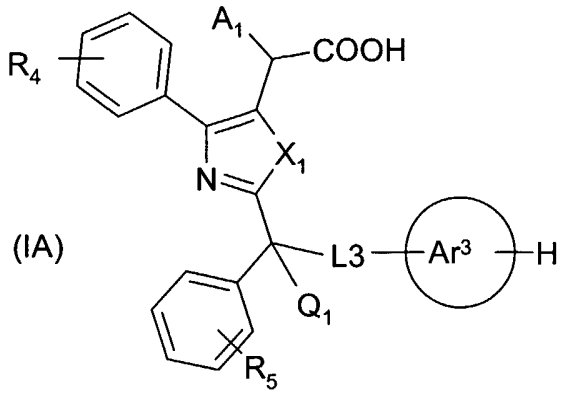
L1 is a bond, $-CR_{11}R_{12}$-, *$-CH_2CR_{11}R_{12}$-, *$-OCR_{11}R_{12}$-, *$-SCR_{11}R_{12}$-, *$-NR_{11}CH_2$- or $-NR_{11}$- wherein R_{11} and R_{12} are independently hydrogen or C_1-C_3 alkyl, the bond marked with an asterisk being the one connected to the ring containing X^1. For example L1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

Ar^3 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 preferrd that

A_1 is hydrogen,

Q_1 is hydrogen,

X_1 is –S-,

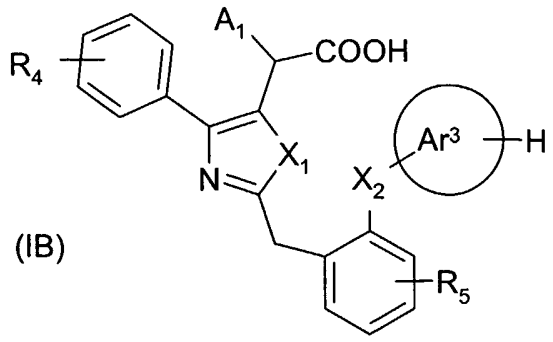
Ar^3 is optionally substituted phenyl,

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 iand 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.

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.

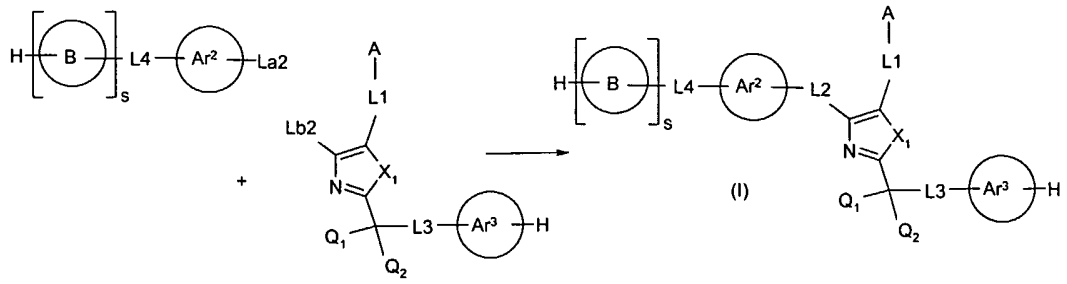
In the case of arthritis and related inflammatory diseases other known drugs include glucocorticoids, NSAIDs (Non Steroidal Anti-Inflammatory Drugs – conventional prostaglandin synthesis inhibitors, COX-2 inhibitors, salicylates), and DMARDs (disease-modifying anti-rheumatic drugs such as methotrexate,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

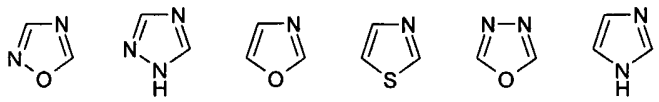
The linker L2 can be formed by joining two appropriately functionalised and, if needed, suitably protected fragments containing La2 and Lb2 as reactive moieties as outlined below. La2 and Lb2 are defined as any moieties that can react by e.g. a nucleophilic substitution, addition to multiple bonds or 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 $H-Z-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$ 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"-$CO-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$ or "leaving group"-$SO_2-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$, respectively. Alternatively, the conversion can be made directly with the acids $HO-CO-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$ and $HO-SO_2-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$, 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 $OCN-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$ 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.

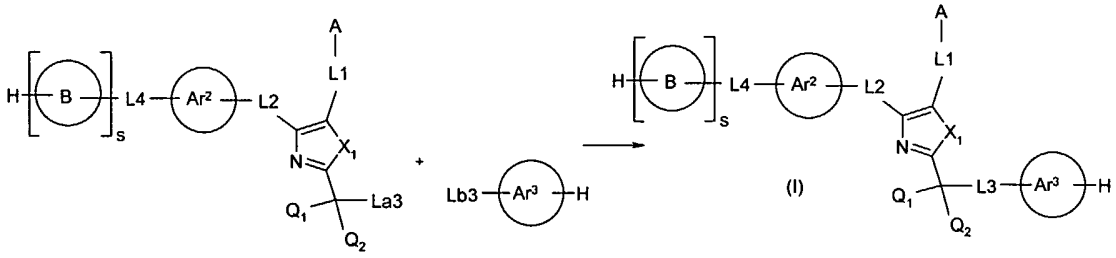
Likewise, L2 being $-(Alk^1)_m-Z-(Alk^2)_p-$ wherein Z is a 5-membered heterocyclic system exemplified by



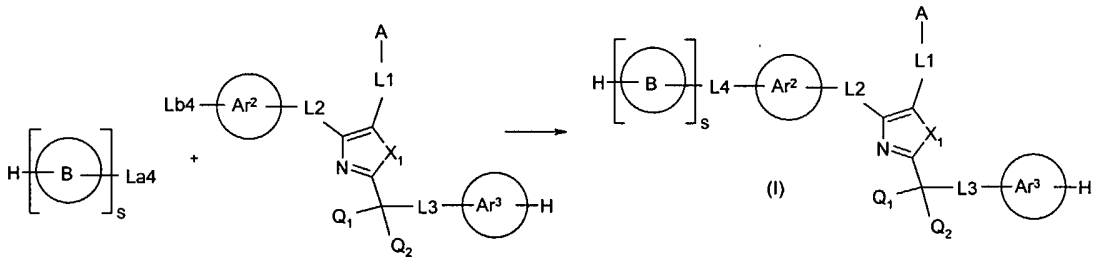
can be made according to standard cyclisation procedures using appropriate solvents, catalysts and temperatures. For example, formation of 1,2,4-triazole can be made with La2 being acylhydrazide and Lb2 being amide or thioamide or the reverse orientation of La2 and Lb2. 1,2,4-Oxadiazole can be formed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

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.

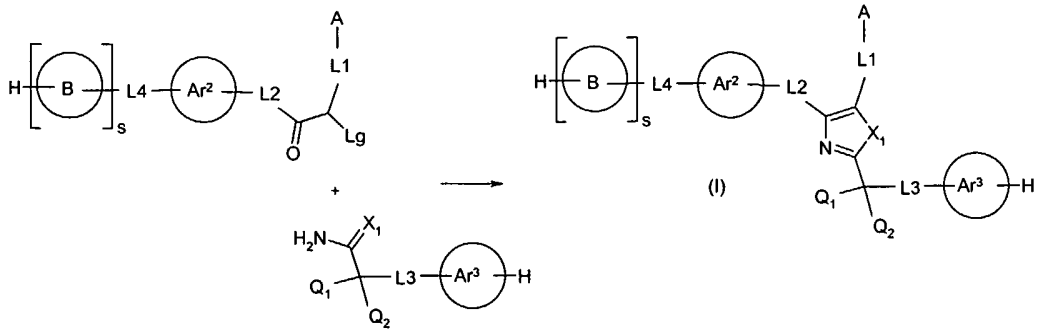


and

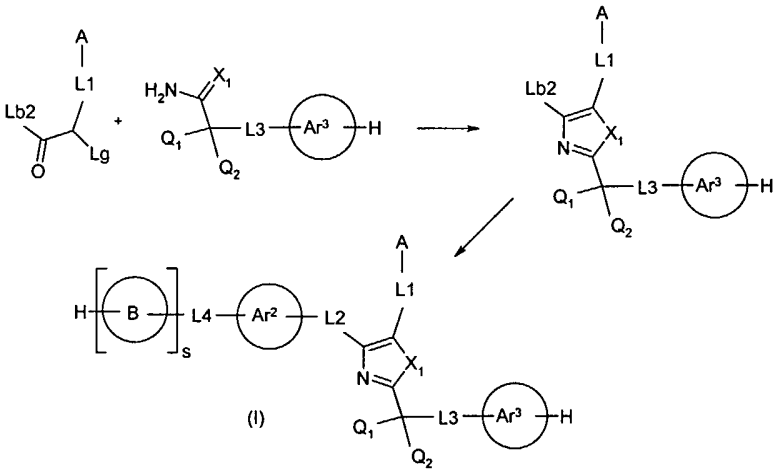


The Ar^1 moiety can also be the central scaffold that is used in connecting the L1, L2 and L3 parts in a stepwise fashion. This can be done via aromatic substitutions of the Ar^1 core to attach L1, L2 and/or L3, which then can be further functionalised to give the final Formula I compounds.

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.

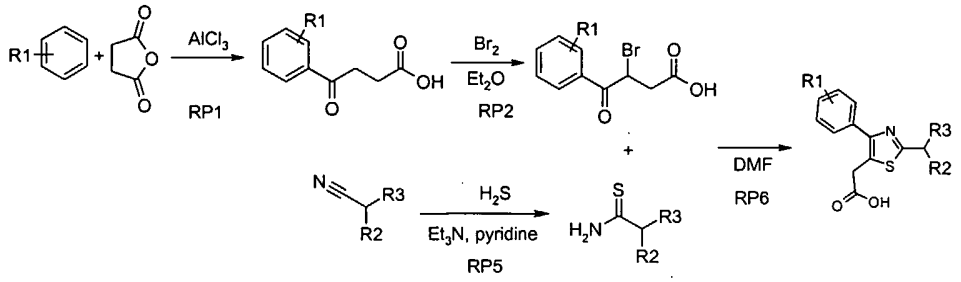
The Examples herein describe specific strategies for the synthesis of compounds (I) wherein X1 is S.

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:

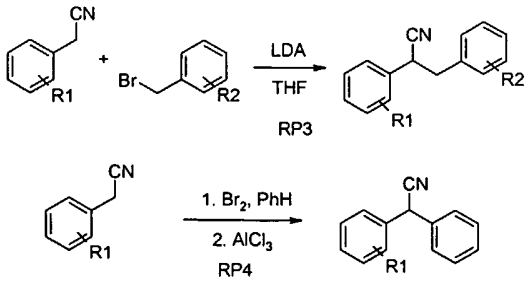
General comments:

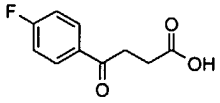
NMR spectra were obtained on a Bruker Avance AMX 300 MHz instrument. For some compounds only seleced characteristic ^{1}H NMR signals are reported. LC/MS was performed on an Agilent 1100-series instrument. LC/MS methods are as follows: An10p8: Column: XTerra MS C18; Flow: 1.0 mL/min; Gradient: 0-5 min: 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:





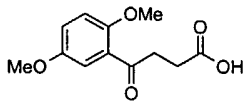
Intermediate-1

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

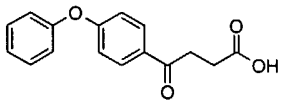
mmol) and cooled to -9 °C under nitrogen. $AlCl_3$ (2.67 g; 20 mmol) was added, and the temperature was kept between -9 and 0 °C for 4½ hours. The reaction was allowed to warm to room temperature and stirred over night. The reaction mixture was poured into aqueous 4 M HCl (10 ml) at 0 °C, and the precipitated 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:



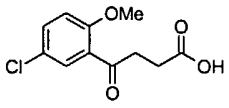
Intermediate-2

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).



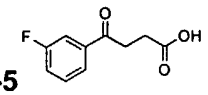
Intermediate-3

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

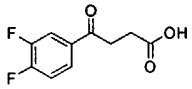
4-(5-Chloro-2-methoxy-phenyl)-4-oxo-butyric acid. ^{1}H NMR (DMSO-d_6): δ 2.53 (t, *J* = 6.6 Hz, 2H), 3.15 (t, *J* = 6.0 Hz, 2H), 3.90 (s, 3H), 7.23 (d, *J* = 8.9 Hz, 1H), 7.53 (d, *J* = 2.6 Hz, 1H), 7.60 (dd. *J* = 2.9, 8.9 Hz, 1H) and 12.11 (br s, 1H).



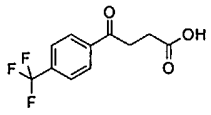
Intermediate-5

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)

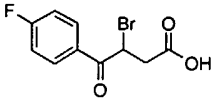
The following compounds were prepared by an analogous procedure:

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).

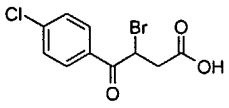
Intermediate-7 

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), 7.76 (d, *J* = 8.3 Hz, 2H), 8.10 (d, *J* = 8.3 Hz, 2H).

Intermediate-8 

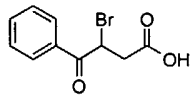
3-Bromo-4-(4-fluoro-phenyl)-4-oxo-butyric acid – Representative Procedure 2 (PR2): 4-(4-Fluoro-phenyl)-4-oxo-butyric acid (1.20 g, 6.12 mmol) was suspended in ether (10 mL) at room temperature. Bromine (0.34 ml, 6.73 mmol) was added drop-wise. After 4 hours, the reaction was concentrated and the residue 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:



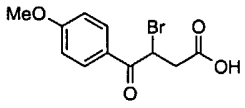
Intermediate-9

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).



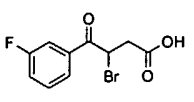
Intermediate-10

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).



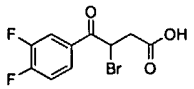
Intermediate-11

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).

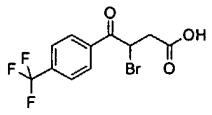


Intermediate-12

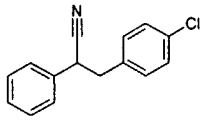
3-Bromo-4-(3-fluoro-phenyl)-4-oxo-butyric acid. ^{1}H NMR ($CDCl_3$): δ 3.18 (m, 1H), 3.54 (m, 1H), 5.39 (m, 1H), 7.34 (m, 1H), 7.50 (m, 1H), 7.83 (m, 2H) and 10.11 (br s, 1H).

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).

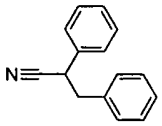
Intermediate-14 

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 

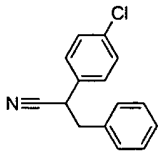
3-(4-Chloro-phenyl)-2-phenyl-propionitrile – Representative Procedure 3 (RP3): The reaction was preformed under N_2 in flame dried glassware. Benzylcyanide (1.2 mL, 10 mmol) was added slowly (over a period of 40 min) to a solution of LDA (10 mmol) in THF (10 mL) at -78°C. The mixture was stirred for 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:



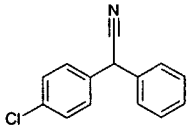
Intermediate-16

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

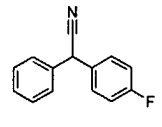
2-(4-Chloro-phenyl)-3-phenyl-propionitrile. ^{1}H NMR ($CDCl_3$): δ 3.16 (m, 2H) and 4.14 (t, *J* = 7.2 Hz, 1H).



Intermediate-18

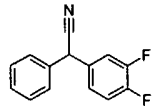
(4-Chloro-phenyl)-phenyl-acetonitrile – Representative Procedure 4 (RP4): The reaction was preformed under N_2 and flamedried glassware. 4-Chlorobenzyl cyanide (1 mL; 7.8 mmol) was dissolved in benzene (10 mL) and heated to reflux. Bromide (442 μL; 8.6 mmol) was added over 30 min. The mixture was stirred 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 7.36 (m, 9H). APT ($CDCl_3$): δ 42.42 (CH).

In an analogous way, the following compounds were made:

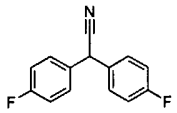


Intermediate-19

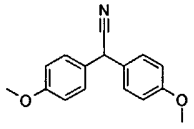
(4-Fluoro-phenyl)-phenyl-acetonitrile. ^{1}H NMR ($CDCl_3$): δ 5.15 (s, 1H), 7.08 (m, 2H), 7.36 (m, 7H).

Intermediate-20 

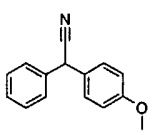
(3,4-Difluoro-phenyl)-phenyl-acetonitrile. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.12 (s, 1H), 7.15 (m, 3H), 7.41 (m, 5H).

Intermediate-21 

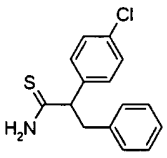
Bis-(4-fluoro-phenyl)-acetonitrile. 4,4`-Difluorobenzhydrol (1 g, 4.54 mmol) was dissolved in TFA (10 mL). Potassium cyanide (620 mg, 9.53 mmol) was added and the mixture was cooled to 0°C. Sulfuric acid (conc., 3 mL) was added slowly. The mixture was stirred at room temperature for 5h then quenched 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 

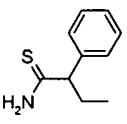
(4-Methoxy-phenyl)-phenyl-acetonitrile. (4-Methoxyphenyl)acetonitrile (5 mL, 37 mmol) was dissolved in dry benzene (10 mL) in a flamedried flask under nitrogen. The mixture was heated to reflux and bromine (1.9 mL, 37 mmol) was added in small portions over 2 h. The mixture was stirred at reflux for 30 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

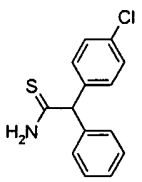
2-(4-Chloro-phenyl)-3-phenyl-thiopropionamide – Representative Procedure 5 (RP5): 2-(4-Chloro-phenyl)-3-phenyl-propionitrile (200 mg, 0.8 mmol) was dissolved in pyridine (5 mL) and triethylamine (1 mL). The mixture was saturated with hydrogen sulfide and stirred under an atmosphere of hydrogen sulfide 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:



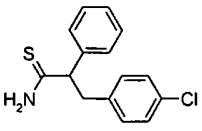
Intermediate-25

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).

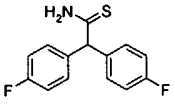


Imtermediate-26

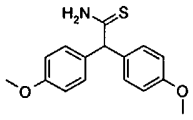
2-(4-Chloro-phenyl)-2-phenyl-thioacetamide. ^{1}H NMR ($CDCl_3$): δ 5.59 (s, 1H).

Intermediate-27 

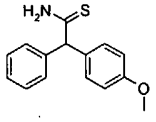
3-(4-Chloro-phenyl)-2-phenyl-thiopropionamide. ^{1}H NMR (DMSO-d_6): δ 3.14 (m, 1H), 3.77 (dd, *J* = 6.6, 13.9 Hz, 1H), 4.00 (t, *J* = 7.73 Hz, 1H).

Intermediate-28 

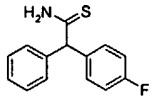
2,2-Bis-(4-fluoro-phenyl)-thioacetamide. ^{1}H NMR ($CDCl_3$): δ 5.57 (s, 1H), 6.76 (br s, 1H (NH)), 7.08 (m, 4H) and 7.23 (m, 4H) and 7.68 (br s, 1H (NH)).

Intermediate-29 

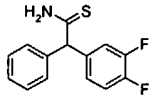
2,2-Bis-(4-methoxy-phenyl)-thioacetamide. LC/MS (an10p8): Rt 2.96 min, *m/z* 288 [M + H]; ^{1}H NMR ($CDCl_3$): δ 3.81 (s, 6H), 5.54 (s, 1H), 6.83 (bs, 1H (NH)), 6.90 (m, 4H), 7.18 (m, 4H), 7.73 (br s, 1H (NH)).

Intermediate-30 

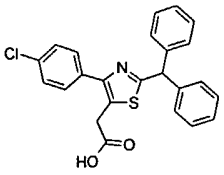
2-(4-Methoxy-phenyl)-2-phenyl-thioacetamide. ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H), 5.59 (s, 1H), 6.83 (bs, 1H (NH)), 6.90 (m, 2H), 7.18 (m, 2H), 7.35 (m, 5H), 7.76 (bs, 1H (NH)).

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 

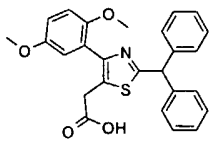
2-(3,4-Difluoro-phenyl)-2-phenyl-thioacetamide. ^{1}H NMR ($CDCl_3$): δ 5.56 (s, 1H), 6.81 (br s, 1H (NH)), 7.04 (m, 1H), 7.14 (m, 2H), 7.25 (m, 2H), 7.38 (m, 3H), 7.92 (br s,1H (NH)).



A1

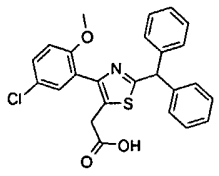
[2-Benzhydryl-4-(4-chloro-phenyl)-thiazol-5-yl]-acetic acid – Representative Procedure 6 (RP6): 3-Bromo-4-(4-chlorophenyl)-4-oxo-butyric acid (119 mg, 0.4 mmol) and 2,2-diphenyl-thioacetamide (91 mg, 0.4 mmol) was dissolved in DMF (1 mL) and heated to 100 °C for 10 minutes in a microwave oven. The reaction 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:



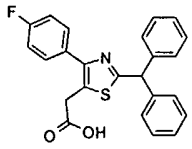
A2

[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), 6.96 (dd, *J* = 8.9 and 3.0 Hz), 7.04 (d, *J* = 8.5 Hz), 7.22-7.45 (m, 10H).



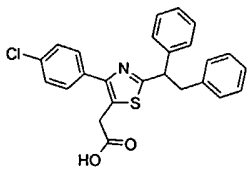
A3

[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), 7.28 (m, 3H), 7.36 (m, 8H), 7.44 (m, 1H).



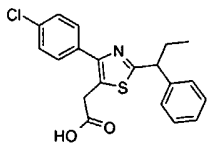
A4

[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).



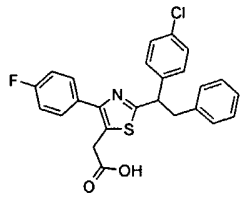
A5

[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)).



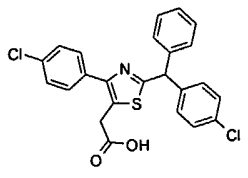
A6

[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].



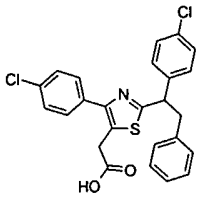
A7

[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)).



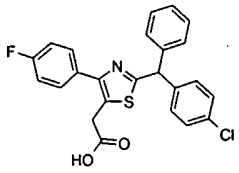
A8

{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).



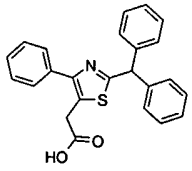
A9

{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)).



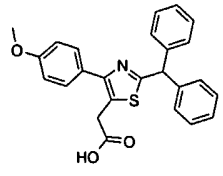
A10

[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).



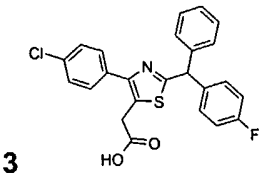
A11

(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 7.60 (m, 2H).



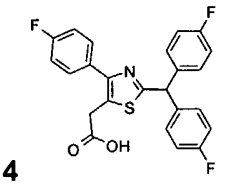
A12

[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).



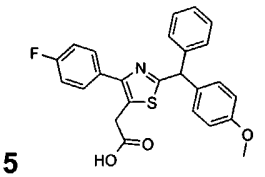
A13

{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).



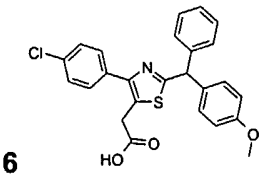
A14

[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).



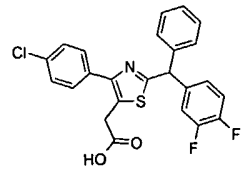
A15

{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), 7.58 (m, 2H). ^{13}C-APT ($CDCl_3$): δ 32.79 (CH_2), 54.62, 55.65 (CH_3/CH).



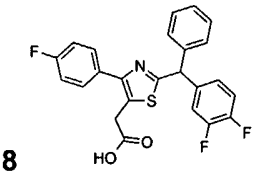
A16

{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).



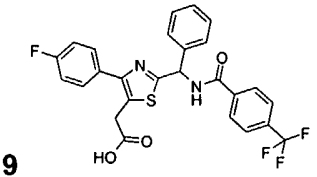
A17

{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).



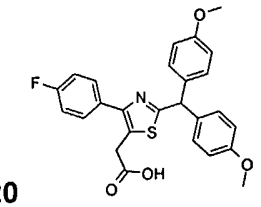
A18

[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).



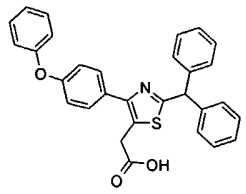
A19

{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)).



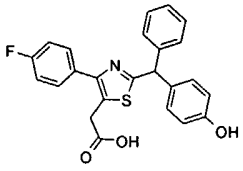
A20

[2-[Bis-(4-methoxy-phenyl)-methyl]-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid. LC/MS (an10p8): Rt 2.17 min, *m/z* 464 [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).



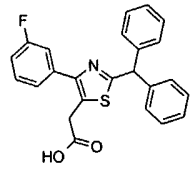
A21

[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).



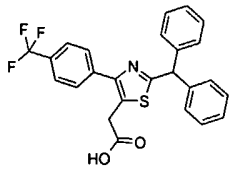
A22

{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).



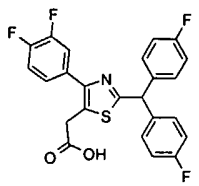
A23

[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).



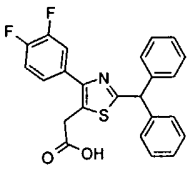
A24

[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 3.88 (s, 2H), 5.81 (s, 1H), 7.04 (m, 4H), 7.18-7.36 (m, 6H), 7.46 (m, 1H).

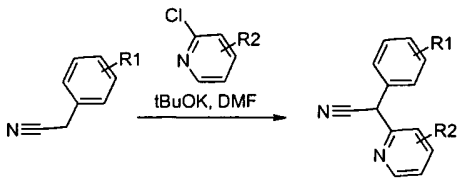


A26

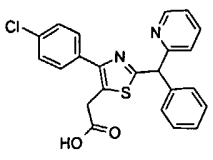
[2-Benzhydryl-4-(3,4-difluoro-phenyl)-thiazol-5-yl]-acetic acid. LC/MS (an10p8): Rt 2.88 min, *m/z* 422 [M + H]; ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 2H), 5.81 (s, 1H), 7.20 (m, 1H), 7.26-7.37 (m, 9H), 7.48 (m, 1H).

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).

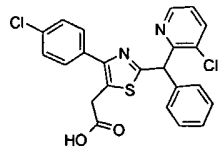


Synthesis of nitrile intermediates – Representative Procedure 7 (RP7): To a cooled (5 °C) solution of Potassium *tert*-butoxide (2.1 mmol) in dry DMF (0.6ml) was added a mixture of the benzonitrile (1 mmol) and the 2-Chloro-pyridine (1.1 mmol) in dry DMF (0.4ml). After O/N stirring at RT, aq. NH_4Cl 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.



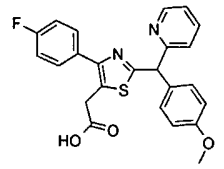
A28

[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 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 3.86 (s, 2H), 6.2 (s, 1H), 7.2-8.0 (m, 12H), 8.7 (d, 1H).



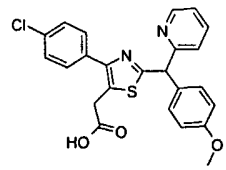
A29

{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 $[M + H]^+$; ^1H 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).



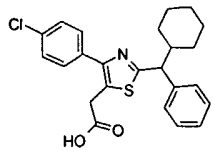
A30

{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 $[M + H]^+$.



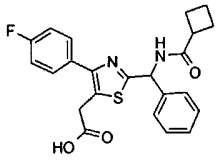
A31

{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 $[M + H]^+$; ^1H 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).



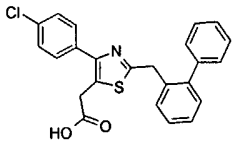
A32

[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 $[M + H]^+$.



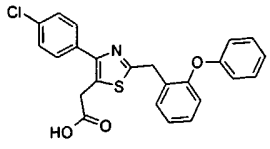
A33

[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).



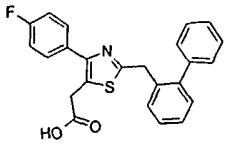
A34

[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).



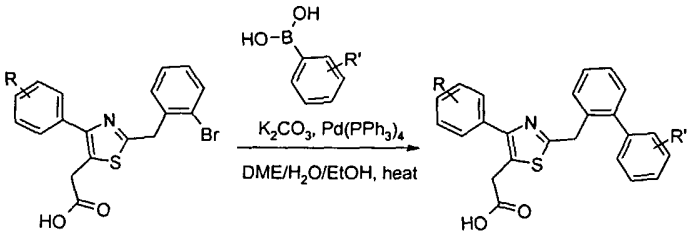
A35

[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).



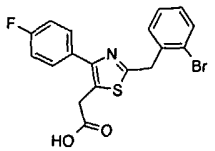
A36

[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).



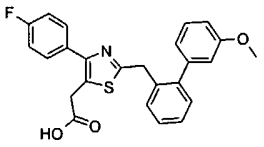
Representative procedure 8 (RP8)

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.



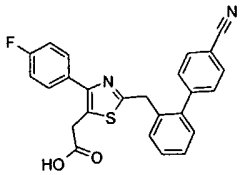
Intermediate-33

[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).



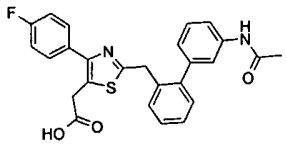
A37

[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).



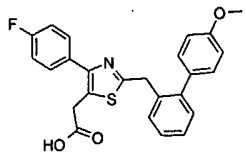
A38

[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

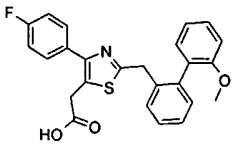
[2-(3'-Acetylamino-biphenyl-2-ylmethyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid. Title compound was prepared from [2-(2-bromo-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid and 3-acetamidobenzene boronic acid according to RP8: LC/MS (an10p8) Rt 2.18 min, *m/z* 460 $[M + H]^+$; ^1H NMR ($CDCl_3$): 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

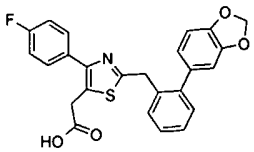
[4-(4-Fluoro-phenyl)-2-(4'-methoxy-biphenyl-2-ylmethyl)-thiazol-5-yl]-acetic acid. Title compound was prepared from [2-(2-bromo-benzyl)-4-(4-fluoro-phenyl)-thiazol-5-yl]-acetic acid and 4-methoxyphenyl boronic acid according to RP8: LC/MS

(an10p8) Rt 2.60 min, *m/z* 433 $[M + H]^+$; ^1H 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).



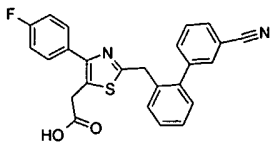
A41

[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 $[M + H]^+$; ^1H 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).



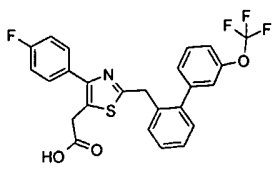
A42

[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 $[M + H]^+$; ^1H 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).



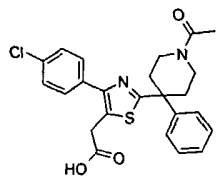
A43

[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 $[M + H]^+$; ^1H 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).



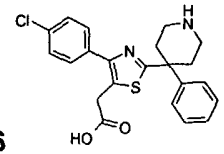
A44

[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 $[M + H]^+$; ^1H 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).



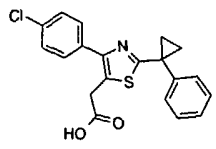
A45

[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-piperidin-4-yl)-2-phenyl-thioacetamide according to RP6: LC/MS (an10p8) Rt 2.32 min, *m/z* 454.5 $[M + H]^+$.



A46

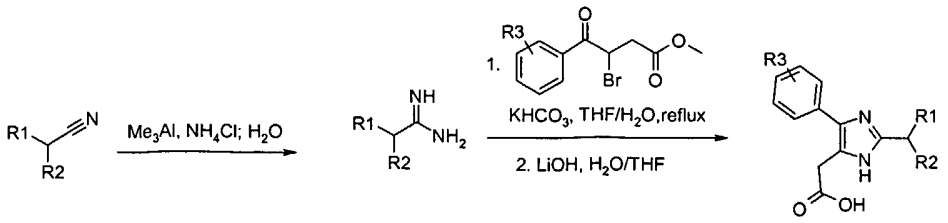
[4-(4-Chloro-phenyl)-2-(4-phenyl-piperidin-4-yl)-thiazol-5-yl]-acetic acid. Title compound, isolated as its HCl salt, was prepared by reacting [2-[(1-acetyl-piperidin-4-yl)-phenyl-methyl]-4-(4-chloro-phenyl)-thiazol-5-yl]-acetic acid with 4N aq. HCl at 95°C for 18 hours, followed by evaporation of solvent: LC/MS (an10p8) Rt 2.07 min, *m/z* 412.4 $[M + H]^+$.

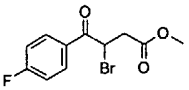


A46

[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 $[M + H]^+$.

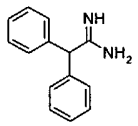
General synthetic route to imidazole analogs





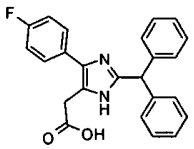
Intermediate-34

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 80 °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 $LiOH \cdot H_2O$ 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):

MSANATLKPLCPILEQMSRLQSHSNTSIRYIDH**AAVLLHGLASLLGLVEN**
GVILFVVGCRMRQTVVTTWVLHLAL**SDLLASASLPFFTYFLAV**GHSWELG
TTF**CKLHSSIFFLNMFASGFL**LSAISLDRCLQVVRPVWAQNHRTVAAAHK
VCLV**LWALAVLNTVPYFVFRDT**ISRLDGRIMCYYNVLLLNPGPDRDATCN
SR**QAALAVSKFLLAFLVPLA**IIASSHAAVSLRLQHRGRRRPGRFVRLVAA
VV**AAFALCWGPYHVFSLLEA**RAHANPGLRPLVWR**GLPFVTSLAFFNSVAN**
PVLYVLTCPDMLRKLRRSLRTVLESVLVDDSELGGAGSSRRRRTSSTARS
ASPLALCSRPEEPRGPARLLGWLLGSCAASPQTGPLNRALSSTSS

Sequence ID CRTH2 (nucleotide sequence):

atgtcggc
caacgccaca ctgaagccac tctgccccat cctggagcag atgagccgtc
tccagagcca
cagcaacacc agcatccgct acatcgacca cgcggccgtg ctgctgcacg
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gctgctgggc ctggtggaga atggagtcat cctcttcgtg gtgggctgcc
gcatgcgcca
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cgtgttcagc ctgctggagg cgcgggcgca cgcaaacccg gggctgcggc
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cggaggaacc
gcggggcccc gcgcgtctcc tcggctggct gctgggcagc tgcgcagcgt
ccccgcagac
gggccccctg 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 **B**ioluminescence **R**esonance **E**nergy **T**ransfer (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

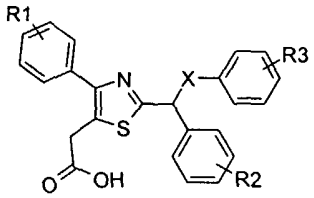
B: IC_{50} value between 0.5 µM and 5 µM

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.

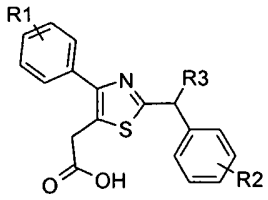
The ability of the compounds above to inhibit prostaglandin D2 induced eosihophil shape change is demonstrated by the examples in Figure 1

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



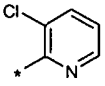
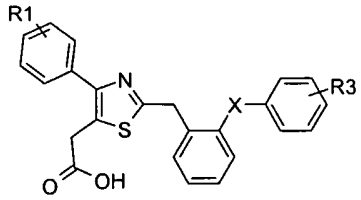
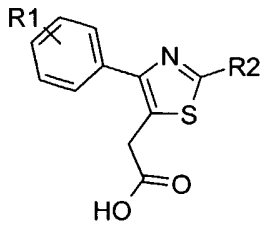
	R1	R2	R3	Binding IC_{50}	Antag. IC_{50}
A28	4-Cl	H		A	B
A29	4-Cl	H		A	
A30	4-F	4-MeO		A	
A31	4-Cl	4-MeO		A	A
A32	4-Cl	H		B	
A6	4-Cl	H	Et	A	

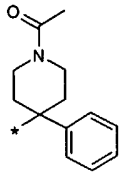
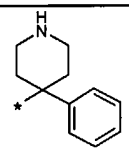
Table 3



	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	

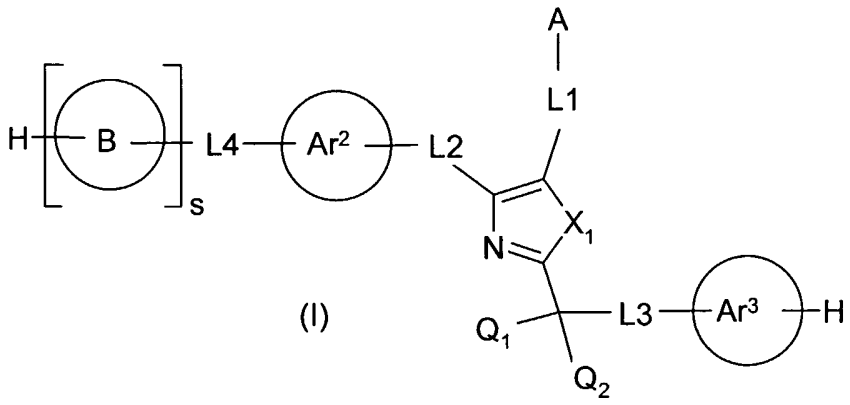
Table 4



	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_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.

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.

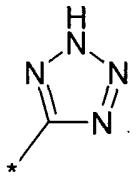
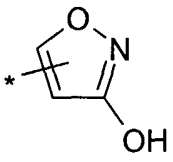
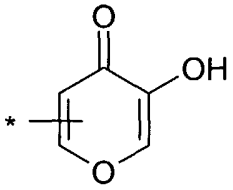
7 A compound as claimed in claim 6 wherein Z is a 1, 2-phenylene radical optionally substituted by one or more of fluoro, chloro, bromo, $(C_1$-$C_3)$alkyl, trifluoromethyl, $(C_1$-$C_3)$alkoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, cyano, $(C_1$-C_3alkyl$)SO_2$-, NH_2SO_2-, $(C_1$-C_3alkyl$)NHSO_2$-, $(C_1$-C_3alkyl$)_2NSO_2$-, -$CONR^AR^B$, and -NR^BCOR^A wherein R^A and R^B are independently hydrogen or a $(C_1$-$C_6)$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,

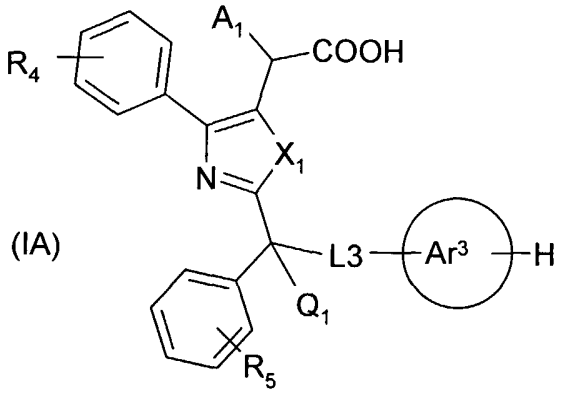
trifluoromethoxy, trifluoromethylthio, dimethylamino, cyano, $(C_1$-C_3alkyl)SO_2-, NH_2SO_2-, $(C_1$-C_3alkyl)$NHSO_2$-, $(C_1$-C_3alkyl)$_2NSO_2$-, -$CONR^AR^B$, and -NR^BCOR^A wherein R^A and R^B are independently hydrogen or a $(C_1$-$C_6)$alkyl group, or R^A and R^B are linked to the same N atom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

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, $(C_1$-$C_3)$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.

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

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



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-.

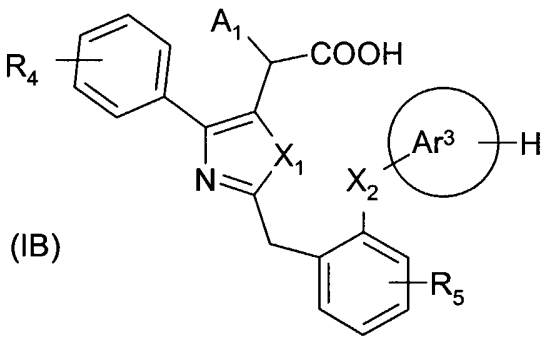
23. A compound as claimed in any of claims 19 to 22 wherein Ar^3 is optionally substituted phenyl.

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 iand 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.

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 fascitis, 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.

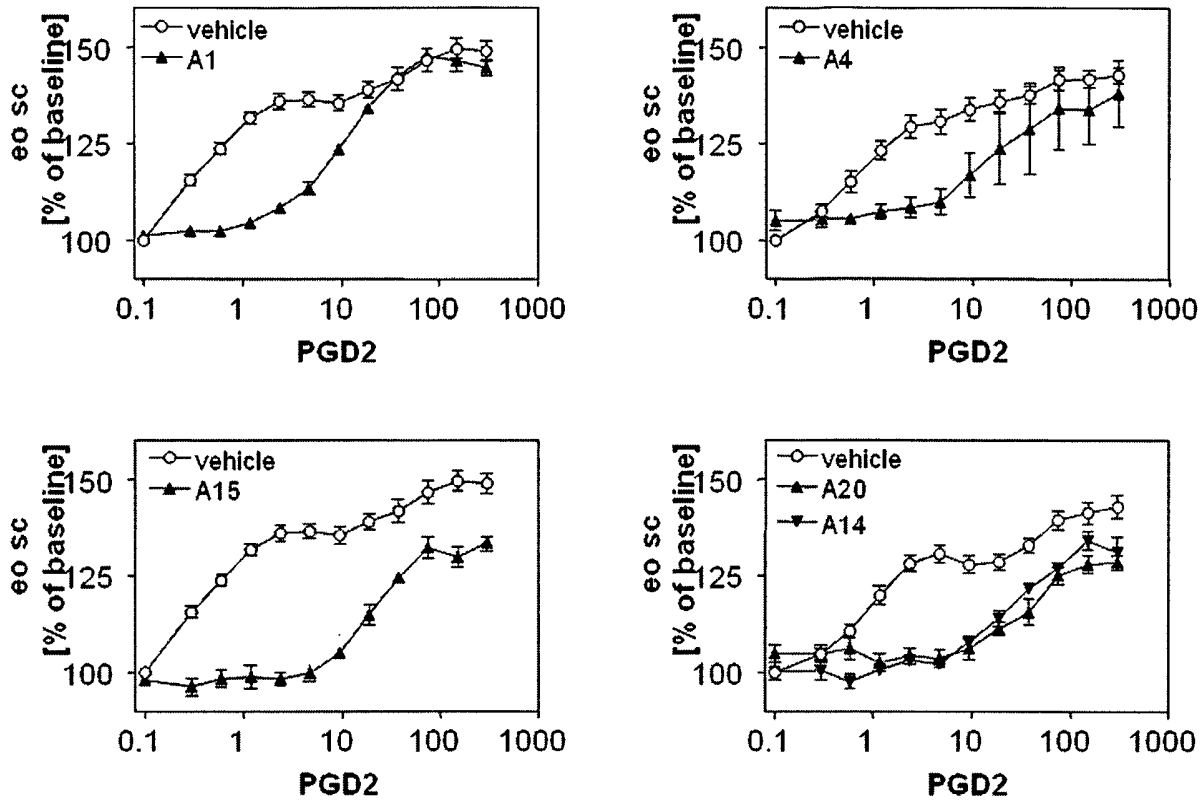

vehicle
A1
eo sc
[% of baseline]
150
125
100
0.1
1
10
100
1000
PGD2
vehicle
A4
eo sc
[% of baseline]
150
125
100
0.1
1
10
100
1000
PGD2
vehicle
A15
eo sc
[% of baseline]
150
125
100
0.1
1
10
100
1000
PGD2
vehicle
A20
A14
eo sc
[% of baseline]
150
125
100
0.1
1
10
100
1000
PGD2

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
X	WO 01/10866 A (JANSSEN PHARMACEUTICA N.V; LACRAMPE, JEAN, FERNAND, ARMAND; FREYNE, ED) 15 February 2001 (2001-02-15) claim 10 page 1, lines 17-22 examples b72,b76-b82,b84-b88,b92,b93,b95-b104,b109 examples b119-b128,b130,b133-b141,b146,b147 ----- -/--	1-18, 34-40

[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
X	US 6 268 363 B1 (LEE HYUN IL ET AL) 31 July 2001 (2001-07-31) column 45 - column 46; compounds 145,148,150	1-18,34
X	WO 03/006015 A (BRISTOL-MYERS SQUIBB PHARMA COMPANY) 23 January 2003 (2003-01-23) example 212; table 2	1-18,34
A	WO 03/101981 A (ASTRAZENECA AB; BIRKINSHAW, TIMOTHY; BONNERT, ROGER; COOK, ANTHONY; RA) 11 December 2003 (2003-12-11) cited in the application claims	1-40
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

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

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9902505 A	21-01-1999	AU 742145 B2	20-12-2001
		AU 8973898 A	08-02-1999
		BR 9811678 A	19-09-2000
		CA 2294145 A1	21-01-1999
		CN 1262679 A	09-08-2000
		EE 200000016 A	16-10-2000
		HR 20000003 A1	31-12-2000
		HU 0004687 A2	28-02-2002
		ID 24390 A	13-07-2000
		JP 2002511882 T	16-04-2002
		NO 20000063 A	10-03-2000
		NZ 502180 A	24-11-2000
		PL 337947 A1	11-09-2000
		SK 183999 A3	14-08-2000
		TR 200000153 T2	21-07-2000
		TW 496865 B	01-08-2002
		ZA 9806089 A	10-01-2000
WO 0110866 A	15-02-2001	AU 780047 B2	24-02-2005
		AU 6160900 A	05-03-2001
		BG 106367 A	30-09-2002
		BR 0013014 A	16-04-2002
		CA 2380759 A1	15-02-2001
		CN 1368972 A	11-09-2002
		CZ 20020356 A3	12-06-2002
		EA 4740 B1	26-08-2004
		EE 200200057 A	15-04-2003
		HU 0202692 A2	28-12-2002
		JP 2003506451 T	18-02-2003
		MX PA02001343 A	22-07-2002
		NO 20020565 A	26-03-2002
		NZ 516506 A	27-02-2004
		PL 353475 A1	17-11-2003
		SK 1642002 A3	04-03-2003
		TR 200200310 T2	21-08-2002
		US 2003114453 A1	19-06-2003
EP 0987265 A	22-03-2000	AT 238301 T	15-05-2003
		AU 769133 B2	15-01-2004
		AU 6082599 A	10-04-2000
		CA 2344390 A1	30-03-2000
		DE 69907233 D1	28-05-2003
		DE 69907233 T2	01-04-2004
		WO 0017195 A1	30-03-2000
		ES 2198958 T3	01-02-2004
		JP 2002526495 T	20-08-2002
		US 2002010177 A1	24-01-2002
US 6268363 B1	31-07-2001	AT 239014 T	15-05-2003
		AU 731272 B2	29-03-2001
		AU 1508399 A	16-06-1999
		BR 9815423 A	17-10-2000
		CA 2310629 A1	10-06-1999
		CN 1279680 A	10-01-2001
		DE 69814167 D1	05-06-2003
		DE 69814167 T2	26-02-2004
		EP 1045846 A1	25-10-2000
		HU 0004238 A2	28-05-2001

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/005882

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6268363 B1		ID 24175 A	13-07-2000
		JP 3548118 B2	28-07-2004
		JP 2001524550 T	04-12-2001
		JP 2002161092 A	04-06-2002
		WO 9928315 A1	10-06-1999
		NZ 504013 A	01-02-2002
		PL 340729 A1	26-02-2001
		RU 2179975 C1	27-02-2002
WO 03006015 A	23-01-2003	NONE	
WO 03101981 A	11-12-2003	AU 2003232712 A1	19-12-2003
		EP 1549634 A1	06-07-2005